Australian guidelines for the clinical care of people with COVID-19
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Disclaimer
The consortium is seeking NHMRC approval of the guideline under section 14A of the National Health and Medical Research Council Act 1992. As part of the approval process (and for the lifetime of the guidelines), public consultation is required. We welcome your feedback and suggestions. Comments can be submitted via the feedback function under each recommendation in Magic or by emailing guidelines@covid19evidence.net.au.

These clinical guidelines are a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are not intended to be proscriptive. They are designed to provide information to assist decision making and have been informed by the highest quality evidence available at the time of compilation. Accordingly, the parties involved in the development of these guidelines shall have no liability to any users of the information contained in this publication for any loss or damage, cost or expense incurred or arising from reliance on the information contained in this publication.
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16. Abbreviations and Acronyms

References
### 4.1 Definition of disease severity for adults

<table>
<thead>
<tr>
<th>Mild illness</th>
<th>An individual with no clinical features suggestive of moderate or more severe disease:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- no OR mild symptoms and signs (fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell)</td>
</tr>
<tr>
<td></td>
<td>- no new shortness of breath or difficulty breathing on exertion</td>
</tr>
<tr>
<td></td>
<td>- no evidence of lower respiratory tract disease during clinical assessment or on imaging (if performed)</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>A stable patient with evidence of lower respiratory tract disease:</td>
</tr>
<tr>
<td></td>
<td>- during clinical assessment, such as</td>
</tr>
<tr>
<td></td>
<td>◦ oxygen saturation 92-94% on room air at rest</td>
</tr>
<tr>
<td></td>
<td>◦ desaturation or breathlessness with mild exertion</td>
</tr>
<tr>
<td></td>
<td>- or on imaging</td>
</tr>
<tr>
<td>Severe illness</td>
<td>A patient with signs of moderate disease who is deteriorating OR</td>
</tr>
<tr>
<td></td>
<td>A patient meeting any of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>- respiratory rate ≥ 30 breaths/min</td>
</tr>
<tr>
<td></td>
<td>- oxygen saturation &lt; 92% on room air at rest or requiring oxygen</td>
</tr>
<tr>
<td></td>
<td>- lung infiltrates &gt; 50%</td>
</tr>
<tr>
<td>Critical illness</td>
<td>A patient meeting any of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>- Respiratory failure (defined as any of)</td>
</tr>
<tr>
<td></td>
<td>◦ severe respiratory failure (PaO₂/FiO₂ &lt; 200)</td>
</tr>
<tr>
<td></td>
<td>◦ respiratory distress or acute respiratory distress syndrome (ARDS)</td>
</tr>
<tr>
<td></td>
<td>◦ deteriorating despite non-invasive forms of respiratory support (i.e. non-invasive ventilation (NIV), or high-flow nasal oxygen (HFNO))</td>
</tr>
<tr>
<td></td>
<td>◦ requiring mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td>- hypotension or shock</td>
</tr>
<tr>
<td></td>
<td>- impairment of consciousness</td>
</tr>
<tr>
<td></td>
<td>- other organ failure</td>
</tr>
</tbody>
</table>

### 4.2 Definition of disease severity for children and adolescents
**Consensus recommendation**

These definitions apply to children under 16 years of age. Depending on the physical size and/or developmental status of the patient, either the paediatric or adult severity grading can be applied.

Cardiorespiratory and vital parameters must be considered within the normal age-appropriate ranges for neonates and children. If criteria fall across different severity classifications, use the more severe classification to manage illness.

<table>
<thead>
<tr>
<th></th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[^1]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild illness</strong></td>
<td>Normal or mildly reduced feeding</td>
<td>No or mild upper respiratory tract symptoms OR No or mild work of breathing</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate illness</strong></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids AND With normal conscious state</td>
<td>Moderate work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) but does not persistently breach Early Warning (e.g. Medical Emergency Team) Criteria[^2] OR Brief self-resolving apnoea (infants)</td>
<td>Requires low-flow oxygen (nasal prongs or mask) to maintain SpO₂ &gt; 95%</td>
</tr>
<tr>
<td><strong>Severe illness</strong></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable</td>
<td>Moderate-severe work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) with breaches of Early Warning (e.g. MET) Criteria OR Apnoea needing support / stimulation (infants)</td>
<td>Requires high-flow oxygen at 2 L/kg/min[^3] to maintain SpO₂ &gt; 95%</td>
</tr>
<tr>
<td><strong>Critical illness</strong></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious</td>
<td>Unable to maintain breathing or prevent apnoea without advanced modes of support OR Abnormal vital signs for age with persistent breaches of Early Warning (e.g. MET) Criteria OR Haemodynamically unstable without inotropic or vasopressor support OR Other organ failure</td>
<td>Requires advanced modes of support to maintain oxygenation High-flow nasal oxygen at &gt; 2 L/kg/min[^3] OR Non-invasive ventilation OR Intubation and mechanical ventilation OR Extracorporeal membrane oxygenation (ECMO)</td>
</tr>
</tbody>
</table>

[^1]: Oxygen saturation target should be modified for patients with cyanotic heart disease.

[^2]: Temperature instability should be considered an abnormal vital sign in infants. Fever is common in children and does not contribute to determination of illness severity in isolation.

[^3]: Infants and neonates < 4 kg may be managed on high-flow nasal cannula oxygen at 2-8 L/min irrespective of weight.

Note: co-morbidities (e.g. preterm infants, oncology, immunosuppressed, etc.) may increase the risk of more severe disease.
5. Monitoring and markers of clinical deterioration

5.1 Monitoring and markers of clinical deterioration

Consensus recommendation

For people with COVID-19, monitor markers of clinical progression, such as rapidly progressive respiratory failure and sepsis, especially on days 5 to 10 after onset of symptoms.
5.2 Pulse oximeters

5.2.1 Pulse oximeters for adults

Consensus recommendation

People with risk factors for deterioration, who are being cared for at home, should be offered monitoring of oxygen saturation with pulse oximetry.

Remark:
For guidance on when to escalate care, please refer to the Pathways to Care Flowchart.

We are aware that the RACGP is developing supporting materials. As soon as these are available we will provide a link to them here.

Risk factors for deterioration* include:

- Older age, e.g. over 50 years for Aboriginal and Torres Strait Islander people, or otherwise over 65 years
- Unvaccinated or partially vaccinated
- Pregnant
- Comorbidities:
  - lung disease, including COPD, asthma or bronchiectasis
  - cardiovascular disease, including hypertension
  - obesity (BMI > 30 kg/m2)
  - diabetes
  - renal failure
  - immunocompromising conditions (** see below)
- Concerns about personal safety or access to care

Use pulse oximetry with adults to assist in assessing and monitoring the severity of respiratory symptoms and detect early deterioration. Provide people with education on how to self-monitor using pulse oximetry and when to call a GP or triple 0.

Be aware that different pulse oximeters have different specifications, and that some can under or overestimate readings especially if the saturation level is borderline. Overestimation has been reported in people with darker skin.

* Evidence enabling us to rank risk factors in order of priority is not yet available.

**Immunocompromising conditions:

- Primary or acquired immunodeficiency:
  - haematological neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency

- Other significantly immunocompromising conditions:
  - immunosuppressive therapy (current or recent)
  - chemotherapy or radiotherapy
  - high-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - all biologics and most disease-modifying anti-rheumatic drugs (DMARDs)

5.2.2 Pulse oximeters for children and adolescents
Children and adolescents with asymptomatic or mild COVID-19 do not routinely require peripheral oxygen saturation monitoring. However, children and adolescents at high risk of deterioration who are being cared for at home should be offered monitoring of peripheral oxygen saturation with pulse oximetry if age-appropriate oximeters and training can be provided and an appropriate pathway for escalation.

Remark:
For guidance on definitions of disease severity for children and adolescents, including peripheral oxygen saturation thresholds, please refer to the specific section in the guideline.

Based on international cohorts [580] potential factors to consider in children or adolescents with mild COVID-19 at high risk* of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity (above the 95th percentile on BMI for age growth chart)

The use of pulse oximetry in children or adolescents to assist in assessing and monitoring the severity of respiratory symptoms and to detect early deterioration should always be in conjunction with clinical assessment of disease severity. Home pulse oximetry should only be used if children and adolescents, their parents or carers have received education on how to self-monitor and when to call a GP or triple 0.

Only age-appropriate pulse oximeters should be used in children. Be aware that different pulse oximeters have different specifications, and that some can under or overestimate readings, especially if the saturation level is borderline. Overestimation has been reported in people with darker skin.

* Evidence enabling us to rank risk factors in order of priority is not yet available.

6. Disease-modifying treatments

6.1 Recommended disease-modifying treatments

6.1.1 Budesonide

6.1.1.1 Budesonide for adults
Conditional recommendation

Consider using inhaled budesonide within 14 days of symptom onset in adults with COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

Remark:
In patients with confirmed COVID-19 who do not require oxygen but who are subsequently hospitalised due to disease progression, budesonide probably decreases the requirement of supplemental oxygen if taken within 14 days of onset of symptoms.

Results are primarily based on the PRINCIPLE trial \([566]\) in which adults were treated with inhaled budesonide (by breath-actuated inhaler) 800 µg twice daily for up to 14 days. Based on the inclusion criteria for this trial, risk factors for disease progression include age ≥ 65 years or ≥ 50 years with one or more of the following comorbidities:

- Diabetes (not treated with insulin)
- Heart disease and/or hypertension
- Asthma or lung disease
- Weakened immune system due to a serious illness or medication (e.g. chemotherapy)
- Mild hepatic impairment
- Stroke or other neurological problem

Approximately 11% and 1% of participants had received one or two doses of vaccine at enrolment, respectively, however results were not reported separately for this population.

Budesonide is safe to use in pregnant and breastfeeding women.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.1.2 Budesonide for children and adolescents

Conditional recommendation

Consider using inhaled budesonide for the treatment of symptomatic COVID-19 in children and adolescents who do not require oxygen and who have one or more risk factors for disease progression.

Remark:
In adult patients with confirmed COVID-19 who do not require oxygen but who are subsequently hospitalised due to disease progression, budesonide probably decreases the requirement of supplemental oxygen if taken within 14 days of onset of symptoms.

Results are primarily based on the PRINCIPLE trial \([566]\), in which adults were treated with inhaled budesonide (by breath actuated inhaler) 800 µg twice daily for up to 14 days. No children or adolescents were included in the trial.

Based on international cohort studies \([580]\), risk factors for disease severity in children include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

Approximately 11% and 1% of participants had received one or two doses of vaccine at enrolment, respectively, however results were not reported separately for this population.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
6.1.2 Casirivimab plus imdevimab (Ronapreve/REGEN-COV)

### 6.1.2.1 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for adults

**Conditional recommendation**

Consider using casirivimab plus imdevimab within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

**Remark:**
In adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.

Included data comes from the three-phase REGEN-COV trial [509][576] in which patients with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Based on inclusion criteria of the trial, risk factors for disease progression include:

- Age ≥ 50 years
- Obesity (BMI ≥ 30 kg/m2)
- Cardiovascular disease (including hypertension)
- Chronic lung disease (including asthma)
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease, including those that are on dialysis
- Chronic liver disease
- Immunocompromised patients (including individuals with rheumatoid arthritis, HIV/AIDS and systemic lupus erythematosus receiving immunosuppressive treatment)

As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms.

The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised patients with mild or asymptomatic COVID-19 is not known.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on *in vitro* data. We will update this recommendation as definitive evidence becomes available.

As of 29 October 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in adult outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*
Conditional recommendation

Consider using casirivimab plus imdevimab in seronegative adults hospitalised with moderate to critical COVID-19.

Remark:
In patients hospitalised with moderate to critical COVID-19 who are seronegative (no detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.

The Taskforce notes that the RECOVERY trial administered a single intravenous 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab in 250 ml 0.9% saline) and assessed baseline serostatus using the Oxford (anti-spike IgG) immunoassay, the use of which has been supported by the UK National SARS-CoV-2-Serology Assay Evaluation Group [516].

It should be noted that the study by Somersan-Karakaya [628] initially included patients requiring ventilation but ceased their recruitment due to safety concerns, however no safety data were provided for these patients.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

The sponsor has not submitted an application to the Therapeutics Goods Administration for use of casirivimab plus imdevimab in hospitalised patients and it is presently not approved for this indication.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Not recommended

Do not use casirivimab plus imdevimab in seropositive adults hospitalised with moderate to critical COVID-19.

Remark:
In patients hospitalised with moderate to critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably has little impact on mortality, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.2.2 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for pregnant or breastfeeding women
Conditional recommendation

Consider using casirivimab plus imdevimab within 7 days of symptom onset in pregnant or breastfeeding women who are outpatients with mild COVID-19 and who have one or more risk factors for disease progression.

Remark:
In non-pregnant adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce has given a conditional recommendation on the use for casirivimab plus imdevimab both within and outside the context of a randomised trial.

Included data comes from the three-phase REGEN-COV trial [509][576] in which patients with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Based on the inclusion criteria of this trial, risk factors for disease progression include:

- Age ≥ 50 years
- Obesity (≥ 30 kg/m2)
- Cardiovascular disease (including hypertension)
- Chronic lung disease (including asthma)
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease, including those that are on dialysis
- Chronic liver disease
- Immunocompromised patients (including individuals with rheumatoid arthritis, HIV/AIDS and systemic lupus erythematosus)

There is uncertainty around the benefits and harms of casirivimab plus imdevimab for pregnant or breastfeeding women with COVID-19, as these women were not eligible in the available trials. Casirivimab plus imdevimab is a human immunoglobulin G (IgG) and may cross the placenta from mother to baby. The potential impact of this is not known. However, it is known that pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby [567]. Casirivimab plus imdevimab can therefore be considered if the benefit justifies the possible but unknown risks.

As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms. Dose adjustment is not required for pregnant or breastfeeding women.

The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised patients with mild or asymptomatic COVID-19 is not known.

There are no available data on the excretion of casirivimab plus imdevimab in human milk, and the potential benefits and risks to a breastfed baby are not known. Human IgGs are known to be excreted in breast milk. A decision whether to discontinue breastfeeding or to abstain from casirivimab plus imdevimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

As of 29 September 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in pregnant or breastfeeding women who are outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
Conditional recommendation

Consider using casirivimab plus imdevimab in pregnant or breastfeeding women who are seronegative patients hospitalised with moderate to critical COVID-19.

Remark:
The Taskforce notes that the RECOVERY trial administered a single intravenous 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab in 250 ml 0.9% saline) and assessed baseline serostatus using the Oxford immunoassay, the use of which has been supported by the UK National SARS-CoV-2-Serology Assay Evaluation Group [516]. Dose adjustment is not required for pregnant or breastfeeding women.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Not recommended

Do not use casirivimab plus imdevimab in seropositive pregnant or breastfeeding women who are hospitalised with moderate to critical COVID-19.

Remark:
In patients hospitalised with moderate to critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably has little impact on mortality, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.2.3 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for children and adolescents
Consensus recommendation

Consider using, in exceptional circumstances, casirivimab plus imdevimab within 7 days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40 kg with mild COVID-19 who are at high risk of deterioration.

Remark:
In adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.

Decisions to provide casirivimab plus imdevimab to a child or adolescent should be based on the individual's combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Included data comes from the three-phase REGEN-COV trial[509][576] in which patients with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Available research does not currently provide enough evidence to determine the benefits of casirivimab plus imdevimab in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from casirivimab plus imdevimab. Based on international cohorts[580] potential factors to consider in mild patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity (above the 95th percentile on BMI for age growth chart)

As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms.

The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised children and adolescents with mild or asymptomatic COVID-19 is not known.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

As of 29 October 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in adult outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Only in research settings

Do not use casirivimab plus imdevimab in children under 12 years of age without risk factors for deterioration who have mild or asymptomatic COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
Consensus recommendation

Consider using, in exceptional circumstances, casirivimab plus imdevimab in **seronegative** children and adolescents aged 12 years and over and weighing at least 40 kg with moderate to critical COVID-19 who are at high risk of disease progression.

Remark:
In adult patients hospitalised with moderate to critical COVID-19 who are seronegative (no detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably reduces the risk of death. The Taskforce notes that the RECOVERY trial administered a single intravenous 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab in 250 ml 0.9% saline) and assessed baseline serostatus using the Oxford immunoassay, the use of which has been supported by the UK National SARS-CoV-2-Serology Assay Evaluation Group [516]. No children or adolescents were included in this trial.

Available research does not currently provide enough evidence to determine the benefits of casirivimab plus imdevimab in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from casirivimab plus imdevimab. Based on international cohorts [580] potential factors to consider in moderate patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on *in vitro* data. We will update this recommendation as definitive evidence becomes available.

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

Not recommended

Do not use casirivimab plus imdevimab in **seropositive** children and adolescents hospitalised with moderate to critical COVID-19.

Remark:
In patients hospitalised with moderate to critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably has little impact on mortality, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

6.1.3 Molnupiravir (Lagevrio)
Consensus recommendation

Consider using molnupiravir within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression, where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

Within the patient population for which molnupiravir is recommended for use (see Remark), decisions about the appropriateness of treatment with molnupiravir should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

* Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of molnupiravir is unclear in partially or fully vaccinated individuals. Additional recommendations for other patient groups are currently under development and will be included in a future version of the guideline.

Remark:

Based on available data, molnupiravir may reduce hospitalisation or death in individuals with PCR-confirmed COVID-19 and mild illness when treated within 5 days of onset of symptoms, however the evidence is limited, effect sizes are small and there are limited safety data. Until further evidence is available, use of molnupiravir should only be considered where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

The Taskforce notes the high level of efficacy in reduction of the composite outcome of hospitalisation or death observed within the interim analysis (n=762; 68 fewer per 1000) and the subsequent reduction in efficacy within the final analysis (n=1408; 29 fewer per 1000) [643]. It is unclear whether or to what extent the significant proportional increase in patients infected with the Delta variant between the interim and final analyses contributes to the observed reduction in efficacy. The efficacy of molnupiravir against the Omicron variant is not known.

Results are based on a single trial in which non-vaccinated adults were treated with 800 mg of molnupiravir twice daily for 5 days. Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- Age ≥ 60 years
- Obesity (BMI ≥ 30 kg/m^2)
- Chronic kidney disease (eGFR 30 - 60 mL/min/1.73m^2 by MDRD), excluding patients on dialysis
- Serious heart conditions such as heart failure, coronary artery disease or cardiomyopathies
- Chronic obstructive pulmonary disease
- Active cancer (excluding minor cancers not associated with immunosuppression, e.g. basal cell carcinomas)
- Immunocompromised state following solid organ transplant
- Sickle cell disease
- Diabetes mellitus

Pregnant & breastfeeding women and children & adolescents were not included in the trial. There are no clinical data for the use of molnupiravir in pregnant women, however animal reproductive studies indicate that molnupiravir may have embryolethal and teratogenic effects at high doses and may result in reduced fetal growth.

Contraception is recommended until 4 days after the final dose of molnupiravir in sexually active women of childbearing potential, and for 3 months in men who are sexually active with a partner of childbearing potential (TGA PI).

The efficacy of molnupiravir in vaccinated or immunocompromised patients is unknown.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.
Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using molnupiravir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunosuppressed or not immunocompetent regardless of vaccination status; or
- have received one or two doses of vaccine and who are at high risk of severe disease on the basis of age and multiple risk factors

**AND** where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

Remark:
Available research does not currently provide enough evidence to determine the benefits of molnupiravir in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from molnupiravir.

There is no evidence evaluating the effectiveness of molnupiravir in partially or fully vaccinated patients. Given this, and the lower risk of deterioration in these patients, it is unlikely that molnupiravir will have a significant treatment benefit in patients who have received three doses of vaccine, unless the patient is immunosuppressed.

There is limited evidence on the effectiveness of molnupiravir in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that molnupiravir will be beneficial for immunosuppressed patients.

Immunocompromising conditions include:

- Primary or acquired immunodeficiency
  - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
  - Other significantly immunocompromising conditions

- Immunosuppressive therapy (current or recent)
  - Chemotherapy, whole body radiotherapy or total lymphoid irradiation
  - High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - All biological disease-modifying anti-rheumatic drugs (DMARDs) and most other (e.g. conventional synthetic) DMARDs [550]

Implications for research

Given the limited evidence of benefit or safety, small effect sizes and absence of evidence evaluating the effectiveness of molnupiravir for SARS-CoV-2 variants of concern, rigorous data collection should be undertaken on indications and key outcomes for patients who receive treatment with molnupiravir.

**6.1.4 Nirmatrelvir plus ritonavir (Paxlovid)**
Conditional recommendation

Consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in unvaccinated adults* with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which nirmatrelvir plus ritonavir is conditionally recommended for use (see Remark), decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

* Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of nirmatrelvir plus ritonavir is unclear in partially or fully vaccinated individuals. See consensus recommendation for guidance on use of nirmatrelvir plus ritonavir in vaccinated patients or in immunocompromised patients regardless of vaccination status.

Remark:
In patients with confirmed COVID-19 who do not require oxygen, nirmatrelvir plus ritonavir probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on a single phase 2/3 trial comparing nirmatrelvir plus ritonavir with placebo in 1219 unvaccinated adults with PCR-confirmed COVID-19 and mild illness. Within this trial participants were treated with oral nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days.

The benefit of nirmatrelvir plus ritonavir is likely to be greatest in those with the greatest risk of severe disease. Based on the population included within the trial, evidence demonstrates a reduction in hospitalisation when used in individuals with one or more of the following risk factors for disease progression:

- Age ≥ 60 years
- Diabetes (requiring medication)
- BMI ≥ 25 kg/m²
- Cardiovascular disease
- Hypertension
- Chronic lung disease

There were insufficient numbers of participants with the following risk factors to determine the extent to which nirmatrelvir plus ritonavir impacts hospitalisation or death, however as these conditions frequently result in poorer outcomes for patients following SARS-CoV-2 infection, they will likely benefit from treatment:

- Chronic kidney disease (but where the eGFR ≥ 30 mL/min)*
- Immunosuppressed (e.g. bone marrow or organ transplantation, primary immune deficiencies, prolonged use of immune-weakening medications)
- Medical related technological dependence (e.g. CPAP not related to COVID-19)
- HIV positive (viral load < 400 copies/mL)
- Neurodevelopmental disorders (e.g. cerebral palsy, Down syndrome)
- Cancer (other than localised skin cancer)
- Sickle cell disease

* Individuals with an eGFR < 30 mL/min were excluded from the trial. In individuals with CKD and an eGFR of 30-60 mL/min, the dose of nirmatrelvir should be halved; i.e. nirmatrelvir/ritonavir 150/100 mg twice daily for 5 days (FDA EUA).

Pregnant & breastfeeding women and children & adolescents were not included in the trial.

Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of nirmatrelvir plus ritonavir is unclear in partially or fully vaccinated individuals.

The study was conducted before the Omicron variant was prevalent. As a result, there are no data regarding the effectiveness of nirmatrelvir plus ritonavir specific to the Omicron variant.

Ritonavir is an inhibitor, inducer and substrate of many enzymes and transporters involved in drug disposition and metabolism. It is a strong inhibitor of CYP3A, reducing the hepatic metabolism and increasing the concentration of nirmatrelvir and other CYP3A substrates. Coadministration of nirmatrelvir-ritonavir is contraindicated with drugs that are highly dependent upon CYP3A for clearance where an elevated concentration may be dangerous (e.g. anti-arrhythmics, antipsychotics, statins, anti-inflammatory, anti-cancer drugs and anticoagulants. Coadministration is also contraindicated with potent CYP3A inducers (e.g. anti-epileptics, rifampin, St John's wort), which can reduce concentrations of nirmatrelvir and/or ritonavir, reducing efficacy and increasing resistance. Induction persists many days after cessation due to time required for clearance of the inducing drug and induced CYP3A.
Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunosuppressed or not immunocompetent regardless of vaccination status; or
- have received one or two doses of vaccine and who are at high risk of severe disease on the basis of age and multiple risk factors.

Remark:
The available research does not currently provide enough evidence to determine the benefits of nirmatrelvir plus ritonavir in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from nirmatrelvir plus ritonavir.

There is no evidence evaluating the effectiveness of nirmatrelvir plus ritonavir in partially or fully vaccinated patients. Given this and the lower risk of deterioration in these patients, it is unlikely that nirmatrelvir plus ritonavir will be particularly valuable in patients who have received three doses of vaccine, unless the patient is immunosuppressed.

There is limited evidence on the effectiveness of nirmatrelvir plus ritonavir in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that nirmatrelvir plus ritonavir will be beneficial for immunosuppressed patients.

Immunocompromising conditions include:

- Primary or acquired immunodeficiency
  - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
  - Other significantly immunocompromising conditions

- Immunosuppressive therapy (current or recent)
  - Chemotherapy, whole body radiotherapy or total lymphoid irradiation
  - High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - All biological disease-modifying anti-rheumatic drugs (DMARDs) and most other (e.g. conventional synthetic) DMARDs [550]

6.1.5 Systemic corticosteroids

6.1.5.1 Corticosteroids for adults
Recommended

Use dexamethasone 6 mg daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Remark:
The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days
- prednisolone: oral (50 mg), daily for up to 10 days
- methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain

It is unclear whether older people living with frailty or cognitive impairment, or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Conditional recommendation against

Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19 in adults who do not require oxygen.

Remark:
Corticosteroids may still be considered for other evidence-based indications in people who have COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.5.2 Corticosteroids for pregnant or breastfeeding women

Recommended

Use dexamethasone 6 mg daily intravenously or orally for up to 10 days in pregnant or breastfeeding women with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

If steroids are indicated for fetal lung maturity in women at risk of preterm birth, a standard antenatal corticosteroid regimen should be used (e.g. intramuscular dexamethasone 6 mg every 12 hours for four doses), followed by 6 mg dexamethasone daily until 10 days has been reached (see 13.1 - Antenatal Corticosteroids).

If steroids are not indicated for fetal lung maturity, use dexamethasone 6 mg daily intravenously or orally for up to 10 days.

Remark:
The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days
- prednisolone: oral (50 mg), daily for up to 10 days

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
Conditional recommendation against

Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19 in pregnant or breastfeeding women who do not require oxygen.

Remark:
Antenatal corticosteroids should still be used for fetal lung maturation in pregnant women at risk of preterm birth who also have COVID-19. Dexamethasone and other corticosteroids should still be used for other evidence-based indications in pregnant and breastfeeding women who have COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.5.3 Corticosteroids for children and adolescents

Conditional recommendation

Consider using dexamethasone daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in children and adolescents with acute COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Remark:
A dose of 6 mg daily is recommended in adults. The RECOVERY trial protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children but it is unclear whether any children were included in the trial. If dexamethasone is not available, an acceptable alternative regimen would be:

- hydrocortisone: intravenous or intramuscular 1 mg/kg/dose, every 6 hours for up to 10 days (to a maximum dose of 50 mg every 6 hours)
- methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain

For specific recommendations on the use of corticosteroids for PIMS-TS see section.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Conditional recommendation against

Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19 in children and adolescents who do not require oxygen.

Remark:
Dexamethasone and other corticosteroids should still be used for other evidence-based indications in children and adolescents who have COVID-19.

For specific recommendations on the use of corticosteroids for PIMS-TS see section.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.6 Other immunomodulating drugs
As of 3 June 2021, the Taskforce has developed conditional recommendations supporting the use of three non-steroidal immunomodulatory agents for the treatment of COVID-19 in hospitalised patients requiring supplemental oxygen. All three treatments demonstrate a mortality benefit when used in this patient population (moderate certainty of evidence), however the Taskforce cautions against the concomitant use of two or more of these immunomodulatory agents due to increased risk of side effects such as opportunistic infection.

All studies that contribute data to analyses underpinning these recommendations compare the treatment of interest with either standard care or placebo. In the absence of data directly comparing one agent to another, it is unclear which of these agents is clinically superior, and thus it is not possible to promote the use of one treatment over another based on clinical evidence alone.

The Taskforce acknowledges the importance of other factors in deciding which treatment is administered, such as availability (e.g. sarilumab has not been approved by the TGA), route of administration and cost. A table providing a comparison of clinical and non-clinical factors between the three recommended immunomodulators can be found [here](#).

It is important to note that as of 17 August 2021, there is a significant shortage of tocilizumab within Australia (TGA statement). As a result, in patients who are receiving supplemental oxygen but are not mechanically ventilated, baricitinib should be considered instead of tocilizumab, unless contraindicated.

### 6.1.6.1 Baricitinib

#### 6.1.6.1.1 Baricitinib for adults

**Conditional recommendation**

Consider using baricitinib in adults hospitalised with COVID-19 who require supplemental oxygen.

**Remark:**

In patients hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for baricitinib both within and outside the context of a randomised trial.

In accordance with the ACTT-2 and COV-BARRIER studies, baricitinib should be administered as a 4 mg oral daily dose for up to 14 days. In patients receiving more intensive oxygen delivery where oral administration is not feasible, administer via nasogastric tube. Consider using a reduced dose of 2 mg daily in patients with an eGFR of between 30 and 60 mL/min/1.73m².

The Taskforce previously recommended baricitinib for use in patients who required supplemental oxygen but not mechanical ventilation or ECMO due to the absence of direct evidence within this population. Data from the COV-BARRIER extension study suggests baricitinib is safe and effective in patients hospitalised with COVID-19 who require mechanical ventilation or ECMO. The Taskforce has subsequently revised the recommendation to include these patients.

The Taskforce notes the current critical shortage of tocilizumab. Therefore, in patients who are receiving supplemental oxygen, baricitinib should be considered as an alternative to tocilizumab, unless contraindicated. For the TGA and Medicine Availability Working Group statements regarding the shortage, click [here](#).

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

#### 6.1.6.1.2 Baricitinib for pregnant or breastfeeding women
Only in research settings

Do not use baricitinib for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

Remark:
This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.6.1.3 Baricitinib for children and adolescents

Only in research settings

Do not use baricitinib for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

Remark:
This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.6.2 Sarilumab

6.1.6.2.1 Sarilumab for adults

Conditional recommendation

Consider using sarilumab for the treatment of COVID-19 in adults who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation.

Remark:
In patients hospitalised with COVID-19 who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation, sarilumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for sarilumab both within and outside the context of a randomised trial.

Uncertainty remains whether sarilumab impacts mortality in patients who require no ventilatory support or low-flow oxygen.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.6.2.2 Sarilumab for pregnant or breastfeeding women
Only in research settings

Do not use sarilumab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

Remark:
This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.6.2.3 Sarilumab for children and adolescents

Only in research settings

Do not use sarilumab for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

Remark:
This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.6.3 Tocilizumab

6.1.6.3.1 Tocilizumab for adults
Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in adults who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

Remark:
In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

The Taskforce notes the current critical shortage of tocilizumab. Therefore, in patients who are receiving supplemental oxygen, baricitinib should be considered as an alternative to tocilizumab, unless contraindicated. For the TGA and Medicine Availability Working Group statements regarding the shortage, click here.

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- Patients > 90 kg: 800 mg tocilizumab
- Patients 66–90 kg: 600 mg tocilizumab
- Patients 41–65 kg: 400 mg tocilizumab
- Patients ≤ 40 kg: 8 mg/kg tocilizumab

In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

6.1.6.3.2 Tocilizumab for pregnant or breastfeeding women
Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in pregnant or breastfeeding women who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

Remark:
In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- Patients > 90 kg: 800 mg tocilizumab
- Patients 66–90 kg: 600 mg tocilizumab
- Patients 41–65 kg: 400 mg tocilizumab
- Patients ≤ 40 kg: 8 mg/kg tocilizumab

In pregnant and breastfeeding women, dosing should be based on body weight at time of clinical need.

In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

For the babies of women who received tocilizumab during pregnancy (after 20 weeks of gestation), live vaccines (rotavirus and BCG) should be avoided in the first six months of life. All non-live vaccinations are safe and should be undertaken (see factsheet).

In women who receive tocilizumab while breastfeeding only, live vaccines (rotavirus and BCG) can be given to the baby (see factsheet).

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

6.1.6.3.3 Tocilizumab for children and adolescents
Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

Remark:
In adult patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections). No children were enrolled in any of the trials included.

There is no established dose for tocilizumab for the treatment of acute COVID-19 in children or adolescents. (The Taskforce notes that RECOVERY is recruiting children and adolescents with PIMS-TS for their trial of tocilizumab [89].) Tocilizumab should be administered as a single intravenous infusion over 60 minutes. Following protocol information in the RECOVERY trial, as well as previous literature on the use of tocilizumab for other indications, the suggested dose is dependent on body weight:

- Infants < 1 year (excluded from RECOVERY trial): dosing from other uses 12 mg/kg [88]
- < 30 kg: 12 mg/kg
- ≥ 30 kg: 8 mg/kg (max 800 mg)

In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab in adults. Use of combined tocilizumab and corticosteroids should be considered in children and adolescents hospitalised with COVID-19 who require oxygen, however, the optimal sequencing of tocilizumab and corticosteroid use is unclear in all populations.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

6.1.7 Remdesivir

6.1.7.1 Remdesivir for adults
Conditional recommendation

Consider using remdesivir in adults with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation.

Remark:
In patients hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [51]. For a full description of the rationale underpinning this decision please see here.

It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Not recommended

Do not start remdesivir in adults hospitalised with COVID-19 who require non-invasive or invasive ventilation.

Remark:
Remdesivir should be continued with the appropriate dose and duration, if it was started prior to requiring ventilation.

Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).

It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

Use of remdesivir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include remdesivir.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

6.1.7.2 Remdesivir for pregnant or breastfeeding women
Conditional recommendation

Consider using remdesivir in pregnant or breastfeeding women hospitalised with moderate to severe COVID-19 who do not require ventilation.

Remark:
In patients hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [51]. For a full description of the rationale underpinning this decision please see here.

The recommended regimen is daily intravenous infusion (200 mg initial dose, 100 mg maintenance), optimal duration of remdesivir treatment is unclear, however current evidence does not suggest a clear benefit of 10 days over 5 days.

On 31 July 2020, the Australian Government provided specific criteria that needed to be met in order to access remdesivir for clinical treatment. These included age ≥ 18 years (or 12–17 years weighing ≥ 40 kg), an oxygen saturation of SpO2 ≤ 92% on room air and requiring supplemental oxygen, and alanine aminotransferase (ALT) < 5 x upper limit of normal (ULN) and/or ALT < 3 x ULN and bilirubin < 2 ULN. Patients with evidence of multiorgan failure, renal failure or those receiving mechanical ventilation for > 48 hours at time of application or extracorporeal membrane oxygenation (ECMO) are unable to receive remdesivir.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [46].

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Not recommended

Do not start remdesivir in pregnant or breastfeeding women hospitalised with COVID-19 who require ventilation.

Remark:
Remdesivir should be continued with the appropriate dose and duration, if it was started prior to requiring ventilation.

Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).

Use of remdesivir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include remdesivir.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

6.1.7.3 Remdesivir for children and adolescents
Conditional recommendation against

Use of remdesivir in children and adolescents with COVID-19 outside of a trial setting should not be considered routinely.

Remark:
If treatment is considered—in exceptional circumstances—it should be in consultation with a clinical reference group, such as the ANZPID COVID-19 Clinical Reference Group. Informed consent from parents/caregivers should also be obtained. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab. Trials of remdesivir in children and adolescents are currently being conducted, this recommendation will be updated once new evidence is available.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

6.1.8 Sotrovimab

6.1.8.1 Sotrovimab for adults
Conditional recommendation

Consider using sotrovimab within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which sotrovimab is conditionally recommended for use (see Remark), decisions about the appropriateness of treatment with sotrovimab should be based on the patient’s individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

* Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of sotrovimab is unclear in partially or fully vaccinated individuals. See consensus recommendation for guidance on use of sotrovimab in vaccinated patients or in immunocompromised patients regardless of vaccination status.

Remark:
In patients with confirmed COVID-19 who do not require oxygen, sotrovimab probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on the COMET-ICE trial [617], in which unvaccinated adults were treated with a single one-hour intravenous infusion of 500 mg of sotrovimab. Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- Diabetes (requiring medication)
- Obesity (BMI ≥ 30 kg/m2)
- Chronic kidney disease (i.e. eGFR < 60 by MDRD)
- Congestive heart failure (NYHA class II or greater)
- Chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion)
- Moderate-to-severe asthma (requiring an inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months)
- Age ≥ 55 years

Pregnant & breastfeeding women and children & adolescents were not included in the trial. However trials are underway in which children over 12 years of age are eligible for inclusion (OPTIMISE-C19, NCT04913675).

The efficacy of sotrovimab in vaccinated or immunocompromised patients is unknown.

As of 28 January 2022, the Taskforce has made conditional recommendations supporting the use of nirmatrelvir plus ritonavir, sotrovimab, and casirivimab plus imdevimab in adult outpatients with mild COVID-19. The relative effectiveness of these agents, or the effectiveness of these agents when used in combination, is unclear.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.
In addition to at-risk unvaccinated adults, also consider using sotrovimab within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunosuppressed or not immunocompetent regardless of vaccination status; or
- have received one or two doses of vaccine and who are at high risk of disease on the basis of age and multiple risk factors

Remark:
Available research does not currently provide enough evidence to determine the benefits of sotrovimab in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from sotrovimab.

There is no evidence evaluating the effectiveness of sotrovimab in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this, and the lower risk of deterioration in these patients, it is unlikely that sotrovimab will have a significant treatment benefit in patients who have received three doses of vaccine, unless the patient is immunosuppressed.

There is no evidence on the effectiveness of sotrovimab in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that sotrovimab will be beneficial for immunosuppressed patients.

Immunocompromising conditions include:

- Primary or acquired immunodeficiency
  - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
  - Other significantly immunocompromising conditions
- Immunosuppressive therapy (current or recent)
  - Chemotherapy, whole body radiotherapy or total lymphoid irradiation
  - High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - All biological disease-modifying anti-rheumatic drugs (DMARDs) and most other (e.g. conventional synthetic) DMARDs [550]

6.1.8.2 Sotrovimab for pregnant women
Conditional recommendation

Consider using sotrovimab for the treatment of COVID-19 within 5 days of symptom onset in pregnant women in the second or third trimester who do not require oxygen and who have one or more additional risk factors for disease progression.

Remark:
*Please note: The Taskforce has made additional recommendations on the use of sotrovimab in immunosuppressed and fully vaccinated patients. These are available below.*

In adult, non-pregnant patients with confirmed COVID-19 who do not require oxygen, sotrovimab probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on the COMET-ICE trial [617], in which non-vaccinated adults were treated with a single one-hour intravenous infusion of 500 mg sotrovimab. Pregnant and breastfeeding women were not included in this trial, and there are currently no data on the effects of sotrovimab on a pregnant woman or baby.

Sotrovimab is a human immunoglobulin G (IgG) and may cross the placenta from mother to baby. The potential impact of this is not known. However, it is known that pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby [567]. Sotrovimab can therefore be considered if the benefit justifies the potential risk.

Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- Pre-gestational diabetes (requiring medication)
- Obesity (BMI > 30 kg/m2)
- Chronic kidney disease (i.e. eGFR < 60 by MDRD)
- Congestive heart failure (NYHA class II or greater)
- Chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion)
- Moderate-to-severe asthma (requiring an inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months)

The efficacy of sotrovimab in vaccinated or immunocompromised patients is unknown.

There are no available data on the excretion of sotrovimab in human milk, and the potential benefits and risks to a breastfed baby are not known. The median elimination half-life of sotrovimab is 49 days [565], and human IgGs are known to be excreted in breast milk. A decision whether to discontinue breastfeeding or to abstain from sotrovimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*
Consensus recommendation

Within the population of pregnant women for whom sotrovimab is conditionally recommended for use (as listed above), decisions about the appropriateness of treatment with sotrovimab should be based on the patient's individual risk of severe disease, on the basis of multiple risk factors, and COVID-19 vaccination status.

Consider using sotrovimab in unvaccinated or partially vaccinated patients and patients who are immunosuppressed regardless of vaccination status.

Do not routinely use sotrovimab in fully vaccinated patients unless immunosuppressed.

Remark:
The available research does not currently provide enough evidence to determine the benefits of sotrovimab in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from sotrovimab.

There is no evidence evaluating the effectiveness of sotrovimab in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this and the lower risk of deterioration in these patients, it is unlikely that sotrovimab will be particularly valuable in fully vaccinated patients, unless the patient is immunosuppressed.

There are no evidence on the effectiveness of sotrovimab in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that sotrovimab will be beneficial for immunosuppressed patients.

Immunocompromising conditions include:

- Primary or acquired immunodeficiency
  - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
  - Other significantly immunocompromising conditions

- Immunosuppressive therapy (current or recent)
  - Chemotherapy or radiotherapy
  - High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - All biologics and most disease-modifying anti-rheumatic drugs (DMARDs) [550]

6.1.8.3 Sotrovimab for children and adolescents
Only in research settings

Do not routinely use sotrovimab outside of randomised trials with appropriate ethical approval for the treatment of COVID-19 in children and adolescents under 12 years of age and without high risk factors for deterioration.

Remark:
Children and adolescents were not included in the COMET-ICE trial. However trials are underway in which children over 12 years of age are eligible for inclusion (OPTIMISE-C19, NCT04913675).

The efficacy of sotrovimab in vaccinated or immunocompromised patients is unknown.

Specific sub-populations may be considered for treatment with sotrovimab, such as children over 12 years with a high risk of deterioration (see recommendation below).

Consensus recommendation

Consider using, in exceptional circumstances, sotrovimab for the treatment of COVID-19 within 5 days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40 kg who do not require oxygen and who are at high risk of deterioration.

Consider using sotrovimab only in unvaccinated or partially vaccinated children and adolescents, or those who are immunosuppressed regardless of vaccination status. Do not routinely use sotrovimab in fully vaccinated patients unless immunosuppressed.

Decisions about the appropriateness of treatment with sotrovimab should be based on the patient’s individual risk of severe disease, on the basis of age or multiple risk factors, and COVID-19 vaccination status.

Remark:
Decisions to provide sotrovimab to a child or adolescent should be based on the individual’s combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Available research does not currently provide enough evidence to determine the benefits of sotrovimab in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from sotrovimab. Based on international cohorts [580] potential factors to consider in patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

There is no evidence evaluating the effectiveness of sotrovimab in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this and the lower risk of deterioration in these patients, it is unlikely that sotrovimab will be particularly valuable in fully vaccinated patients, unless the patient is immunosuppressed.

There is no evidence on the effectiveness of sotrovimab in immunosuppressed children and adolescents. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that sotrovimab will be beneficial for immunosuppressed patients.

6.2 Disease-modifying treatments that are not recommended

6.2.1 Aspirin
Not recommended

Do not use aspirin for the treatment of COVID-19.

Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of aspirin for treatment of COVID-19 may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include aspirin.

Aspirin may still be considered for other evidence-based indications in people who have COVID-19.

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.2.2 Azithromycin

Not recommended

Do not use azithromycin for the treatment of COVID-19.

Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of azithromycin may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include azithromycin.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.3 Colchicine

Not recommended

Do not use colchicine for the treatment of COVID-19.

Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of colchicine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include colchicine.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.4 Convalescent plasma
Not recommended


Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of convalescent plasma may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include convalescent plasma.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.5 Hydroxychloroquine

Not recommended

Do not use hydroxychloroquine for the treatment of COVID-19.

Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of hydroxychloroquine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include hydroxychloroquine.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.6 Hydroxychloroquine plus azithromycin

Not recommended

Do not use hydroxychloroquine plus azithromycin for the treatment of COVID-19.

Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Although certainty of the evidence is low, this recommendation is supported by the observation that neither hydroxychloroquine nor azithromycin as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.2.7 Interferon β-1a
Not recommended

Do not use subcutaneous or intravenous interferon β-1a for the treatment of COVID-19.

Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of subcutaneous or intravenous interferon β-1a may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include interferon β-1a.

Information regarding the use of inhaled interferon β-1a for the treatment of COVID-19 can be found [here](#).

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.8 Interferon β-1a plus lopinavir-ritonavir

Not recommended


Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Although certainty of the evidence is low, this recommendation is supported by the observation that neither intravenous interferon β-1a nor lopinavir-ritonavir as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.9 Lopinavir-ritonavir

Not recommended


Remark:
This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of lopinavir-ritonavir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include lopinavir-ritonavir.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
6.3 Disease-modifying treatments not recommended outside of clinical trials

6.3.1 Antiandrogens

6.3.1.1 Dutasteride

Only in research settings

Do not use dutasteride for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Dutasteride should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use dutasteride to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.2 Antineoplastics

6.3.2.1 Angiotensin 2 receptor agonist (C21)

Only in research settings

Do not use the angiotensin 2 receptor agonist C21 for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
C21 should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use C21 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.2.2 Camostat mesilate
Only in research settings

Do not use camostat mesilate for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Camostat mesilate should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use camostat mesilate to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
6.3.3 Antiparasitic, antifungals and other anti-infective agents

6.3.3.1 Chloroquine

Only in research settings

Do not use chloroquine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Chloroquine should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use chloroquine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.3.2 Doxycycline

Only in research settings

Do not use doxycycline for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Doxycycline should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in older people living with frailty and those receiving palliative care. Until further evidence is available, do not use doxycycline to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

Trials are not recommended in pregnant and breastfeeding patients, as doxycycline is contra-indicated in this group.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.3.3 Ivermectin

Only in research settings

Do not use ivermectin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Ivermectin should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ivermectin to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

6.3.3.4 Ivermectin plus doxycycline
Only in research settings

Do not use ivermectin plus doxycycline for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Ivermectin plus doxycycline should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ivermectin plus doxycycline to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.3.3.5 Nitazoxanide

Only in research settings

Do not use nitazoxanide for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Nitazoxanide should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use nitazoxanide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.4 Antihypertensives

6.3.4.1 Telmisartan

Only in research settings

Do not use telmisartan for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Telmisartan should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use telmisartan to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.5 Antithrombotic, antiplatelets and related therapies

6.3.5.1 Sulodexide
6.3.6 Antivirals

6.3.6.1 Baloxavir marboxil

Only in research settings

Do not use baloxavir marboxil for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Baloxavir marboxil should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use baloxavir marboxil to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.6.2 Darunavir-cobicistat

Only in research settings

Do not use darunavir-cobicistat for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Darunavir-cobicistat should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use darunavir-cobicistat to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.6.3 Enisamium
Only in research settings
Do not use enisamium for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Enisamium should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use enisamium to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.6.4 Favipiravir

Only in research settings
Do not use favipiravir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Favipiravir should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use favipiravir to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.6.5 Sofosbuvir-daclatasvir

Only in research settings
Do not use sofosbuvir-daclatasvir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Sofosbuvir-daclatasvir should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sofosbuvir-daclatasvir to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.6.6 Triazavirin
Only in research settings

Do not use triazavirin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Triazavirin should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use triazavirin for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.6.7 Umifenovir

Only in research settings

Do not use umifenovir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Umifenovir should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use umifenovir for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.7 Corticosteroids
6.3.8 Human and blood derived products

6.3.8.1 Human umbilical cord mesenchymal stem cells

Only in research settings

Do not use human umbilical cord mesenchymal stem cells for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Human umbilical cord mesenchymal stem cells should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use human umbilical cord mesenchymal stem cells (hUC-MSCs) to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.8.2 Intravenous immunoglobulin

Only in research settings

Do not use immunoglobulin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Intravenous immunoglobulin should still be considered for other evidence-based indications in people who have COVID-19.

This recommendation does not apply to the use of immunoglobulin in children and adolescents when managing PIMS-TS, Kawasaki disease or toxic shock syndrome related to COVID-19 (see section for specific guidance). The Taskforce is currently developing recommendations for the management of these conditions in children and adolescents with COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use combination immunoglobulin plus methylprednisolone to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.8.3 Intravenous immunoglobulin plus methylprednisolone
Only in research settings

Do not use immunoglobulin plus methylprednisolone for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Intravenous immunoglobulin plus methylprednisolone should still be considered for other evidence-based indications in people who have COVID-19.

This recommendation does not apply to the use of immunoglobulin plus methylprednisolone in children and adolescents when managing PIMS-TS, Kawasaki disease or toxic shock syndrome related to COVID-19 (see section for specific guidance). The Taskforce is currently developing recommendations for the management of these conditions in children and adolescents with COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use combination immunoglobulin plus methylprednisolone to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
6.3.9 Immunomodulating drugs

6.3.9.1 Anakinra

Only in research settings

Do not use anakinra for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Anakinra should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use anakinra to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.3.9.2 Lenzilumab

Only in research settings

Do not use lenzilumab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use lenzilumab for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.9.3 Ruxolitinib

Only in research settings

Do not use ruxolitinib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Ruxolitinib should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ruxolitinib to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.9.4 Tofacitinib
Only in research settings

Do not use tofacitinib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Tofacitinib should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use tofacitinib for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.10 Interferons

6.3.10.1 Interferon β-1a (inhaled)

Only in research settings

Do not use inhaled interferon β-1a for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Inhaled interferon β-1a should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use inhaled interferon β-1a to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.10.2 Interferon β-1b

Only in research settings

Do not use interferon β-1b for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Interferon β-1b should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use interferon β-1b to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.10.3 Interferon gamma
**6.3.10.4 Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)**

Only in research settings

Do not use IFN-κ plus TFF2 for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
IFN-κ plus TFF2 should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use IFN-κ plus TFF2 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**6.3.10.5 Peginterferon lambda**

Only in research settings

Do not use peginterferon lambda for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Peginterferon lambda should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use peginterferon lambda to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**6.3.11 Other antibody related therapies**

**6.3.11.1 Bamlanivimab**
Only in research settings

Do not use bamlanivimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bamlanivimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.11.2 Bamlanivimab plus etesevimab

Only in research settings

Do not use bamlanivimab plus etesevimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Bamlanivimab plus etesevimab should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bamlanivimab plus etesevimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.11.3 Regdanvimab

Only in research settings

Do not use the monoclonal antibody regdanvimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use regdanvimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.12 Other therapies

6.3.12.1 Aprepitant
Only in research settings

Do not use aprepitant for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Aprepitant should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use aprepitant to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.12.2 Bromhexine hydrochloride

Only in research settings

Do not use bromhexine hydrochloride for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Bromhexine hydrochloride should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bromhexine hydrochloride for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.12.3 Fluvoxamine

Only in research settings

Do not use fluvoxamine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Fluvoxamine should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use fluvoxamine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.12.4 Recombinant human granulocyte colony-stimulating factor (rhG-CSF)
Only in research settings

Do not use rhG-CSF for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Recombinant human granulocyte colony-stimulating factor should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use rhG-CSF to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
6.3.13 Vitamins, supplements and cofactors

6.3.13.1 Combined metabolic activators (CMA)

Only in research settings

Do not use combined metabolic activators (CMA) for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Combined metabolic activators (CMA) should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use CMA to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.13.2 N-acetylcysteine

Only in research settings

Do not use N-acetylcysteine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
N-acetylcysteine should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use N-acetylcysteine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.13.3 Vitamin C

Only in research settings

Do not use vitamin C for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Vitamin C should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use vitamin C to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
6.3.13.4 Vitamin D analogues (calcifediol/cholecalciferol)

Only in research settings

Do not use vitamin D analogues for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Vitamin D analogues should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use vitamin D analogues to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.13.5 Zinc

Only in research settings

Do not use zinc for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
Zinc should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use zinc to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.3.14 Other disease-modifying treatments

Consensus recommendation

For people with COVID-19, do not use other disease-modifying treatments outside of randomised trials with appropriate ethical approval.

Remark: Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use other disease-modifying treatments in these populations unless they are eligible to be enrolled in trials.

6.4 Disease-modifying treatments under review

6.4.1 Tixagevimab plus cilgavimab (Evusheld)

6.5 Disease-modifying treatments not currently under review
7. Chemoprophylaxis

7.1 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for post-exposure prophylaxis

Conditional recommendation

Consider using subcutaneous casirivimab plus imdevimab as prophylaxis in seronegative or PCR-negative close household contacts of individuals with confirmed COVID-19.

Remark:
The use of prophylactic casirivimab plus imdevimab probably reduces the risk of symptomatic and asymptomatic COVID-19 infection in seronegative household contacts of individuals with confirmed COVID-19 when used within 4 days of exposure. In settings for which serology testing is not readily available, consider using in unvaccinated adult household contacts who have risk factors for developing severe disease, return a negative PCR result and are considered unlikely to have had previous SARS-CoV-2 infection.

Results are based on one trial, in which 1200 mg of casirivimab plus imdevimab (600 mg of each) was administered subcutaneously to close household contacts of individuals with confirmed COVID-19 \cite{568}. Participants were healthy individuals aged 12 years or older who were seronegative for SARS-CoV-2 antibodies at the time of treatment.

The following should be considered when determining the appropriateness of treatment:

- Vaccinated individuals were excluded from the trial—the ability of casirivimab plus imdevimab to prevent COVID-19 infection in this population is not known.
- The effectiveness of casirivimab plus imdevimab in preventing COVID-19 infection in patients who are seropositive to SARS-CoV-2 antibodies or who are immunosuppressed is not known.
- In individuals who go on to develop COVID-19, the impact of prophylactic casirivimab plus imdevimab on subsequent outcomes of interest, such as hospitalisation, requirement of supplemental oxygen or mortality, is not known.

The Taskforce recognises that subcutaneous casirivimab plus imdevimab may be administered to household contacts who were PCR-negative at the time of testing, but become PCR-positive by the time of receiving casirivimab plus imdevimab. Although the Taskforce does not currently recommend casirivimab plus imdevimab for PCR-positive individuals with asymptomatic or mildly symptomatic COVID-19, this treatment is unlikely to result in harm.

This trial was conducted in a population exposed to a mixture of SARS-CoV-2 variants, but before the emergence and dominance of the Delta variant. The effectiveness of casirivimab plus imdevimab in populations exposed to the Delta variant of SARS-CoV-2 has not been established.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

7.2 Hydroxychloroquine for pre-exposure prophylaxis
Not recommended
For healthcare workers with no active COVID-19, do not use hydroxychloroquine for pre-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

Remark:
Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use hydroxychloroquine for pre-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

7.3 Hydroxychloroquine for post-exposure prophylaxis

Not recommended
For people exposed to individuals with SARS-CoV-2 infection, do not use hydroxychloroquine for post-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

Remark:
Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use hydroxychloroquine for post-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

7.4 Tixagevimab plus cilgavimab (Evusheld) for pre-exposure prophylaxis

7.5 Tixagevimab plus cilgavimab (Evusheld) for post-exposure prophylaxis

8. Respiratory support in adults

8.1 Respiratory management

Consensus recommendation

Guiding principles of care
For patients with COVID-19 receiving respiratory support, use single and negative pressure rooms wherever possible. If none are available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients. Ensure contact, droplet and airborne precautions are in place. Healthcare workers should be fully vaccinated and wearing fit-tested N95 masks.

Remark:
The additional relative risk of infection to healthcare workers associated with specific oxygen therapies and respiratory support is uncertain but is thought to add minimal additional risk in an environment where transmission of infection with COVID-19 is already high.
When caring for patients with COVID-19, clinicians need to determine a target range of oxygen saturation to titrate oxygen therapy. Advisable target ranges of oxygen saturation are:

- 92–96% in most patients
- 88–92% in patients at risk of hypercapnia

All awake patients receiving respiratory support should be educated on proning (see section 8.7) and should be encouraged/assisted to prone for as long as is practicable.

**Conventional oxygen therapy can be delivered by:**

- Nasal prongs at 1–4 L/min (FiO2 approx. 0.24-0.36) to maintain oxygen saturation within the target range.
- Mask at 6–10 L/min (FiO2 approx. 0.35-0.60) to maintain oxygen saturation within the target range.
- Non-rebreather mask 15L/min (FiO2 approx. 1.00) to maintain oxygen saturation within the target range.
- High-flow nasal oxygen (HFNO) therapy with flow rates up to 60L/min with an oxygen/air blender supplying oxygen at FiO2, 0.21-1.00 to maintain oxygen saturation within the target range. It delivers high flow oxygen that is humidified and heated, via large diameter nasal cannula.

**Non-invasive ventilation can be delivered by:**

- Continuous positive airway pressure (CPAP), a mode of non-invasive ventilation which applies continuous positive airway pressure (with or without entrained oxygen). It can aid in alveolar recruitment and optimise oxygen delivery. CPAP is generally used for hypoxaemic respiratory failure.
- Bilevel positive pressure support (e.g. BiPAP), another mode of non-invasive ventilation which provides a higher level of pressure during the inspiratory phase to enhance ventilation, while a lower level of positive pressure is delivered during the expiratory phase (known as positive end-expiratory pressure (PEEP)). Supplemental oxygen can also be delivered through the device. Bilevel positive pressure support is generally used when there is hypercapnia with or without hypoxaemia.

**Conditional recommendation**

For patients with COVID-19 who have hypoxaemic respiratory failure and are unable to maintain oxygen saturations within target range despite oxygen delivery by nasal prongs or mask, consider using CPAP.

The evidence suggests that continuous positive airway pressure (CPAP) therapy is preferred for patients with persistent hypoxaemia associated with COVID-19 (defined as requiring an FiO2 ≥ 0.4 to maintain oxygen saturation in their target range). Adjust continuous positive airway pressure as required, most patients require pressures of 10 to 12 cmH2O. Excessive pressures may increase the risk of pneumothorax. Titrate oxygen to maintain oxygen saturation in the target range. There is currently insufficient direct evidence available to support the use of bilevel positive pressure support in the setting of COVID-19.

If CPAP is not available or not tolerated, consider HFNO as an alternative using the same safety parameters.

Patients receiving CPAP (and/or HFNO) for COVID-19, monitor closely at all times and liaise with ICU in case of deterioration. Do not delay endotracheal intubation and invasive mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies.

8.2 Respiratory management of the deteriorating patient
Consensus recommendation

Do not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies.

Remark:
Patients can deteriorate rapidly 5 to 10 days after onset of symptoms.

The net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and an advance care directive or plan if available, and consideration of the patient’s expected short- and long-term responses to more invasive forms of treatment.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.3 Videolaryngoscopy

Conditional recommendation

In adults with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.4 Neuromuscular blockers

Info Box

Neuromuscular blocking agents (NMBAs) are a pharmaceutical intervention that may facilitate protective lung ventilation in patients who are mechanically ventilated with moderate to severe acute respiratory distress syndrome (ARDS). NMBAs may reduce patient-ventilator dyssynchrony and facilitate improved oxygenation by various mechanisms, including reducing the inspiratory muscle effort and the work of breathing, and reducing ventilator-induced lung injury.

Conditional recommendation against

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

Remark:
However, if protective lung ventilation cannot be achieved, consider using NMBAs for up to 48 hours. If indicated, consider cisatracurium as first-line agent, if cisatracurium is not available alternatives include atracurium or vecuronium by infusion.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.5 Positive end-expiratory pressure
Consensus recommendation

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, consider using a higher PEEP strategy (PEEP > 10 cm H2O) over a lower PEEP strategy.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.6 Prone positioning

Info Box

Positioning the patient in a face-down (prone) position may help to open up (recruit) collapsed alveoli and improve oxygen levels in the blood.

8.6.1 Prone positioning for adults

Consensus recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

Remark:
Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

Net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Conditional recommendation

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning for at least 3 hours per day as tolerated. When positioning a patient in prone, ensure proning is used with caution and accompanied by close monitoring of the patient. Use of prone positioning should not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised less invasive respiratory therapies.

 Remark:
For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, prone positioning for as long as tolerated (ideally 8 hours or more) is likely to increase benefits.

Vulnerable people who are treated outside the ICU, for example people who are older and living with frailty, cognitive impairment or unable to communicate, may especially be at increased risk of harm from proning. Despite the potential risks of awake proning associated with frailty, there may be benefits for this group. The net clinical benefit for each individual patient should be considered on a case-by-case basis.

Currently, the evidence indicates that prone positioning probably decreases treatment failure and the need for intubation, with no increase in harms. Prone positioning should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.6.2 Prone positioning for pregnant and postpartum women

Consensus recommendation

For mechanically ventilated pregnant women with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

Remark:
Current reports suggest prone ventilation in adult patients is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff, and that minimises the risk of adverse events, e.g. accidental extubation.

Proning of a pregnant woman should avoid abdominal compression and ensure a woman’s hips and chest are supported. In the absence of specialised equipment, proning can be performed using pillows and blankets.

Proning can be challenging in late gestation and delivery of the baby may be warranted.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Consensus recommendation

For pregnant and postpartum women with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a pregnant woman in prone, care should be taken to support the gravid uterus to reduce aorta-caval compression. Women who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation. Birth of the baby should be considered when it may enhance maternal resuscitation or be beneficial to the fetus.

Remark:
Current reports suggest prone ventilation in adult patients is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

Proning of a pregnant woman should avoid abdominal compression and ensure a woman’s hips and chest are supported. In the absence of specialised equipment, it can be performed using pillows and blankets.

Proning can be challenging in late gestation and delivery of the baby may be warranted.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.6.3 Prone positioning and CPR

Consensus recommendation

For patients with COVID-19 in prone position requiring cardiopulmonary resuscitation (CPR), where safe and feasible, return the patient to supine position and commence resuscitation.

If returning the patient to supine position is not safe and feasible, commence CPR in prone position. Once it is safe and feasible, return the patient to supine position and continue the resuscitation process.

Remark:
When caring for patients with COVID-19, consider the options available for providing cardiopulmonary resuscitation (CPR) when instituting prone positioning.

It is reasonable to provide CPR in the prone position when supine CPR cannot be feasibly or safely implemented, and the airway is secured.

Returning the patient to supine position should only be performed when there are suitable resources to minimise risk of harm to staff and patients, e.g. accidental extubation, venous or arterial line dislodgement.

Provision of CPR for patients in prone position should be performed where there are hospital guidelines, and training in provision of prone CPR has been undertaken.

Decisions to commence CPR should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker in advance of need.

Consideration should also be given to whether prone positioning has contributed to the need for CPR, for example by including abdominal compression and obstruction to venous return.

8.7 Recruitment manoeuvres
Patients receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an 'open lung approach' to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure (incremental PEEP, stepwise or staircase); and high driving pressures.

Consensus recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider using recruitment manoeuvres.

If recruitment manoeuvres are used, do not use staircase or stepwise (incremental PEEP) recruitment manoeuvres.

Remark: This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.8 Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is a form of life support that removes blood from the body via large cannulae, oxygenates and removes carbon dioxide from the blood external to the patient, and then returns the blood to the body.

Venovenous (VV) ECMO provides oxygenation support for the lungs only, while venoarterial (VA) ECMO supports the heart and lungs.

8.8.1 ECMO for adults

Conditional recommendation

Consider early referral to an ECMO centre for patients developing refractory respiratory failure in mechanically ventilated adults with COVID-19 (despite optimising ventilation, including proning and neuromuscular blockers).

Remark:
Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected patients with COVID-19 and severe ARDS.

Net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.8.2 ECMO for pregnant and postpartum women
Consensus recommendation

Consider referral to an ECMO centre for venovenous ECMO in mechanically ventilated pregnant women with COVID-19 and refractory respiratory failure (despite optimising ventilation, including proning). Delivery of the baby prior to ECMO to enhance maternal resuscitation should be considered on a case-by-case basis.

Remark:
Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected pregnant women with COVID-19 and severe ARDS.

The decision on whether to use ECMO should be taken in consultation with the woman’s family, as well as obstetric and intensive care specialists. Key considerations include gestational age, fetal viability, fetal well-being and the risks and benefits to mother and baby.

Early referral to an ECMO centre is preferred.

As pregnant and postpartum women may have haemostatic alterations, anticoagulation regimens may need to be modified appropriately.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9. Respiratory support in neonates, children and adolescents

9.1 Requiring non-invasive respiratory support

9.1.1 High-flow nasal oxygen and non-invasive ventilation

Info Box

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where warmed, humidified oxygen is delivered at high-flow rates.

Non-invasive ventilation (NIV) refers to any type of positive pressure support delivered without an endotracheal tube during spontaneous breathing. Supplemental oxygen can also be delivered through the device.

HFNO or NIV should be considered when low-flow oxygen is unable to maintain target peripheral oxygen saturation and/or to treat respiratory distress. Target peripheral oxygen saturations may vary in neonates, children and adolescents with co-morbid conditions, such as preterm birth, cyanotic congenital heart disease or chronic lung disease.
Consensus recommendation

Consider using high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) therapy for neonates, children and adolescents with hypoxaemia or respiratory distress associated with COVID-19 and not responding to low-flow oxygen. Use it with caution and pay strict attention to staff safety, including the use of appropriate PPE.

Remark:
The preferred location for high-flow nasal oxygen is a negative pressure room or a single room with the door closed. If these locations are not immediately available then HFNO or NIV should not be withheld if indicated. However, it should be recognised that this therapy may pose an aerosol risk to staff and other patients, and appropriate precautions should be used.

In children and adolescents with COVID-19 for whom HFNO or NIV is appropriate for an alternate clinical presentation (e.g. concomitant bronchiolitis or severe asthma), ensure airborne and other infection control precautions are also optimised.

Consider early transfer in the deteriorating neonate, child or adolescent to a specialised paediatric or neonatal critical care unit.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.1.2 Prone positioning (non-invasive)

Consensus recommendation

For neonates, children and adolescents with COVID-19 and respiratory symptoms who are receiving non-invasive respiratory support, consider prone positioning if patient co-operation is possible. When positioning a patient prone, ensure it is used with caution and close monitoring of the patient.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.1.3 Respiratory management of the deteriorating child

Consensus recommendation

Consider endotracheal intubation and mechanical ventilation in neonates, children and adolescents with COVID-19 who are deteriorating despite optimised, non-invasive respiratory support.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2 Requiring invasive mechanical ventilation

9.2.1 Prone positioning (mechanical ventilation)
Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning if there are no contraindications.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.2 Positive end-expiratory pressure (PEEP)

Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and moderate to severe ARDS with atelectasis, consider using a higher PEEP strategy over a lower PEEP strategy. The absolute PEEP values that constitute a high and low PEEP strategy will depend on age and patient size.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.3 Recruitment manoeuvres

Info Box

Neonates, children and adolescents receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an 'open lung approach' to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure, or the use of escalating mean airway pressure during high-frequency oscillatory ventilation (incremental PEEP, stepwise or staircase); and high driving pressures.

Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxic respiratory failure characterised by severe atelectasis unresponsive to other ventilation strategies, consider using recruitment manoeuvres.

Remark:
In neonates and infants, staircase or stepwise incremental recruitment manoeuvres should only be performed using mean airway pressure in a high-frequency oscillatory ventilation mode. Staircase or stepwise (incremental PEEP) recruitment manoeuvres should not be performed during conventional ventilation.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.4 Neuromuscular blockers
Conditional recommendation against

For intubated neonates, children and adolescents with COVID-19, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

However, if effective lung-protective ventilation cannot be achieved, consider targeted intermittent use of NMBAs. If indicated, the choice of NMBA should be guided by the age group and regional practice.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.5 High-frequency oscillatory ventilation (HFOV)

Info Box

High-frequency oscillatory ventilation (HFOV) is a specialised mode of respiratory support via an endotracheal tube that delivers very small tidal volumes at a rate much faster than normal breathing rates (> 2 Hz). It is used as a rescue therapy in neonates and children for severe respiratory failure when conventional mechanical ventilation is not effective. In neonates with severe respiratory failure, HFOV reduces need for ECMO. HFOV requires specialist equipment, and nursing and medical expertise.

Consensus recommendation

Do not routinely use HFOV as a first line mode of mechanical ventilation in neonates, children and adolescents with severe COVID-19. HFOV should be limited to a rescue therapy in neonates and children not responding to conventional mechanical ventilation in a specialist centre with experience with HFOV.

HFOV delivers gas at very high flow rates. This may increase the aerosol-generating potential compared to other forms of respiratory support used in intensive care. This may limit the suitability of HFOV in patients with COVID-19 unless strict attention to staff safety and infection control measures can be applied.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.6 Videolaryngoscopy

Conditional recommendation

In neonates, children and adolescents with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.7 Extracorporeal membrane oxygenation (ECMO)
Consensus recommendation

Consider early referral to an ECMO centre for venovenous or venoarterial ECMO in mechanically ventilated neonates, children and adolescents with COVID-19 with refractory respiratory or cardiovascular failure despite optimising other critical care interventions.

Remark:
Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected neonates, children and adolescents with severe or critical COVID-19 and no contraindications for ECMO, such as severe, irreversible organ dysfunction.

The decision on whether to use ECMO should be taken in consultation with the child’s family. Key considerations include pre-existing conditions and the suitability of anticoagulation.

Early referral to an ECMO centre is preferred.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

10. Venous thromboembolism (VTE) prophylaxis

10.1 VTE prophylaxis for adults

Conditional recommendation

Use prophylactic doses of anticoagulants, preferably low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily), in adults with moderate, severe or critical COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding. Where the estimated glomerular filtration rate (eGFR) (see below) is less than 30 mL/min/1.73m2, unfractionated heparin or clearance-adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily).

Remark:
For body weights outside 50–90 kg or heights outside 150–180 cm, calculate the body surface area (BSA) and multiply the eGFR by BSA/1.73.

The Taskforce notes that in critical illness, creatinine-based estimation of kidney function can be unreliable.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Conditional recommendation against

Do not routinely offer therapeutic anticoagulant dosing in adults with moderate, severe or critical COVID-19. There is no additional indication for therapeutic dosing for anticoagulants in adults with severe or critical COVID-19 beyond current standard best practice.

Remark:
This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

10.2 VTE prophylaxis for pregnant and postpartum women
Pregnant women in general are at an increased risk of venous thromboembolism (VTE). Hospitalised pregnant women with an acute infective illness (such as COVID-19) are at even greater risk of VTE. However, the exact duration of increased risk of VTE in association with COVID-19 infection is not yet established.

All pregnant and postpartum women should undergo a documented assessment of risk factors for VTE on admission to hospital, if COVID-19 is diagnosed, if COVID-19 severity changes and postpartum. The use of pharmacological prophylaxis in women should be accompanied by other measures to prevent VTE, such as anti-embolism stockings and sequential compression devices.

Consensus recommendation

For pregnant or postpartum women who are admitted to hospital (for any indication) and who have COVID-19, use prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding or imminent birth. Prophylactic anticoagulants should be continued for at least 14 days after discharge or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

Remark:
- Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function.
- For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.
- There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Consensus recommendation

For pregnant women with severe or critical COVID-19, or where there are additional risk factors for VTE, consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 109/L. Prophylactic anticoagulants should be continued for at least four weeks after discharge or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

Remark:
- Dosing is dependent on pre-pregnancy body weight and current renal function. For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.
- There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.
- Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.
- In some situations, continuation of LMWH throughout the rest of pregnancy and postpartum may be required. Involvement of specialist obstetricians, obstetric medicine physicians, haematologists or other physicians with expertise in VTE in pregnant women would be warranted.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Consensus recommendation

For pregnant or postpartum women who are self-isolating at home with mild COVID-19 and where additional risk factors for VTE are present, consider using prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding or imminent birth. Prophylactic anticoagulants should be continued for at least 14 days or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

For pregnant or postpartum women who are self-isolating at home with mild COVID-19 and who have no additional risk factors for VTE, routine pharmacological prophylaxis is not recommended.

Remark:
- Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function. For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.
- There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.
- Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Consensus recommendation

For postpartum women who have had COVID-19 during pregnancy, consider using at least 14 days of prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding. Increased duration of six weeks should be considered if severe or critical COVID-19 and/or additional risk factors for VTE are present.

Remark:
- Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function. For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.
- There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.
- Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

10.3 VTE prophylaxis for children and adolescents

Consensus recommendation

For children and adolescents admitted to hospital with COVID-19, refer to local thromboprophylaxis protocols and seek expert advice.

Remark:
- There is insufficient evidence in children and adolescents to recommend a modified thromboprophylaxis regimen.
- Consider known risk factors for initiating thromboprophylaxis in children and adolescents.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

11. Therapies for existing indications in patients with COVID-19

11.1 ACEIs/ARBs in patients with COVID-19
Recommended

In patients with COVID-19 who are receiving ACEIs/ARBs, there is currently no evidence to deviate from usual care and these medications should be continued unless contraindicated.

Remark:
Stopping these medications abruptly can lead to acute heart failure or unstable blood pressure.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

11.2 ACEIs in postpartum women

Consensus recommendation

In postpartum women with COVID-19 who have hypertension requiring treatment with ACE inhibitors, there is currently no evidence to deviate from usual care. These medications should be initiated or continued unless otherwise contraindicated.

Remark:
ACE inhibitors are contraindicated in the antenatal period due to risk of fetal and neonatal harm.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

11.3 Steroids for people with asthma or COPD with COVID-19

Consensus recommendation

Use inhaled or oral steroids for the management of people with co-existing asthma or chronic obstructive pulmonary disease (COPD) and COVID-19 as you would normally for viral exacerbation of asthma or COPD. Do not use a nebuliser.

Remark:
This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

11.4 Oestrogen-containing therapies
Consensus recommendation

Consider stopping oral menopausal hormone therapy (MHT), also known as hormone replacement therapy (HRT), in women with mild or moderate COVID-19.

Before restarting oral MHT, review the indication for this. If MHT is continued, consider using a transdermal preparation.

Remark:
Decisions around stopping hormone therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patients individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Consensus recommendation

Stop oral menopausal hormone therapy (MHT) in women with severe or critical COVID-19.

Before restarting oral MHT, review the indication for this and consider transitioning to a transdermal preparation.

Remark:
Decisions around stopping hormone therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patients individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Consensus recommendation

In women who have COVID-19 and who are taking oestrogen-containing contraception, manage these medications as per usual care.

In women who stop or suspend contraception when they have COVID-19, restart contraception at the time of discharge or when acute symptoms have resolved.

Remark:
Decisions around stopping oestrogen-containing contraception should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patients individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

12. Timing of surgery following COVID-19 infection
Conditional recommendation against

Do not routinely perform elective surgery within eight weeks of recovery from acute illness, following a diagnosis of SARS-CoV-2 infection, unless outweighed by the risk of deferring surgery, such as disease progression or clinical priority.

Remark:
Informed consent and, where deemed necessary, shared decision-making with a valid substitute decision-maker, should include discussion about the potential increased risk of surgery following a diagnosis of COVID-19 and in the presence of post-acute COVID-19 symptoms.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Conditional recommendation

For people undergoing elective surgery following a diagnosis of SARS-CoV-2 infection, consider carrying out multisystem preoperative assessment in consultation with a unit familiar with the assessment of people recovering from COVID-19.

Remark:
This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

13. Pregnancy and perinatal care

Info Box

For recommendations on disease modifying treatments, chemoprophylaxis, venous thromboembolism (VTE) prophylaxis and respiratory support in pregnant or breastfeeding women, and ACE inhibitors in postpartum women, please see sections above. We are continually working on updating all recommendations to reflect special populations, including pregnant and breastfeeding women.

13.1 Antenatal corticosteroids

Consensus recommendation

The use of antenatal corticosteroids for women at risk of preterm birth is supported as part of standard care, independent of the presence of COVID-19.

Remark:
There are clear benefits to using antenatal corticosteroids for women at risk of preterm birth at less than 34 weeks’ gestation. There is currently no evidence to suggest that antenatal corticosteroids cause additional maternal or fetal harm in the setting of COVID-19 when used for this indication. They should therefore be given where indicated.

The Taskforce has separate recommendations regarding the use of dexamethasone as a disease-modifying treatment in pregnant or breastfeeding women for COVID-19. Women with COVID-19 who are on oxygen and receiving dexamethasone do not require additional doses of corticosteroids for fetal lung maturation.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

13.2 Magnesium sulfate
Consensus recommendation

The use of magnesium sulfate in pregnancy for fetal neuroprotection for women at risk of preterm birth is supported as part of standard care, independent of the presence of COVID-19.

The use of magnesium sulfate in pregnancy for the management of severe pre-eclampsia or eclampsia is supported as part of standard care, independent of the presence of COVID-19.

Remark:
There are clear benefits to using magnesium sulfate for fetal neuroprotection for women at risk of preterm birth, particularly prior to 32 weeks' gestation [571].

There are also clear benefits to using magnesium sulfate for women with severe pre-eclampsia or eclampsia [570].

There is currently no evidence to suggest that magnesium sulfate can cause additional maternal or fetal harm (such as pulmonary oedema) in the setting of COVID-19 when used for this indication. Magnesium sulfate should therefore be given where indicated.

In pregnant women with COVID-19 who are receiving magnesium sulfate, renal function and fluid balance should be monitored. If renal impairment develops, the dose of magnesium sulfate may need to be adjusted or withheld accordingly.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

13.3 Mode of birth

Conditional recommendation

For pregnant women with COVID-19, mode of birth should remain as per usual care.

Remark:
There is currently no evidence to indicate that caesarean section for women with COVID-19 reduces the risk of vertical transmission to the newborn. Mode of birth should continue as per usual care. Respiratory deterioration due to COVID-19 may prompt urgent delivery on an individual basis.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

13.4 Delayed umbilical cord clamping

Consensus recommendation

Delayed umbilical cord clamping is supported as part of standard care, independent of the presence of COVID-19.

Remark:
There is currently no evidence that delayed umbilical cord clamping affects the risk of vertical transmission of COVID-19.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

13.5 Skin-to-skin contact
Consensus recommendation

Early skin-to-skin contact after birth and during the postnatal period is supported, independent of the presence of COVID-19. However, parents with COVID-19 should use infection prevention and control measures (mask and hand hygiene).

Remark:
Early skin-to-skin contact refers to placing the naked baby prone on the parent's bare chest immediately after birth.

Skin-to-skin contact should be encouraged and continue as per usual practice in other postnatal and neonatal settings, such as neonatal ICU and postnatal wards, providing infection prevention and control measures are maintained.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

13.6 Breastfeeding

Conditional recommendation

Breastfeeding is supported irrespective of the presence of COVID-19. However, women with COVID-19 who are breastfeeding should use infection prevention and control measures (mask and hand hygiene) while infectious.

Remark:
There is currently no evidence to indicate that breastfeeding increases the risk of vertical transmission to the newborn. As there are substantial known benefits for breastfeeding, women should be supported to initiate or continue breastfeeding. If the baby is being fed with expressed breast milk or formula, the same infection prevention and control measures (mask and hand hygiene) should be used.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

13.7 Rooming-in

Conditional recommendation

For women with COVID-19 who have given birth, support rooming-in of mother and newborn in the birth suite and on the postnatal ward when both mother and baby are well. However, women with COVID-19 should use infection prevention and control measures (mask and hand hygiene).

Remark:
There is currently no evidence to indicate that a woman with a known COVID-19 infection should be separated from her newborn to prevent transmission. As there are substantial known benefits for keeping mother and newborn together postpartum, women should be supported to be with their newborn as per usual care.

Women with COVID-19 should be encouraged and supported in using good hand hygiene before and after handling their baby, and using a mask while in close contact with their baby. To the extent possible, these women should practice physical distancing when not feeding or caring for the baby.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

14. Child and adolescent care
For recommendations on disease-modifying treatments, chemoprophylaxis and respiratory support in children and adolescents please see sections above. We are continually working on updating all recommendations to reflect special populations, including children and adolescents.

14.1 Paediatric Inflammatory Multisystem Syndrome (PIMS-TS)

The Taskforce endorses the PIMS-TS case definition from the Royal College of Paediatrics and Child Health (United Kingdom) [467].

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated C-reactive protein (CRP) and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features*. This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).

3. SARS-CoV-2 PCR testing may be positive or negative. All stable children should be discussed as soon as possible with specialist services to ensure prompt treatment (paediatric infectious disease / cardiology / rheumatology). There should be a low threshold for referral to paediatric intensive care using normal pathways.

* Additional features include:

Clinical
- All: persistent fever > 38.5°C
- Most: oxygen requirement, hypotension
- Some: abdominal pain, confusion, conjunctivitis, cough, diarrhoea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting

Imaging and electrocardiogram (ECG)
- Echocardiogram and ECG: myocarditis, valvulitis, pericardial effusion, coronary artery dilatation
- Chest x-ray: patchy symmetrical infiltrates, pleural effusion
- Abdominal ultrasound scan: colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly
- Computed tomography (CT) chest: as for chest x-ray—may demonstrate coronary artery abnormalities if with contrast

Laboratory
- All: abnormal fibrinogen, absence of potential causative organisms (other than SARS-CoV-2), high CRP, high D-dimers, high ferritin, hypoalbuminaemia, lymphopaenia, neutrophilia in most – normal neutrophils in some
- Some: acute kidney injury, anaemia, coagulopathy, high IL-10 (if available)**, high IL-6 (if available)**, neutrophilia, proteinuria, raised creatine kinase (CK), raised lactic acid dehydrogenase (LDH), raised triglycerides, raised troponin, thrombocytopenia, transaminitis

** These assays are not widely available. CRP can be used as a surrogate marker for IL-6.

Additionally, in Australia the PAEDS network definition may be used for case reporting and identification of suspected cases. For a comparison of PIMS-TS / MIS-C international definitions click here.

Consensus recommendation

Children and adolescents who have suspected or confirmed PIMS-TS should be managed by and discussed with a multidisciplinary team. Because of the potential for rapid deterioration, early consultation with experts and consideration of early transfer to a paediatric hospital with intensive care facilities to manage children are recommended for patients with suspected or confirmed PIMS-TS.

14.1.1 Intravenous immunoglobulin (IVIG) plus corticosteroids
Conditional recommendation

Consider using intravenous immunoglobulin (2 g/kg per dose) in combination with methylprednisolone in children and adolescents who meet PIMS-TS criteria.

Remark:
Intravenous immunoglobulin should be considered for all children with complete or incomplete Kawasaki disease, irrespective of whether it may be related to COVID-19. Depending on the age and the phenotype expression of PIMS-TS, combination therapy of IVIG and corticosteroids should be considered as a first-line therapy. This is particularly relevant for older children with myocardial dysfunction, as opposed to younger children with a more Kawasaki disease-like phenotype.

Note that the oncotic load from a large IVIG dose should be considered when administering this agent to children with myocardial dysfunction. For selected cases of PIMS-TS with severe myocardial dysfunction, corticosteroid treatment alone and/or delayed use of IVIG may be beneficial.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

14.1.2 Corticosteroids

Consensus recommendation

Consider using corticosteroids (irrespective of oxygen status) as adjuvant therapy for children and adolescents diagnosed with PIMS-TS.

Remark:
Intravenous corticosteroids (e.g. methylprednisolone) may be given before, or in combination with, intravenous immunoglobulin. Corticosteroids should be considered as the next treatment option for children who remain unwell (tachycardia, need for vasoactive support) 24 hours after infusion of intravenous immunoglobulin, particularly if they have ongoing pyrexia or have not received corticosteroids as a first-line treatment.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

14.1.3 Other immunomodulatory agents

Consensus recommendation

Additional immunomodulatory agents for PIMS-TS (anti IL-1, anti IL-6 or anti-TNF) should be considered as a third-line option in children and adolescents with PIMS-TS who do not respond to intravenous immunoglobulin and corticosteroids.

Remark:
Before initiating additional immunomodulatory therapies, all PIMS-TS patients need to be discussed with a multidisciplinary team and interventions carefully considered. Immunomodulatory agents previously used that have an acceptable risk–benefit ratio include:

- Anakinra (IL-1 receptor antagonist)
- Infliximab (TNF inhibitor)
- Tocilizumab (IL-6 receptor antagonist)

Consider testing for infections that may be unmasked by the use of these agents.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
14.1.4 Aspirin and antithrombotic agents

Consensus recommendation

Children who are treated for PIMS-TS with intravenous immunoglobulin or other agents should also be prescribed low-dose aspirin (3–5 mg per kg once daily for at least 6 weeks).

Remark:
Additional measures to be considered to prevent venous thrombosis associated with PIMS-TS include:

- Anticoagulation therapy
- Compression stockings (in children older than 12 years of age)

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

15. Post-COVID-19

15.1 Assessment and diagnosis of post-COVID-19 condition

Good practice statement

Assessing the probability diagnosis

- Confirm that the person had COVID-19 (by checking that they had a positive PCR test), or is likely to have had COVID-19 (by checking that they have had symptoms consistent with a SARS-CoV-2 infection and/or known contact with a positive case or high-risk setting). Document details of the acute illness.
- Check the current symptoms and ask the person about their concerns, functioning and wishes in terms of their needs.
- Assess whether the current symptoms are likely to be related to acute COVID-19.
- Assess whether the symptoms may be related to, or are exacerbated by, comorbid conditions [618].
Consensus recommendation

The following symptoms and signs have been described by people with post-COVID-19 infection [606][607][608]:

- **Pulmonary symptoms**
  - Shortness of breath
  - Cough

- **Neurological symptoms**
  - Fatigue
  - Headache
  - Cognitive dysfunction
  - Sleep disturbance
  - Loss of smell
  - Paraesthesia

- **Renal disease**

- **Thromboembolism**

- **Psychological symptoms**
  - Anxiety
  - Depression
  - Mood swings
  - *Note that fatigue and sleep disturbance may also indicate the emergence of a mental health condition*

- **Cardiac symptoms**
  - Chest pain

- **Musculoskeletal symptoms**
  - Non-specific pain
  - Myalgia

- **Fever**
  - Low-grade fevers

- **Reduced activity and functional level**

- **Reduced nutritional status and weight loss**

- **Post-intensive care syndrome (PICS)**
  - PICS refers to one or more of the following symptoms that people experience following care in ICU: anxiety, depression, cognitive impairment, memory loss, muscle weakness, dysphagia and reduced quality of life [610][611].

In some people, both adults and children, symptoms corresponding to multisystem inflammatory syndrome [CDC 2021] have been reported [609].

This list of symptoms and signs will be updated as new evidence emerges.

### 15.2 Management and care of people with post-COVID-19 condition

### 16. Abbreviations and Acronyms
1. Reading Guide

Treatment of novel coronavirus disease 2019 (COVID-19) is a rapidly expanding area of research, with an unprecedented global effort underway to combat this disease. As a result, recommendations based on current evidence are likely to become outdated quickly as new primary studies are published. The living evidence approach facilitates rapid updating of recommendations. By frequently incorporating the most up-to-date evidence, these methods ensure that the currency of each recommendation remains high.

It is anticipated that these living recommendations will be updated weekly as and when new evidence is available. This will be reflected in the publication of a new version in which changes made to a specific recommendation or supporting information are highlighted to emphasise the update.

The guideline consists of two layers

1. The Recommendation

Recommendation for (Green)
A strong recommendation is given when there is high-certainty evidence showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, patients will want the recommended intervention.

Recommendation against (Red)
A strong recommendation against the intervention is given when there is high-certainty evidence showing that the overall disadvantages of the intervention are clearly greater than the benefits. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.

Conditional Recommendation for (Yellow)
A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when patient preferences vary.

Conditional Recommendation against (Orange)
A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when patient preferences vary.

Only in research settings (Orange)
An “only in research settings” recommendation is given when there is insufficient evidence to determine if an intervention is either beneficial or harmful. When an “only in research” recommendation is given, the panel recommends that the intervention should only be considered in a randomised clinical trial with appropriate ethical approval. In any other circumstance, the intervention is not recommended.

Consensus Recommendation (Bluish-Purple)
A consensus recommendation can be given for or against the intervention. This type of recommendation is used when there is not enough evidence to give an evidence-based recommendation, but the panel still regards it as important to give a recommendation.

2. Supporting information

Click on the recommendation to learn more about the basis of the recommendation. Note that early recommendations are primarily adapted from other guidelines and/or based on the consensus of the guideline panel, and supporting information will be limited. Additional information will be added as recommendations are updated in light of new evidence.

Evidence profile: The overall effect estimates and references to the studies.
Summary: Overview and brief review of the underlying evidence.
Certainty of the evidence:
- High: We are very sure that the true effect is close to the estimated effect.
- Moderate: We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is significantly different.
- Low: We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.
- Very low: We have very little confidence in the estimated effect. The true effect is likely to be significantly different from that estimated effect.

Evidence to decision: Brief description of beneficial and harmful effects, certainty of evidence and considerations of patient preferences.
Rationale: Description of how the above elements were weighted in relation to each other and resulted in the current recommendation direction and strength.
Practical information: Practical information regarding the treatment and information on any special patient considerations.
Adaption: If the recommendation is adapted from another guideline you can find more information here.
Feedback: If you are logged in as a user, you can comment here on specific recommendations. See here for guidance on how to log in.
References: Reference list for the recommendation.

The gradation of evidence quality and recommendation strength used is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). For a quick and informative introduction to GRADE, the article Understanding GRADE: an introduction by Goldet & Howick is recommended (J Evid Based Med 2013;6(1):50-4). See also http://www.gradeworkinggroup.org.
2. Introduction

Novel coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its identification in December 2019, COVID-19 has spread around the world and was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on 30 January 2020 [1].

People infected with the COVID-19 virus are most likely to only experience mild symptoms and recover without requiring special treatment. However, some people will experience moderate or severe disease. Older people and those with underlying diseases or medical conditions (such as cardiovascular disease, diabetes, chronic respiratory disease and cancer) are more likely to develop serious illness that require special care and treatment [362].

Clinical guidelines are integral to ensuring that healthcare decisions are based on the best available evidence. Since the emergence of the COVID-19 pandemic, many national and international organisations have released guidelines related to different aspects of the management of people with COVID-19. With the support of the National Health and Medical Research Council (NHMRC), the National COVID-19 Clinical Evidence Taskforce was established to develop (in partnership with a range of national professional societies and organisations) living guidelines for clinical management and care of people with suspected or confirmed COVID-19.

Recommendations within this guideline were developed in collaboration with the organisations listed below. All member organisations are part of the steering committee and formally endorse the guideline. The Steering Committee is governed by a consensus based decision-making process, for more details on the methods and processes of the Taskforce please see the Methods and processes section of this guideline.

- Australian Living Evidence Consortium (Coordinating Lead)
- Cochrane Australia (Secretariat)
- Allied Health Professions Australia
- Australasian Association of Academic Primary Care
- Australasian College for Emergency Medicine
- Australasian College for Infection Prevention and Control
- Australasian College of Paramedicine
- Australasian Sleep Association
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
- Australasian Society for Infectious Diseases
- Australian Association of Gerontology
- Australian College of Critical Care Nurses
- Australian College of Midwives
- Australian College of Nursing
- Australian College of Rural and Remote Medicine
- Australian COVID-19 Palliative Care Working Group
- Australian and New Zealand College of Anaesthetists
- Australian and New Zealand Intensive Care Society
- Australian and New Zealand Society for Geriatric Medicine
- Australian Primary Health Care Nurses Association
- Australian Resuscitation Council
- Australian Society of Anaesthetists
- College of Emergency Nursing Australasia
- CRANApplus
- National Aboriginal Community Controlled Health Organisation
- Rehabilitation Medicine Society of Australia and New Zealand
- Royal Australasian College of Physicians
- Royal Australasian College of Surgeons
- Royal Australian College of General Practitioners
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists
- Society of Hospital Pharmacists of Australia
- Thoracic Society of Australia and New Zealand
- Thrombosis and Haemostasis Society of Australia and New Zealand

Publication approval

Version 42 of these guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 22 December 2021, under Section 14A of the National Health and Medical Research Council Act 1992. In approving the guideline recommendations, NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of 5 years. To see the full version 42 click here.

NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian health care setting.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

Updating and public consultation

A considerable volume of research related to the care of people with COVID-19 is ongoing and will potentially impact clinical recommendations. To ensure these guidelines are updated rapidly in response to new and important evidence, the underpinning knowledge syntheses and recommendations will be reviewed and updated on an ongoing basis. It is anticipated that these living recommendations will be updated weekly as and when new evidence is available. This will be reflected in the publication of a new version in which changes made to a specific recommendation or supporting information are highlighted in order to emphasise the update.

The Taskforce will seek NHMRC approval of the guideline under section 14A of the National Health and Medical Research Council Act 1992 on an ongoing basis as new recommendations are added or existing recommendations are changed. As part of the approval
process (and for the lifetime of the guidelines), public consultation is required. We welcome your feedback and suggestions. Comments can be submitted via the feedback function under each recommendation in MAGIC, see the reading guide in the above section for guidance, or by emailing guidelines@covid19evidence.net.au.

Purpose
The purpose of this guideline is to provide health professionals and patients with up-to-date, evidence-based recommendations to guide shared decision-making in the treatment of COVID-19. The guideline contains specific and actionable recommendations for selected, well-defined clinical problems (i.e. what needs to be done and who it is relevant to). It does not define the individuals responsible for providing care, nor does it consider the social or economic implications of guideline adherence.

Scope
This guideline aims to provide specific, patient-focused recommendations on management and care of people with suspected or confirmed COVID-19. With the exception of chemoprophylaxis for the prevention of infection in people exposed to COVID-19, the guideline does not include other interventions used in the prevention of COVID-19 infection or transmission. Within each recommendation, the patient population of interest is specified.

Consumer-centred care in the context of COVID-19
Consumer-centred care is the provision of health care that is respectful of, or responsive to, the needs, preferences and values of consumers. Consumer-centred care “...redefines the relationships in health care by placing an emphasis on collaborating with people of all ages, at all levels of care, and in all health care settings.” [5][12]

The key principles of consumer-centred care include:
- respect for patients’ preferences and values
- emotional support
- physical comfort
- information, communication and education
- continuity and transition
- coordination of care
- involvement of family and friends
- access to care [6]

In the context of COVID-19, we need to acknowledge the barriers and inequities experienced by consumers. Groups who will face greater barriers and inequities than others include, but are not limited to people with a disability or cognitive impairment, complex and chronic health needs, stigmatised health conditions and people from culturally or linguistically diverse backgrounds [7].

The Australian Charter of Healthcare Rights (2nd edition) outlines the basic rights that patients and consumers are entitled to receive. These rights are particularly important in the current context. Rights of particular note include:
- access to healthcare services and treatment that meet needs
- safety through safe and high-quality health care in an environment that feels safe
- respect as an individual, with culture, identity, beliefs and choices recognised
- partnership through open and honest communication with healthcare providers
- information about their conditions and the possible benefits and risks of different tests and treatments, waiting times and costs and access to health information to support informed consent
- privacy and security of personal and health information maintained [8]

COVID-19 requires clinical responsiveness to new and emerging treatments, including a significant degree of uncertainty as new treatments emerge. However, consumer preferences and values must remain central in the provision of healthcare and be balanced with the needs of the health service and public health concerns. Health services remain responsible for ensuring that their work remains patient centred. In the context of COVID-19, key concepts include ensuring:
- equity in resource allocation and provision of care
- choice and agency of the consumer
- ethical provision of care at all times

Informed consent is a further component of consumer-centred care and underpins consideration of treatment options for COVID-19 by consumers, families and carers.

Informed consent
Informed consent forms an essential component of the moral right of individuals to autonomy over their own bodies [9]. Informed consent is generally understood to be a person’s voluntary decision about their health care that is made with knowledge and understanding of the benefits and risks involved [10][11].

In practical terms, informed consent is the process by which a healthcare professional provides appropriate information to a consumer about their treatment options, associated risks and benefits, fees, charges and possible additional costs, and supports them to make a decision about their care. From a legal perspective, informed consent should comply with jurisdictional legislation and best practice and is defined in terms of an agreement or process by which, having provided the relevant information, the rights of individuals to agree or to refuse treatment are upheld. This is particularly important where there are issues relating to impaired capacity of a person to consent [10].

Consent processes help deliver services that are more closely aligned with the priorities and concerns of the community. This has a range of benefits, including improved health outcomes and a more efficient allocation of resources. In this way, informed consent processes are important in developing a genuinely consumer-focused health system.

For ethical decision-making, decisions about whether care is provided and in what form must be informed by the preferences of patients as well as clinical judgement [9]. Any changes affecting the existing plan or access to treatment must be considered with the patient, and the consented plan drafted and followed.
The National Health and Medical Research Council (NHMRC) Guidelines: Communicating with Patients addresses the content of information that should be provided, and states the patient needs to be advised of the possible or likely nature of the procedure or treatment [and] the proposed approach, including:

- what the proposed approach entails
- the expected benefits
- common side effects and material risks
- whether the procedure is conventional or experimental
- who will perform the procedure or treatment
- other options for management of the complaint
- the realistic expectations for the outcome of the procedure or treatment
- the time and cost involved, including any out-of-pocket expenses and any potential costs should further treatment be required [13]

These principles underpin the Australian Health Practitioner Regulation Agency (AHPRA) standards for healthcare professionals, including medical and allied health practitioners, and nurses and midwives to support informed consent by patients about their health care [11].

While in the context of COVID-19, decisions may be being made at greater speed and in more resource-constrained environments than other health care environments, efforts must be made as far as practical to ensure that consumers are involved in their care.

In practical terms, informed consent processes should support the role of consumers as genuine partners in health care and promote consumer involvement in decision-making. Shared decision-making practices as between a treating team and consumer (patients as partners in care) should be standard practice. Consideration must be paid to people with complex communication needs, including those who communicate in ways other than speech and have limited capacity to make decisions about their health care. All consumers should be actively involved in decisions about their treatment and care to the extent they wish to be, and they should be supported to do so [9].

Note on the language in the pregnancy and perinatal care recommendations
The Taskforce recognises that individuals have diverse gender identities. Terms such as pregnant person, childbearing people and parent can be used to avoid gendering birth, and those who give birth, as feminine. However, because women are also marginalised and oppressed in most places around the world, we have continued to use the terms woman, mother or maternity. When we use these words, it is not meant to exclude those who give birth and do not identify as women.

Note on caring for children and adolescents in the context of COVID-19
The Taskforce regards child- and family-centred care indispensable in managing the health and wellbeing of children and adolescents, and urges continuity of child-centred services, with a particular focus on equity of access. We support efforts to ensure children are able to remain in contact with parents, carers and families despite COVID-19 and recognise this may require specific attention to infection control management practices and may involve adjunctive use of technology such as video-calling. Health facilities should have plans to manage these issues for children and adolescents. We endorse the approach and goals established by the United Nations Policy Brief: the impact of COVID-19 on children [4].

Child-centred services include among others: schooling, nutrition programs, maternal and newborn care, immunisation services, sexual and reproductive health services, HIV treatment, mental health and psychosocial services, birth registration, community-based child protection programs, out-of-home care, and case management for children requiring supplementary personalised care, including those living with long-term medical conditions, disabilities and victims of abuse or family violence [4]. Particularly relevant for the Australian context is to ensure continuity of Aboriginal and Torres Strait Islander child services.

Note on people requiring palliative care and older people living with frailty or cognitive impairment
The Taskforce recognises the need for specific recommendations and considerations for older people living with frailty or cognitive impairment. These populations are particularly vulnerable and have been reported as having an increased risk of mortality due to COVID-19 [2]. The Taskforce’s Palliative and Aged Care Panel provides clinical expertise to ensure these populations are appropriately considered in our guidance. The following definitions have been agreed for these populations:

- **Older people with frailty or cognitive impairment and COVID-19**
  This population includes older people (usually over 65 years of age) with impairments of physical, cognitive and/or physiological function, or who have frailty. Frailty is a multifaceted syndrome that includes physical impairments and higher susceptibility to disease [3]. Comorbidities are often present, such as cerebrovascular disease, dementia, heart failure and chronic lung disease [3].

- **People requiring palliative care and COVID-19**
  This population includes people with COVID-19 whose prognosis due to co-existing advanced progressive disease is limited or uncertain, or people with critical COVID-19 illness where recovery is not expected.

**Target audience**
These recommendations are applicable to individuals responsible for the care of people with COVID-19. These include health professionals, individuals providing support and education to people with COVID-19, and people with diagnosed or suspected COVID-19 themselves.

Individuals such as policymakers, practice managers, researchers and students may elect to use or adopt these recommendations for purposes other than the treatment of COVID-19; however these individuals do not represent the target audience. Additional considerations not addressed within this guideline are required when using these recommendations for any purpose other than for the treatment or support of individuals with COVID-19.
How to cite this guideline


3. Methods and processes

Methods and processes
Information about the methods and processes used is described in the technical report and the search methods document. Information about our governance structure and members' details is available here. Our policy on the use of media statements, preprints and other non-peer-reviewed papers in formulating recommendations is available here.

Scientific publications


Conflicts of interest
Our policy for managing conflicts of interest and the template used for collecting the declarations of interest can be found on the website here and here. A summary of the declarations of interests can be found here.

Public consultation
We welcome feedback and suggestions. Comments can be submitted via the feedback function under each recommendation in MAGIC or by emailing guidelines@covid19evidence.net.au. Feedback and responses to comments received to date is available here.
4. Definition of disease severity
4.1 Definition of disease severity for adults

<table>
<thead>
<tr>
<th>Consensus recommendation</th>
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<tbody>
<tr>
<td><strong>Mild illness</strong></td>
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<td><strong>Moderate illness</strong></td>
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<td><strong>Severe illness</strong></td>
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**Adaptation**
The definitions of disease severity are adapted from published definitions from China [15], Italy [16] and Alfred Health (Melbourne) [17].

4.2 Definition of disease severity for children and adolescents
Consensus recommendation

These definitions apply to children under 16 years of age. Depending on the physical size and/or developmental status of the patient, either the paediatric or adult severity grading can be applied.

Cardiorespiratory and vital parameters must be considered within the normal age-appropriate ranges for neonates and children. If criteria fall across different severity classifications, use the more severe classification to manage illness.

<table>
<thead>
<tr>
<th>Mild illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[^1]</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Normal or mildly reduced feeding</td>
<td>No or mild upper respiratory tract symptoms OR No or mild work of breathing</td>
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<table>
<thead>
<tr>
<th>Moderate illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[^1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids AND With normal conscious state</td>
<td>Moderate work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) but does not persistently breach Early Warning (e.g. Medical Emergency Team) Criteria[^2] OR Brief self-resolving apnoea (infants)</td>
<td>Requires low-flow oxygen (nasal prongs or mask) to maintain SpO₂ &gt; 95%</td>
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<tr>
<th>Severe illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[^1]</th>
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<tbody>
<tr>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable</td>
<td>Moderate-severe work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) with breaches of Early Warning (e.g. MET) Criteria OR Apnoea needing support / stimulation (infants)</td>
<td>Requires high-flow oxygen at 2 L/kg/min[^3] to maintain SpO₂ &gt; 95%</td>
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<tr>
<th>Critical illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[^1]</th>
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<tr>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious</td>
<td>Unable to maintain breathing or prevent apnoea without advanced modes of support OR Abnormal vital signs for age with persistent breaches of Early Warning (e.g. MET) Criteria OR Haemodynamically unstable without inotropic or vasopressor support OR Other organ failure</td>
<td>Requires advanced modes of support to maintain oxygenation High-flow nasal oxygen at &gt; 2 L/kg/min[^3] OR Non-invasive ventilation OR Intubation and mechanical ventilation OR Extracorporeal membrane oxygenation (ECMO)</td>
<td></td>
</tr>
</tbody>
</table>

[^1] Oxygen saturation target should be modified for patients with cyanotic heart disease.

[^2] Temperature instability should be considered an abnormal vital sign in infants. Fever is common in children and does not contribute to determination of illness severity in isolation.

[^3] Infants and neonates < 4 kg may be managed on high-flow nasal cannula oxygen at 2-8 L/min irrespective of weight.
Note: co-morbidities (e.g. preterm infants, oncology, immunosuppressed, etc.) may increase the risk of more severe disease.
5. Monitoring and markers of clinical deterioration

The primary panel for the recommendation in this section is the Primary and Chronic Care Panel. Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. In addition, all our recommendations are reviewed by the Consumer Panel.

5.1 Monitoring and markers of clinical deterioration

Consensus recommendation

For people with COVID-19, monitor markers of clinical progression, such as rapidly progressive respiratory failure and sepsis, especially on days 5 to 10 after onset of symptoms.

Adaptation

The recommendation for monitoring and markers of clinical deterioration is adapted from published recommendations by the World Health Organization [362], National Institute for the Infectious Diseases (Italy) [16] and Surviving Sepsis Campaign [360]. Wording has been adapted for clarity and applicability to the Australian context.

5.2 Pulse oximeters

5.2.1 Pulse oximeters for adults
Consensus recommendation

People with risk factors for deterioration, who are being cared for at home, should be offered monitoring of oxygen saturation with pulse oximetry.

For guidance on when to escalate care, please refer to the Pathways to Care Flowchart.

We are aware that the RACGP is developing supporting materials. As soon as these are available we will provide a link to them here.

Risk factors for deterioration* include:

- Older age, e.g. over 50 years for Aboriginal and Torres Strait Islander people, or otherwise over 65 years
- Unvaccinated or partially vaccinated
- Pregnant
- Comorbidities:
  - lung disease, including COPD, asthma or bronchiectasis
  - cardiovascular disease, including hypertension
  - obesity (BMI > 30 kg/m2)
  - diabetes
  - renal failure
  - immunocompromising conditions (** see below)
- Concerns about personal safety or access to care

Use pulse oximetry with adults to assist in assessing and monitoring the severity of respiratory symptoms and detect early deterioration. Provide people with education on how to self-monitor using pulse oximetry and when to call a GP or triple 0.

Be aware that different pulse oximeters have different specifications, and that some can under or overestimate readings especially if the saturation level is borderline. Overestimation has been reported in people with darker skin.

* Evidence enabling us to rank risk factors in order of priority is not yet available.

**Immunocompromising conditions:

- Primary or acquired immunodeficiency:
  - haematological neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency

- Other significantly immunocompromising conditions:
  - immunosuppressive therapy (current or recent)
  - chemotherapy or radiotherapy
  - high-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - all biologics and most disease-modifying anti-rheumatic drugs (DMARDs)

5.2.2 Pulse oximeters for children and adolescents
**Consensus recommendation**

Children and adolescents with asymptomatic or mild COVID-19 do not routinely require peripheral oxygen saturation monitoring. However, children and adolescents at high risk of deterioration who are being cared for at home should be offered monitoring of peripheral oxygen saturation with pulse oximetry if age-appropriate oximeters and training can be provided and an appropriate pathway for escalation.

*For guidance on definitions of disease severity for children and adolescents, including peripheral oxygen saturation thresholds, please refer to the specific section in the guideline.*

Based on international cohorts [580] potential factors to consider in children or adolescents with mild COVID-19 at high risk* of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity (above the 95th percentile on BMI for age growth chart)

The use of pulse oximetry in children or adolescents to assist in assessing and monitoring the severity of respiratory symptoms and to detect early deterioration should always be in conjunction with clinical assessment of disease severity. Home pulse oximetry should only be used if children and adolescents, their parents or carers have received education on how to self-monitor and when to call a GP or triple 0.

Only age-appropriate pulse oximeters should be used in children. Be aware that different pulse oximeters have different specifications, and that some can under or overestimate readings, especially if the saturation level is borderline. Overestimation has been reported in people with darker skin.

* Evidence enabling us to rank risk factors in order of priority is not yet available.
6. Disease-modifying treatments

Several classes of therapies are currently under investigation to determine their effectiveness in treating COVID-19. These include, but are not limited to, antivirals (remdesivir, lopinavir-ritonavir), antimalarials (hydroxychloroquine, chloroquine), interleukin receptor agonists (tocilizumab, anakinra), corticosteroids (dexamethasone) and convalescent plasma. The categories of disease-modifying treatments being considered can be seen in the table below. We are continually monitoring new research for randomised trials that evaluate any disease-modifying treatments for COVID-19.

While national and international guidelines published early in the pandemic did not support the use of disease-modifying therapies in treating people with COVID-19 (except in the context of clinical trials), this is now changing as evidence for certain treatments emerges.

### Disease-modifying treatments

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents that may have activity against SARS-CoV-2</td>
<td>Antimalarials</td>
</tr>
<tr>
<td>Antivirals</td>
<td></td>
</tr>
<tr>
<td>Convalescent plasma</td>
<td></td>
</tr>
<tr>
<td>Agents that may have activity against the associated cytokine-release syndrome</td>
<td>Tocilizumab, Anakinra (IL1RA) Corticosteroids</td>
</tr>
<tr>
<td>Other and ancillary agents</td>
<td>ACE inhibitors NSAIDs</td>
</tr>
<tr>
<td>Blood purification systems for reducing cytokines in ICU</td>
<td>Cytokine removal</td>
</tr>
</tbody>
</table>

The primary panel for the recommendations in this section is the Disease-Modifying Treatment and Chemoprophylaxis Panel.

Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. The remaining panels review recommendations when relevant to their specific population group. In addition, all our recommendations are reviewed by the Consumer Panel.

6.1 Recommended disease-modifying treatments

6.1.1 Budesonide

6.1.1.1 Budesonide for adults
Evidence To Decision

Conditional recommendation

Consider using inhaled budesonide within 14 days of symptom onset in adults with COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

In patients with confirmed COVID-19 who do not require oxygen but who are subsequently hospitalised due to disease progression, budesonide probably decreases the requirement of supplemental oxygen if taken within 14 days of onset of symptoms.

Results are primarily based on the PRINCIPLE trial [566] in which adults were treated with inhaled budesonide (by breath-actuated inhaler) 800 µg twice daily for up to 14 days. Based on the inclusion criteria for this trial, risk factors for disease progression include age ≥ 65 years or ≥ 50 years with one or more of the following comorbidities:

- Diabetes (not treated with insulin)
- Heart disease and/or hypertension
- Asthma or lung disease
- Weakened immune system due to a serious illness or medication (e.g. chemotherapy)
- Mild hepatic impairment
- Stroke or other neurological problem

Approximately 11% and 1% of participants had received one or two doses of vaccine at enrolment, respectively, however results were not reported separately for this population.

Budesonide is safe to use in pregnant and breastfeeding women.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Results show that inhaled budesonide probably decreases the requirement of supplemental oxygen in adult outpatients subsequently hospitalised with COVID-19. Based on current evidence, inhaled budesonide appears to have an acceptable safety profile when used to treat patients with COVID-19.

Certainty of the Evidence

Certainty of the evidence is moderate for requirement of supplemental oxygen (due to serious imprecision based on reliance on a single study), and low for all-cause mortality, invasive mechanical ventilation, hospitalisation, ICU admission, serious adverse events and clinical recovery (due to very serious imprecision based on reliance on a single study, wide confidence intervals and/or few events).

Preference and values

We have no systematically collected information regarding patients’ preferences and values.

Pregnant and breastfeeding women

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. However, budesonide is used for other indications in pregnancy (such as asthma) and no harm has been shown for women or their babies.

Children and adolescents

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for
Rationale

In adults who do not require oxygen and who have one or more risk factors for disease progression, budesonide decreases the risk of requiring supplemental oxygen. Because of this, the Taskforce gives a conditional recommendation for inhaled budesonide both within and outside a randomised trial.

Resources and other considerations

Inhaled budesonide is widely available and affordable. Use of budesonide for the treatment of symptomatic COVID-19 in adults who do not require oxygen and who have one or more risk factors for disease progression is unlikely to have an impact on availability of these drugs for other indications.

Equity

We have no systematically collected evidence regarding impact on equity. Since inhaled budesonide is widely available and affordable, no negative impact is expected.

Acceptability

Although we have no systematically collected evidence regarding acceptability, inhaled budesonide is likely to be acceptable to both patients and clinicians.

Feasibility

The use of inhaled budesonide is likely to be feasible because it is already widely used for other indications. There are no known issues with availability of this drug.

Inhaled budesonide (AstraZeneca Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers: 80877, 80876, 80875; AusPAR). As of 3 December 2021, budesonide is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Rationale

In adults who do not require oxygen and who have one or more risk factors for disease progression, budesonide decreases the risk of requiring supplemental oxygen. Because of this, the Taskforce gives a conditional recommendation for inhaled budesonide both within and outside a randomised trial.

Clinical Question/ PICO

- **Population:** Patients with COVID-19
- **Intervention:** Budesonide
- **Comparator:** Standard care

Summary

Evidence indicates a probable reduction in the need for supplemental oxygen in adults with symptomatic COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

What is the evidence informing this recommendation?

Evidence comes from two randomised trials that compared inhaled budesonide with standard care in over 1900 adults in the community with mild COVID-19 [211][566]. The majority of data comes from the PRINCIPLE trial, which included adults with symptomatic COVID-19 who had one or more risk factors for disease progression.

Study characteristics

Mean age of participants was ~64 years and 52% were women. The majority of patients had one or more
comorbidities, including high blood pressure requiring medication (45%), diabetes (21%) and heart problems (16%).

**What are the main results?**

Budesonide probably decreases the requirement for supplemental oxygen (RR 0.69, CI 95% 0.49 to 0.98; 1559 patients from 1 study), Budesonide may improve clinical recovery and reduce hospitalisation, however we are unsure if budesonide has an impact on death, invasive mechanical ventilation, ICU admission or serious adverse events.

**Our confidence in the results**

Certainty of the evidence is moderate for requirement of supplemental oxygen (due to serious imprecision based on reliance on a single study), and low for all-cause mortality, invasive mechanical ventilation, hospitalisation, ICU admission, serious adverse events and clinical recovery (due to very serious imprecision based on reliance on a single study, wide confidence intervals and/or few events).

For children and adolescents, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included study).

**Additional information**

Common side effects and harms associated with budesonide are dysphonia, oropharyngeal candidiasis and bruising.

Budesonide is safe to use in pregnancy and during breastfeeding but has not been tested in this population to treat COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.61 (CI 95% 0.22 — 1.67) Based on data from 1,586 participants in 1 studies.</td>
<td>5 per 1000</td>
<td>8 per 1000</td>
<td>Low Due to very serious imprecision ²</td>
<td>Budesonide may have little impact on death (16 events).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.94 (CI 95% 0.44 – 1.98) Based on data from 1,560 participants in 1 studies.</td>
<td>5 per 1000</td>
<td>17 per 1000</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>Budesonide may have little impact on invasive mechanical ventilation (27 events).</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.69 (CI 95% 0.49 — 0.98) Based on data from 1,559 participants in 1 studies.</td>
<td>5 per 1000</td>
<td>64 per 1000</td>
<td>Moderate Due to serious imprecision ⁸</td>
<td>Budesonide probably decreases supplemental oxygen slightly (123 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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</tr>
<tr>
<td>Hospitalisation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.45 (CI 95% 0.12 — 1.69) Based on data from 1,732 participants in 2 studies. (^7) (Randomized controlled)</td>
<td>Control arm of reference used for intervention.</td>
<td>125 per 1000</td>
<td>56 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision (^8)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.48 (CI 95% 0.23 — 1.01) Based on data from 1,550 participants in 1 studies. (^7) (Randomized controlled)</td>
<td>Control arm of reference used for intervention.</td>
<td>27 per 1000</td>
<td>13 per 1000</td>
<td>Low Due to very serious imprecision (^10)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.51 (CI 95% 0.09 — 2.76) Based on data from 1,586 participants in 1 studies. (^11) (Randomized controlled)</td>
<td>Control arm of reference used for intervention.</td>
<td>5 per 1000</td>
<td>3 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision (^12)</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.2 (CI 95% 1.1 — 1.32) Based on data from 1,586 participants in 1 studies. (^13) (Randomized controlled)</td>
<td>Control arm of reference used for intervention.</td>
<td>488 per 1000</td>
<td>586 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision (^14)</td>
</tr>
</tbody>
</table>

1. Systematic review \([543]\) with included studies: PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. Imprecision: very serious. due to few events, Only data from one study.
4. Imprecision: very serious. Only data from one study, due to few events.
5. Systematic review \([543]\) with included studies: PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review \([543]\) with included studies: Ramakrishnan 2021, PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to not being placebo controlled, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Wide confidence intervals.
10. Imprecision: very serious. Only data from one study, due to few events.
6.1.1.2 Budesonide for children and adolescents

**Conditional recommendation**

Consider using inhaled budesonide for the treatment of symptomatic COVID-19 in children and adolescents who do not require oxygen and who have one or more risk factors for disease progression.

*In adult patients with confirmed COVID-19 who do not require oxygen but who are subsequently hospitalised due to disease progression, budesonide probably decreases the requirement of supplemental oxygen if taken within 14 days of onset of symptoms.*

Results are primarily based on the PRINCIPLE trial [566], in which adults were treated with inhaled budesonide (by breath actuated inhaler) 800 µg twice daily for up to 14 days. No children or adolescents were included in the trial.

Based on international cohort studies [580], risk factors for disease severity in children include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

Approximately 11% and 1% of participants had received one or two doses of vaccine at enrolment, respectively, however results were not reported separately for this population.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

**Practical Info**

In the PRINCIPLE trial a fixed dosing of 800 µg twice daily for up to 14 days was used [566]. It is unclear what the most appropriate dosage is for children and adolescents. Based on other indications, dry powder budesonide inhaler (Pulmicort Turbuhaler™) is used for treating asthma, usually in children over 7 years of age, and the dose can range from 200–800 µg per day, in divided doses two, three or four times a day [581] but most usually in two divided doses. For younger children, or those who are unable to use the Turbuhaler, budesonide can also be administered with a nebuliser. Nebulised doses range from 2 mg as a single dose for croup to 0.5–1 mg twice daily [582].

**Evidence To Decision**

**Benefits and harms**

Results show that inhaled budesonide probably decreases the requirement of supplemental oxygen in adult outpatients subsequently hospitalised with COVID-19. Based on current evidence, inhaled budesonide appears to...
have an acceptable safety profile when used to treat patients with COVID-19.

**Certainty of the Evidence**

Certainty of the evidence is low for requirement of supplemental oxygen (due to serious imprecision based on reliance on a single study, and indirectness), and very low for all-cause mortality, invasive mechanical ventilation, hospitalisation, ICU admission, serious adverse events and clinical recovery (due to very serious imprecision based on reliance on a single study, indirectness, wide confidence intervals and/or few events).

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values.

**Pregnant or breastfeeding patients**

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

**Children and adolescents**

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**

Inhaled budesonide is widely available and affordable. Use of budesonide for the treatment of symptomatic COVID-19 in adults who do not require oxygen and who have one or more risk factors for disease progression is unlikely to have an impact on availability of these drugs for other indications.

**Equity**

We have no systematically collected evidence regarding impact on equity. Since inhaled budesonide is widely available and affordable, no negative impact is expected.

**Acceptability**

Although we have no systematically collected evidence regarding acceptability, inhaled budesonide is likely to be acceptable to both patients and clinicians.

**Feasibility**

The use of inhaled budesonide is likely to be feasible because it is already widely used for other indications. There are no known issues with availability of this drug.

Inhaled budesonide (AstraZeneca Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers: 80877, 80876, 80875; AusPAR). As of 3 December 2021, budesonide is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.
Rationale

In adults who do not require oxygen and who have one or more risk factors for disease progression, budesonide decreases the risk of requiring supplemental oxygen. Because of this, the Taskforce gives a conditional recommendation for inhaled budesonide both within and outside a randomised trial.

Given the benefit observed in the adult population and the ample experience of use and safety profile in children, the Taskforce gives a conditional recommendation for its use in children and adolescents.

Clinical Question/ PICO

| Population: | Special populations with COVID-19 |
| Intervention: | Budesonide |
| Comparator: | Standard care |

Summary

Evidence indicates a probable reduction in the need for supplemental oxygen in adults with symptomatic COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

What is the evidence informing this recommendation?

Evidence comes from two randomised trials that compared inhaled budesonide with standard care in over 1900 adults in the community with mild COVID-19 [211][566]. The majority of data comes from the PRINCIPLE trial, which included adults with symptomatic COVID-19 who had one or more risk factors for disease progression.

Study characteristics

Mean age of participants was ~64 years and 52% were women. The majority of patients had one or more comorbidities, including high blood pressure requiring medication (45%), diabetes (21%) and heart problems (16%).

What are the main results?

Budesonide probably decreases the requirement for supplemental oxygen (RR 0.69, CI 95% 0.49 to 0.98; 1559 patients from 1 study). Budesonide may improve clinical recovery and reduce hospitalisation, however we are unsure if budesonide has an impact on death, invasive mechanical ventilation, ICU admission or serious adverse events.

Our confidence in the results

Certainty of the evidence is moderate for requirement of supplemental oxygen (due to serious imprecision based on reliance on a single study), and low for all-cause mortality, invasive mechanical ventilation, hospitalisation, ICU admission, serious adverse events and clinical recovery (due to very serious imprecision based on reliance on a single study, wide confidence intervals and/or few events).

For children and adolescents, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included study).

Additional information

Common side effects and harms associated with budesonide are dysphonia, oropharyngeal candidiasis and bruising.

Budesonide is safe to use in pregnancy and during breastfeeding but has not been tested in this population to treat COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.61 (CI 95% 0.22 – 1.67) Based on data from 1,586 participants in 1</td>
<td>Standard care</td>
<td>Budesonide</td>
<td>Very low Due to very serious imprecision, Due</td>
<td>We are uncertain whether budesonide improves or worsen all-cause mortality</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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</tr>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Timeframe</strong></td>
<td><strong>Study results and measurements</strong></td>
<td><strong>Comparator</strong></td>
<td><strong>Intervention</strong></td>
<td><strong>Certainty of the Evidence (Quality of evidence)</strong></td>
</tr>
<tr>
<td>of commencing treatment</td>
<td>9 Critical studies. ³ (Randomized controlled)</td>
<td>Relative risk 0.94 (CI 95% 0.44 – 1.98) Based on data from 1,560 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Standard care</td>
<td>Budesonide</td>
<td>Low Due to serious indirectness</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.69 (CI 95% 0.49 – 0.98) Based on data from 1,559 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Standard care</td>
<td>Budesonide</td>
<td>Low Due to serious indirectness</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>6 Important</td>
<td>Relative risk 0.45 (CI 95% 0.12 – 1.69) Based on data from 1,732 participants in 2 studies. ⁷ (Randomized controlled)</td>
<td>Standard care</td>
<td>Budesonide</td>
<td>Very low Due to serious risk of bias and serious indirectness</td>
</tr>
<tr>
<td>ICU admission</td>
<td>6 Important</td>
<td>Relative risk 0.48 (CI 95% 0.23 – 1.01) Based on data from 1,550 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td>Standard care</td>
<td>Budesonide</td>
<td>Very low Due to serious risk of bias and serious indirectness</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>6 Important</td>
<td>Relative risk 0.51 (CI 95% 0.09 – 2.76) Based on data from 1,586 participants in 1 studies. ¹¹ (Randomized controlled)</td>
<td>Standard care</td>
<td>Budesonide</td>
<td>Very low Due to serious risk of bias and serious indirectness</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td></td>
<td>Relative risk 1.2 (CI 95% 1.1 – 1.32)</td>
<td>Standard care</td>
<td>Budesonide</td>
<td>Very low Due to serious risk of bias and serious indirectness</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Budesonide</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
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<td>------------------------</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>Based on data from 1,586 participants in 1 studies. (Randomized controlled)</td>
<td>per 1000</td>
<td>per 1000</td>
<td>risk of bias and serious imprecision. Due to serious indirectness</td>
<td>Improves or worsens clinical recovery.</td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td>Difference: 98 more per 1000 (CI 95% 49 more – 156 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Due to few events, Only data from one study.
4. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, due to few events.
6. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
8. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to not being placebo controlled. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.
10. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, due to few events.
12. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to no placebo arm. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study, due to few events.
14. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study, Wide confidence intervals.

### 6.1.2 Casirivimab plus imdevimab (Ronapreve/REGEN-COV)

#### 6.1.2.1 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for adults
**Conditional recommendation**

Consider using casirivimab plus imdevimab within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

In adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.

Included data comes from the three-phase REGEN-COV trial [509][576] in which patients with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Based on inclusion criteria of the trial, risk factors for disease progression include:

- Age ≥ 50 years
- Obesity (BMI ≥ 30 kg/m2)
- Cardiovascular disease (including hypertension)
- Chronic lung disease (including asthma)
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease, including those that are on dialysis
- Chronic liver disease
- Immunocompromised patients (including individuals with rheumatoid arthritis, HIV/AIDS and systemic lupus erythematosus receiving immunosuppressive treatment)

As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms.

The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised patients with mild or asymptomatic COVID-19 is not known.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

As of 29 October 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in adult outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

### Evidence To Decision

#### Benefits and harms

Casirivimab plus imdevimab decreases the incidence of adverse and serious adverse events, and probably decreases hospitalisation. We are unsure if casirivimab plus imdevimab has an impact on mortality, mechanical ventilation, ICU admission or discontinuation due to adverse events.

#### Certainty of the Evidence

Certainty of the evidence is low for the critical outcomes of mortality and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events).
Preference and values
We have no systematically collected information regarding patients’ preferences and values.

Pregnant or breastfeeding patients
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations
The limited availability of casirivimab plus imdevimab, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity
We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of casirivimab plus imdevimab may affect equity based on geographic area and access to casirivimab plus imdevimab.

Acceptability
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

Feasibility
Intravenous casirivimab plus imdevimab (Ronapreve; Roche Products Pty Ltd) was granted provisional approval by the Therapeutic Goods Administration on 15 October 2020 for the treatment of COVID-19 under the Black Triangle Scheme (ARTG numbers: 374310, 373839; AusPAR).
Implementability could be affected by limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale
General adult population
In adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces the risk of hospitalisation. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside a randomised trial.

Clinical Question/ PICO

| Population: | Outpatients with mild COVID-19 |
| Intervention: | Casirivimab plus imdevimab |
| Comparator: | Placebo |
Summary

There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 adult outpatients with mild COVID-19 [509][576] and 207 asymptomatic outpatients [635]. Two trials are linked—one presents results from the phase I-II portion [509] and the second from the phase III portion of the study [576]. The third study included asymptomatic patients who had close contacts with confirmed COVID-19 individuals [635].

Publication status

One study is only available as a preprint (Weinreich et al. posted to medRxiv on 12 June 2021 [509]) and has therefore not been peer reviewed.

Study characteristics

Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 2400 mg or 8000 mg REGEN-COV (1:1 casirivimab:imdevimab). The larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose, revising their protocol midway to include one 1200 mg or 2400 mg dose. In O’Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding patients were ineligible.

What are the main results?

Casirivimab plus imdevimab decreases the incidence of adverse events (RR 0.74, CI 95% 0.64 to 0.86; 5842 patients in 2 studies) and serious adverse events (RR 0.34, CI 95% 0.25 to 0.48; 6622 patients in 3 studies), and probably decreases hospitalisation (RR 0.30, CI 95% 0.20 to 0.44; 4261 patients in 2 studies). We are unsure if casirivimab plus imdevimab has an impact on death, mechanical ventilation, ICU admission or discontinuation due to adverse events.

Our confidence in the results

Certainty of the evidence is low for the critical outcomes of death and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse events and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information

The Taskforce notes that as of 15 October 2021, the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention REGEN-COV</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.2 (CI 95% 0.04 — 1.02) Based on data from 4,057 participants in 1 studies. ² (Randomized controlled)</td>
<td>4 per 1000 (Randomized controlled)</td>
<td>1 per 1000 (Randomized controlled)</td>
<td>Low Due to very serious imprecision ²</td>
<td>Casirivimab plus imdevimab may have little impact on death (10 events).</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>Difference: 3 fewer per 1000 (CI 95% 4 fewer — 0 fewer)</td>
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<tr>
<td>9 Critical</td>
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<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<tr>
<td><strong>Mechanical ventilation</strong></td>
<td>Within 28 days of commencing</td>
<td>Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies. ³</td>
<td>Placebo</td>
<td>REGEN-COV</td>
<td>Low Due to very serious imprecision ⁴</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
<td>(Randomized controlled)</td>
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<td></td>
<td></td>
<td>⁴ Critical</td>
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<tr>
<td><strong>ICU admission</strong></td>
<td>Within 28 days of commencing</td>
<td>Relative risk 0.32 (CI 95% 0.14 — 0.71) Based on data from 3,432 participants in 1 studies. ³</td>
<td>Placebo</td>
<td></td>
<td>Low Due to very serious imprecision ⁶</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
<td>(Randomized controlled)</td>
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<td>⁵ Important</td>
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<tr>
<td><strong>Adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 5,842 participants in 2 studies. ⁷</td>
<td>Placebo</td>
<td></td>
<td>High</td>
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<td>(Randomized controlled)</td>
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<td>⁶ Important</td>
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<tr>
<td><strong>Serious adverse event</strong></td>
<td>End of follow-up</td>
<td>Relative risk 0.34 (CI 95% 0.25 — 0.48) Based on data from 6,622 participants in 3 studies. ⁸</td>
<td>Placebo</td>
<td></td>
<td>High</td>
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<tr>
<td><strong>Discontinuation due to adverse event</strong></td>
<td>During treatment</td>
<td>Based on data from 780 participants in 1 studies. ⁹</td>
<td>Placebo</td>
<td></td>
<td>Low Due to very serious imprecision ¹⁰</td>
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<td>⁸ Important</td>
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<tr>
<td><strong>Hospitalisation</strong></td>
<td>Within 28 days of commencing</td>
<td>Relative risk 0.3 (CI 95% 0.2 — 0.44) Based on data from 4,261 participants in 2 studies. ¹¹</td>
<td>Placebo</td>
<td></td>
<td>Moderate Due to serious imprecision ¹²</td>
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<tr>
<td></td>
<td>treatment</td>
<td>(Randomized controlled)</td>
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<td>⁹ Important</td>
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</table>

2. Imprecision: very serious. due to low event numbers. Only data from one study.


4. Imprecision: very serious. Only data from one study, due to few events.

5. Systematic review [506] with included studies: Weinreich 2021 p III. **Baseline/comparator:** Control arm of reference used for intervention.

6. Imprecision: very serious. Only data from one study, due to low event numbers.


10. Imprecision: very serious. due to few events. Only data from one study, Wide confidence intervals.


12. Imprecision: serious. majority of data comes from a single study.

**Conditional recommendation**

Consider using casirivimab plus imdevimab in **seronegative** adults hospitalised with moderate to critical COVID-19.

In patients hospitalised with moderate to critical COVID-19 who are seronegative (no detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.

The Taskforce notes that the RECOVERY trial administered a single intravenous 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab in 250 ml 0.9% saline) and assessed baseline serostatus using the Oxford (anti-spike IgG) immunoassay, the use of which has been supported by the UK National SARS-CoV-2-Serology Assay Evaluation Group [516].

It should be noted that the study by Somersan-Karakaya [628] initially included patients requiring ventilation but ceased their recruitment due to safety concerns, however no safety data were provided for these patients.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

The sponsor has not submitted an application to the Therapeutics Goods Administration for use of casirivimab plus imdevimab in hospitalised patients and it is presently not approved for this indication.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

**Evidence To Decision**

**Benefits and harms**

In patients hospitalised with moderate to critical COVID-19 who are seronegative (i.e. no detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab decreases the incidence of death. In addition, casirivimab plus imdevimab may decrease duration of hospital stay and increase discharge from hospital at 28 days.

Although no direct safety data have been reported for hospitalised patients in the included trials, data that focus on...
non-hospitalised asymptomatic and mild patients in these trials suggest that casirivimab plus imdevimab has an acceptable safety profile.

**Older people living with frailty or cognitive impairment**
People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

**People requiring palliative care**
There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

**Pregnant or breastfeeding women**
There is uncertainty around the benefits and harms of casirivimab plus imdevimab for pregnant or breastfeeding women with COVID-19 as no details were reported in the trials for these populations.

**Children or adolescents**
Although children under 12 years of age were eligible for inclusion within the second phase of the casirivimab plus imdevimab arm of the RECOVERY trial, results were not presented separately for this subgroup and it is unclear how many children were included. As a result, there remains uncertainty around the benefits and harms of casirivimab plus imdevimab for children and adolescents with COVID-19.

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**Certainty of the Evidence**

Certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

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**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that since there are probable mortality benefits, most informed patients hospitalised due to COVID-19 and who are seronegative would agree with the recommendation and opt for casirivimab plus imdevimab.

**Pregnant or breastfeeding patients**
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

**Children and adolescents**
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

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**Resources and other considerations**

The Taskforce notes that measurement of serostatus is required to determine whether a patient is seronegative and will thus benefit from treatment with casirivimab plus imdevimab. The RECOVERY trial used a novel ELISA assay (the Oxford immunoassay) for such measurements as it has demonstrated high sensitivity and specificity without additional optimisation, however other high throughput SARS-CoV-2 antibody immunoassays are available. The unavailability of casirivimab plus imdevimab, as well as the high cost of treatment, are also limiting factors preventing widespread use of this treatment.
Rationale

General adult population
In patients hospitalised with moderate to critical COVID-19 who are seronegative for SARS-CoV-2 antibodies, casirivimab plus imdevimab reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside a randomised trial.

Clinical Question/ PICO

Population: Patients hospitalised with COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Standard care

Summary
Evidence indicates a reduction in death in seronegative patients hospitalised with mild-to-critical COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline [510], and one randomised trial that compared casirivimab plus imdevimab with placebo in 1336 patients hospitalised with mild-to-moderate COVID-19, approximately half of whom were seronegative at baseline [628].

Publication status
Both studies are only available as preprints (posted to medRxiv on 16 June 2021 [510] and 10 November 2021 [628]) and have therefore not been peer reviewed.

Study characteristics
Median age of participants was 62 years in both studies. Women comprised 37% of participants in RECOVERY and 47% in Somersan-Karakaya et al. Within RECOVERY, patients received a single intravenously administered 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab) or standard care. Twelve children (12–18 years) were included in RECOVERY but data were not reported separately. In Somersan-Karakaya et al patients received a single intravenously administered dose of 8000 mg REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab), 2400 mg REGEN-COV (1200 mg casirivimab plus 1200 mg imdevimab) or placebo. Children were ineligible for inclusion. Pregnant and breastfeeding women were ineligible in both trials.

Both trials separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming the appropriateness of this approach. The full
ICEMAN analysis can be found here.

**What are the main results?**

Results demonstrate that casirivimab plus imdevimab reduces death in seronegative patients (50 fewer deaths per 1000; RR 0.82, CI 95% 0.73 to 0.91; 3673 patients in 2 studies). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.

For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in RECOVERY, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in administration.

**Our confidence in the results**

In seronegative patients certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is high for all-cause mortality, and moderate for mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

Although the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression, as of 19 November 2021 it is not approved for use in hospitalised patients.

### Table: Outcomes and Measurements

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention REGEN-COV</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 0.81 (CI 95% 0.56 — 1.17) Based on data from 10,982 participants in 2 studies.¹ (Randomized controlled)</td>
<td>9 Critical</td>
<td>201 per 1000</td>
<td>163 per 1000</td>
<td>High Casirivimab plus imdevimab decreases all-cause mortality</td>
</tr>
<tr>
<td>Invasive mechanical ventilation [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 1 (CI 95% 0.89 — 1.13) Based on data from 9,198 participants in 1 studies.² (Randomized controlled)</td>
<td>9 Critical</td>
<td>105 per 1000</td>
<td>105 per 1000</td>
<td>Moderate Due to serious imprecision ³ Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients].</td>
</tr>
</tbody>
</table>

1. (Randomized controlled)
2. (Randomized controlled)
3. Due to serious imprecision
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged from hospital [All patients]</td>
<td>Within 28 days of commencing treatment</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate</td>
<td>Casirivimab plus imdevimab probably has little impact on discharge from hospital [total]</td>
</tr>
<tr>
<td>Relative risk 1.01 (CI 95% 0.98 — 1.04)</td>
<td>Based on data from 9,785 participants in 1 studies.</td>
<td>690 per 1000</td>
<td>697 per 1000</td>
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<tr>
<td>Relative risk 1.03 (CI 95% 0.98 — 1.08)</td>
<td>Based on data from 10,982 participants in 2 studies.</td>
<td>701 per 1000</td>
<td>722 per 1000</td>
<td>High</td>
<td>Casirivimab plus imdevimab increases discharged from hospital</td>
</tr>
<tr>
<td>Relative risk 0.64 (CI 95% 0.36 — 1.15)</td>
<td>Based on data from 3,673 participants in 2 studies.</td>
<td>283 per 1000</td>
<td>181 per 1000</td>
<td>Moderate</td>
<td>Casirivimab plus imdevimab decreases all-cause mortality [seronegative]</td>
</tr>
<tr>
<td>Relative risk 0.88 (CI 95% 0.73 — 1.06)</td>
<td>Based on data from 3,083 participants in 1 studies.</td>
<td>135 per 1000</td>
<td>119 per 1000</td>
<td>Moderate</td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seronegative patients].</td>
</tr>
<tr>
<td>Relative risk 0.98 (CI 95% 0.95 — 1.01)</td>
<td>Based on data from 6,632 participants in 1 studies.</td>
<td>740 per 1000</td>
<td>725 per 1000</td>
<td>High</td>
<td>Casirivimab plus imdevimab probably has little impact on discharged from hospital [seropositive]</td>
</tr>
<tr>
<td>Relative risk 1.11 (CI 95% 1.06 — 1.16)</td>
<td>Based on data from 3,673 participants in 2 studies.</td>
<td>600 per 1000</td>
<td>666 per 1000</td>
<td>Moderate</td>
<td>Casirivimab plus imdevimab probably increases discharged from hospital [seronegative]</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td>Treatment</td>
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<td>6 Important</td>
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<tr>
<td>All-cause mortality (seropositive)</td>
<td>Relative risk 1.01 (CI 95% 0.91 -- 1.12) Based on data from 7,202 participants in 2 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>High</td>
<td>Casirivimab plus imdevimab has little or no difference on all-cause mortality (seropositive)</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>163 per 1000 Difference: 2 more per 1000 (CI 95% 15 fewer -- 20 more)</td>
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<tr>
<td>Invasive mechanical ventilation (seropositive)</td>
<td>Relative risk 1.08 (CI 95% 0.92 -- 1.26) Based on data from 6,702 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Moderate Due to serious imprecision 16</td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation (seropositive patients).</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>83 per 1000 Difference: 7 more per 1000 (CI 95% 7 fewer -- 22 more)</td>
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<tr>
<td>Discharged from hospital (seropositive)</td>
<td>Relative risk 0.98 (CI 95% 0.95 -- 1.01) Based on data from 6,632 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Moderate Due to serious imprecision 18</td>
<td>Casirivimab plus imdevimab probably has little impact on discharge from hospital (seropositive patients).</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>740 per 1000 Difference: 15 fewer per 1000 (CI 95% 37 fewer -- 7 more)</td>
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<tr>
<td>Serious Adverse Events</td>
<td>Relative risk 0.85 (CI 95% 0.71 -- 1.03) Based on data from 1,410 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Low Due to very serious imprecision 20</td>
<td>Casirivimab plus imdevimab may decrease new serious adverse events</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>279 per 1000 Difference: 42 fewer per 1000 (CI 95% 81 fewer -- 8 more)</td>
<td></td>
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<tr>
<td>Duration of hospital stay (All patients) Days</td>
<td>Lower better Based on data from: 9,785 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Moderate Due to serious imprecision 22</td>
<td>Casirivimab plus imdevimab probably has little impact on duration of hospital stay (all patients).</td>
</tr>
<tr>
<td>Days</td>
<td>10 (Median)</td>
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<td></td>
<td>17</td>
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<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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</tr>
<tr>
<td>hospital stay</td>
<td>Lower better Based on data from: 3,153 participants in 1 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Due to very serious imprecision.</td>
<td>imdevimab may decrease duration of hospital stay [seronegative patients].</td>
</tr>
</tbody>
</table>

3. **Imprecision: serious.** Only data from one study.
5. **Imprecision: serious.** Only data from one study.
8. **Imprecision: serious.** Wide confidence intervals.
10. **Imprecision: serious.** Only data from one study.
13. **Imprecision: serious.** Wide confidence intervals.
16. **Imprecision: serious.** Only data from one study.
18. **Imprecision: serious.** Only data from one study.
20. **Imprecision: very serious.** Only data from one study, Low number of patients, Wide confidence intervals.
22. **Imprecision: serious.** Only data from one study.
23. Systematic review [504]. **Baseline/comparator**: Control arm of reference used for intervention.
24. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.
Not recommended

Do not use casirivimab plus imdevimab in \textit{seropositive} adults hospitalised with moderate to critical COVID-19.

\textit{In patients hospitalised with moderate to critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably has little impact on mortality, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.}

This is a \textit{moderate priority} recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

### Evidence To Decision

#### Benefits and harms

**General adult population**

Evidence indicates no difference between casirivimab plus imdevimab and standard care in incidence of death, requirement of mechanical ventilation or duration of hospital stay. There was no adverse event data reported within the RECOVERY trial, however data from studies focused on asymptomatic and mild outpatients suggests that casirivimab plus imdevimab has an acceptable safety profile.

#### Certainty of the Evidence

Certainty of the evidence is moderate for all-cause mortality, mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

#### Preference and values

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

#### Resources and other considerations

As casirivimab plus imdevimab is not recommended in seropositive patients there are no resource considerations.

#### Equity

As casirivimab plus imdevimab is not recommended in seropositive patients there are no equity considerations.

#### Acceptability

As casirivimab plus imdevimab is not recommended in seropositive patients there are no acceptability
Rationale

Based on the available evidence, casirivimab plus imdevimab is no more effective than standard care in treating SARS-CoV-2 seronegative patients with COVID-19. We therefore recommend that casirivimab plus imdevimab should not be used.

Clinical Question/ PICO

**Population:** Patients hospitalised with COVID-19  
**Intervention:** Casirivimab plus imdevimab  
**Comparator:** Standard care

Summary

Evidence indicates a reduction in death in seronegative patients hospitalised with mild-to-critical COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline [510]; and one randomised trial that compared casirivimab plus imdevimab with placebo in 1336 patients hospitalised with mild-to-moderate COVID-19, approximately half of whom were seronegative at baseline [628].

**Publication status**

Both studies are only available as preprints (posted to medRxiv on 16 June 2021 [510] and 10 November 2021 [628]) and have therefore not been peer reviewed.

**Study characteristics**

Median age of participants was 62 years in both studies. Women comprised 37% of participants in RECOVERY and 47% in Somersan-Karakaya et al. Within RECOVERY, patients received a single intravenously administered 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab) or standard care. Twelve children (12–18 years) were included in RECOVERY but data were not reported separately. In Somersan-Karakaya et al patients received a single intravenously administered dose of 8000 mg REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab), 2400 mg REGEN-COV (1200 mg casirivimab plus 1200 mg imdevimab) or placebo. Children were ineligible for inclusion. Pregnant and breastfeeding women were ineligible in both trials.

Both trials separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming the appropriateness of this approach. The full ICEMAN analysis can be found here.

**What are the main results?**

Results demonstrate that casirivimab plus imdevimab reduces death in seronegative patients (50 fewer deaths per 1000; RR 0.82, CI 95% 0.73 to 0.91; 3673 patients in 2 studies). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.

For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in RECOVERY, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in
administration.

**Our confidence in the results**

In seronegative patients certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is high for all-cause mortality, and moderate for mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

Although the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression, as of 19 November 2021 it is not approved for use in hospitalised patients.

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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [All patients]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.81 (CI 95% 0.56 — 1.17) Based on data from 10,982 participants in 2 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>High</td>
<td>Casirivimab plus imdevimab decreases all-cause mortality</td>
</tr>
<tr>
<td>Invasive mechanical ventilation [All patients]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1 (CI 95% 0.89 — 1.13) Based on data from 9,198 participants in 1 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients]</td>
</tr>
<tr>
<td>Discharged from hospital [All patients]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.98 — 1.04) Based on data from 9,785 participants in 1 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably has little impact on discharge from hospital [total]</td>
</tr>
<tr>
<td>Discharged from hospital [All patients]</td>
<td>Relative risk 1.03 (CI 95% 0.98 — 1.08) Based on data from</td>
<td></td>
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<td>Casirivimab plus imdevimab increases discharged from</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td><strong>All-cause mortality</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>10,982 participants in 2 studies. 6 (Randomized controlled)</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate Due to serious imprecision 8</td>
<td>Casirivimab plus imdevimab decreases all-cause mortality [seronegative]</td>
</tr>
<tr>
<td><strong>Invasive mechanical ventilation</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.64 (CI 95% 0.36 — 1.15) Based on data from 3,673 participants in 2 studies. 7 (Randomized controlled)</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate Due to serious imprecision 10</td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seronegative patients]</td>
</tr>
<tr>
<td><strong>Discharged from hospital</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.73 — 1.06) Based on data from 3,083 participants in 1 studies. 9 (Randomized controlled)</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>High</td>
<td>Casirivimab plus imdevimab probably has little impact on discharged from hospital [seropositive]</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.91 — 1.12) Based on data from 7,202 participants in 2 studies. 14 (Randomized controlled)</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>High</td>
<td>Casirivimab plus imdevimab has little or no difference on all-cause mortality [seropositive]</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td><strong>Invasive mechanical ventilation</strong> [seropositive]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.08 (CI 95% 0.92 – 1.26) Based on data from 6,702 participants in 1 studies. 15 (Randomized controlled)</td>
<td><strong>Standard care</strong></td>
<td><strong>REGEN-COV</strong></td>
<td><strong>Moderate</strong></td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seropositive patients].</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>83 per 1000</td>
<td>90 per 1000</td>
<td><strong>Moderate</strong> Due to serious imprecision</td>
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<td></td>
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<td>Difference: 7 more per 1000 (CI 95% 7 fewer – 22 more)</td>
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<tr>
<td><strong>Discharged from hospital</strong> [seropositive]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.95 – 1.01) Based on data from 6,632 participants in 1 studies. 17 (Randomized controlled)</td>
<td><strong>Standard care</strong></td>
<td><strong>REGEN-COV</strong></td>
<td><strong>Moderate</strong> Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably has little impact on discharge from hospital [seropositive patients].</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>740 per 1000</td>
<td>725 per 1000</td>
<td><strong>Moderate</strong> Due to serious imprecision</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 15 fewer per 1000 (CI 95% 37 fewer – 7 more)</td>
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</tr>
<tr>
<td><strong>Serious Adverse Events</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.85 (CI 95% 0.71 – 1.03) Based on data from 1,410 participants in 1 studies. 19 (Randomized controlled)</td>
<td><strong>Standard care</strong></td>
<td><strong>REGEN-COV</strong></td>
<td><strong>Low</strong> Due to very serious imprecision</td>
<td>Casirivimab plus imdevimab may decrease new serious adverse events</td>
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<tr>
<td></td>
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<td></td>
<td>279 per 1000</td>
<td>237 per 1000</td>
<td><strong>Low</strong> Due to very serious imprecision</td>
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<td></td>
<td></td>
<td></td>
<td>Difference: 42 fewer per 1000 (CI 95% 81 fewer – 8 more)</td>
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<tr>
<td><strong>Duration of hospital stay</strong> [All patients]</td>
<td>Days</td>
<td>Lower better Based on data from: 9,785 participants in 1 studies. 21 (Randomized controlled)</td>
<td><strong>Standard care</strong></td>
<td><strong>REGEN-COV</strong></td>
<td><strong>Moderate</strong> Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably has little impact on duration of hospital stay [all patients].</td>
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<td></td>
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<td></td>
<td>10 (Median)</td>
<td>10 (Median)</td>
<td><strong>Moderate</strong> Due to serious imprecision</td>
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<td></td>
<td></td>
<td></td>
<td>CI 95%</td>
<td></td>
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<tr>
<td><strong>Duration of hospital stay</strong> [seronegative]</td>
<td>Days</td>
<td>Lower better Based on data from: 3,153 participants in 1 studies. 23 (Randomized controlled)</td>
<td><strong>Standard care</strong></td>
<td><strong>REGEN-COV</strong></td>
<td><strong>Low</strong> Due to very serious imprecision</td>
<td>Casirivimab plus imdevimab may decrease duration of hospital stay [seronegative patients].</td>
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<td></td>
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<td>17 (Median)</td>
<td>13 (Median)</td>
<td><strong>Low</strong> Due to very serious imprecision</td>
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<td></td>
<td></td>
<td></td>
<td>CI 95%</td>
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</tbody>
</table>

3. **Imprecision: serious.** Only data from one study.
5. **Imprecision: serious.** Only data from one study.


8. Imprecision: serious. Wide confidence intervals.


10. Imprecision: serious. Only data from one study.


15. Systematic review [504] with included studies: RECOVERY 2021 seropositive. **Baseline/comparator:** Control arm of reference used for intervention.


17. Systematic review [504] with included studies: RECOVERY 2021 seropositive. **Baseline/comparator:** Control arm of reference used for intervention.


20. Imprecision: very serious. Only data from one study, Low number of patients, Wide confidence intervals.

21. Systematic review [504]. **Baseline/comparator:** Control arm of reference used for intervention.

22. Imprecision: serious. Only data from one study.

23. Systematic review [504]. **Baseline/comparator:** Control arm of reference used for intervention.

24. Imprecision: very serious. Only data from one study, Wide confidence intervals.

### 6.1.2.2 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for pregnant or breastfeeding women
Consider using casirivimab plus imdevimab within 7 days of symptom onset in pregnant or breastfeeding women who are outpatients with mild COVID-19 and who have one or more risk factors for disease progression.

In non-pregnant adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce has given a conditional recommendation on the use for casirivimab plus imdevimab both within and outside the context of a randomised trial.

Included data comes from the three-phase REGEN-COV trial [509][576] in which patients with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Based on the inclusion criteria of this trial, risk factors for disease progression include:

- Age ≥ 50 years
- Obesity (≥ 30 kg/m²)
- Cardiovascular disease (including hypertension)
- Chronic lung disease (including asthma)
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease, including those that are on dialysis
- Chronic liver disease
- Immunocompromised patients (including individuals with rheumatoid arthritis, HIV/AIDS and systemic lupus erythematosus)

There is uncertainty around the benefits and harms of casirivimab plus imdevimab for pregnant or breastfeeding women with COVID-19, as these women were not eligible in the available trials. Casirivimab plus imdevimab is a human immunoglobulin G (IgG) and may cross the placenta from mother to baby. The potential impact of this is not known. However, it is known that pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby [567]. Casirivimab plus imdevimab can therefore be considered if the benefit justifies the possible but unknown risks.

As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms. Dose adjustment is not required for pregnant or breastfeeding women.

The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised patients with mild or asymptomatic COVID-19 is not known.

There are no available data on the excretion of casirivimab plus imdevimab in human milk, and the potential benefits and risks to a breastfed baby are not known. Human IgGs are known to be excreted in breast milk. A decision whether to discontinue breastfeeding or to abstain from casirivimab plus imdevimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

As of 29 September 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in pregnant or breastfeeding women who are outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

There is uncertainty around the benefits and harms of casirivimab plus imdevimab for pregnant or breastfeeding women with mild COVID-19, as these women were not eligible in the available trials. Casirivimab plus imdevimab is a human immunoglobulin G (IgG) and may cross the placenta from mother to baby. The potential impact of this is not known. However, it is known that pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby [567]. Casirivimab plus imdevimab can therefore be considered if the benefit justifies the possible but unknown risks.

As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms. Dose adjustment is not required for pregnant or breastfeeding women.

The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised patients with mild or asymptomatic COVID-19 is not known.

There are no available data on the excretion of casirivimab plus imdevimab in human milk, and the potential benefits and risks to a breastfed baby are not known. Human IgGs are known to be excreted in breast milk. A decision whether to discontinue breastfeeding or to abstain from casirivimab plus imdevimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

As of 29 September 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in pregnant or breastfeeding women who are outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
women with COVID-19.

In non-pregnant adults, casirivimab plus imdevimab decreases the incidence of adverse events (RR 0.74, CI 95% 0.64 to 0.86; 5842 patients in 2 studies) and serious adverse events (RR 0.34, CI 95% 0.25 to 0.48; 6,622 patients in 3 studies), and probably decreases hospitalisation (RR 0.30, CI 95% 0.20 to 0.44; 4,261 patients in 2 studies). We are unsure if casirivimab plus imdevimab has an impact on mortality, mechanical ventilation, ICU admission or discontinuation due to adverse events.

There are currently no data on the effects of casirivimab plus imdevimab on a pregnant woman or baby as pregnant and breastfeeding women were excluded from the available trials. However, it is known that casirivimab plus imdevimab has health benefits when used for this indication in non-pregnant adult patients with mild disease and who have risk factors for disease progression. Pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby.

As this therapy uses immunoglobulin G (IgG) monoclonal antibodies, they would be expected to cross the placenta. Other IgG products have been safely used in pregnant women when their use is indicated.

There are no available data on the presence of casirivimab plus imdevimab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk.

Certainty of the Evidence

Certainty of the evidence is low for the critical outcomes of mortality and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse events and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events). For pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Preference and values

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point.

Resources and other considerations

The limited availability of casirivimab plus imdevimab, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of casirivimab plus imdevimab may affect equity based on geographic area and access to casirivimab plus imdevimab.

Acceptability

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.
Rationale
In non-pregnant adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces the risk of hospitalisation.

There are currently no data on the effects of casirivimab plus imdevimab on a pregnant woman or baby as pregnant or breastfeeding women were excluded from the available trials. However, it is known that casirivimab plus imdevimab confers health benefits when used in non-pregnant adult patients with mild disease and have risk factors for disease progression. Pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby [567]. Casirivimab plus imdevimab can therefore be considered if the benefit justifies the possible but unknown risks.

As this therapy uses immunoglobulin G (IgG) monoclonal antibodies, they would be expected to cross the placenta. Other IgG products have been safely used in pregnant women when their use is indicated.

There are no available data on the presence of casirivimab plus imdevimab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. A decision whether to discontinue breastfeeding or to abstain from casirivimab plus imdevimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

Because of these factors, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside a randomised trial.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Pregnant or breastfeeding outpatients with mild COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Casirivimab plus imdevimab</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Summary
There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 non-pregnant adult outpatients with mild COVID-19 [509][576] and 207 asymptomatic outpatients [?]. Two trials are linked—one presents results from the phase I-II portion [509] and the second from the phase III portion of the study [576]. The third study included asymptomatic patients who had close contacts with confirmed COVID-19 individuals [?]. Pregnant and breastfeeding women were ineligible in the available trials.

Publication status
Two studies are only available as preprints (Weinreich et al. posted to medRxiv on 12 June 2021[509] and O’Brien et al. posted to medRxiv on 15 June 2021[?]) and have therefore not been peer reviewed.

Study characteristics
Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 2400 mg or 8000 mg REGEN-COV (1:1 casirivimab:imdevimab). The larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose, revising their protocol midway to include one 1200 mg or 2400 mg dose. In O’Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding women were ineligible.
What are the main results?
In non-pregnant adults, casirivimab plus imdevimab decreases the incidence of adverse events (RR 0.74, CI 95% 0.64 to 0.86; 5842 patients in 2 studies) and serious adverse events (RR 0.34, CI 95% 0.25 to 0.48; 6622 patients in 3 studies), and probably decreases hospitalisation (RR 0.30, CI 95% 0.20 to 0.44; 4261 patients in 2 studies). We are unsure if casirivimab plus imdevimab has an impact on death, mechanical ventilation, ICU admission or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is low for the critical outcomes of death and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse events and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Taskforce notes that as of 15 October 2021, the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression.

### Table of Outcome Study results and measurements Comparator Intervention REGEN-COV Certainty of the Evidence (Quality of evidence) Plain language summary
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Placebo</th>
<th>Intervention</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.2 (CI 95% 0.04 — 1.02) Based on data from 4,057 participants in 1 studies.</td>
<td>Placebo</td>
<td>4 per 1000</td>
<td>Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies.</td>
<td>REGEN-COV</td>
<td>1 per 1000</td>
<td>3 fewer per 1000 (CI 95% 4 fewer – 0 fewer)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies.</td>
<td>Placebo</td>
<td>4 per 1000</td>
<td>Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies.</td>
<td>REGEN-COV</td>
<td>1 per 1000</td>
<td>3 fewer per 1000 (CI 95% 4 fewer – 0 fewer)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.32 (CI 95% 0.14 — 0.71) Based on data from 3,432 participants in 1 studies.</td>
<td>Placebo</td>
<td>13 per 1000</td>
<td>Relative risk 0.32 (CI 95% 0.14 — 0.71) Based on data from 3,432 participants in 1 studies.</td>
<td>REGEN-COV</td>
<td>4 per 1000</td>
<td>9 fewer per 1000 (CI 95% 11 fewer — 4 fewer)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 5,842 participants in 2 studies.</td>
<td>Placebo</td>
<td>132 per 1000</td>
<td>Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 5,842 participants in 2 studies.</td>
<td>REGEN-COV</td>
<td>98 per 1000</td>
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</tr>
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<td>Outcome Timeframe</td>
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<tr>
<td>6 Important</td>
<td>34 fewer per 1000 (CI 95% 48 fewer — 18 fewer)</td>
<td>REGEN-COV</td>
<td>Placebo</td>
<td>High</td>
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<tr>
<td>37 per 1000</td>
<td>24 fewer per 1000 (CI 95% 28 fewer — 19 fewer)</td>
<td>Placebo</td>
<td>REGEN-COV</td>
<td>Low</td>
<td>Casirivimab plus imdevimab may have little impact on serious adverse events (140 events).</td>
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</tr>
<tr>
<td>45 per 1000</td>
<td>31 fewer per 1000 (CI 95% 36 fewer — 25 fewer)</td>
<td>Placebo</td>
<td>REGEN-COV</td>
<td>Moderate</td>
<td>Casirivimab plus imdevimab probably decreases hospitalisation slightly</td>
<td></td>
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</tr>
</tbody>
</table>

2. **Imprecision: very serious.** Due to low event numbers, Only data from one study.
4. **Imprecision: very serious.** Only data from one study, due to few events.
5. Systematic review [506] with included studies: Weinreich 2021 p III. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: very serious.** Only data from one study, due to low event numbers.
10. **Imprecision: very serious.** Due to few events, Only data from one study, Wide confidence intervals.
12. **Imprecision: serious.** Majority of data comes from a single study.
Conditional recommendation

Consider using casirivimab plus imdevimab in pregnant or breastfeeding women who are **seronegative patients** hospitalised with moderate to critical COVID-19.

The Taskforce notes that the RECOVERY trial administered a single intravenous 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab in 250 ml 0.9% saline) and assessed baseline serostatus using the Oxford immunoassay, the use of which has been supported by the UK National SARS-CoV-2-Serology Assay Evaluation Group [516]. Dose adjustment is not required for pregnant or breastfeeding women.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

This is a **moderate priority** recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

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Clinical Question/ PICO

**Population:** Patients hospitalised with COVID-19  
**Intervention:** Casirivimab plus imdevimab  
**Comparator:** Standard care

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Summary

Evidence indicates a reduction in death in seronegative patients hospitalised with mild-to-critical COVID-19.

What is the evidence informing this recommendation?

Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline [510], and one randomised trial that compared casirivimab plus imdevimab with placebo in 1336 patients hospitalised with mild-to-moderate COVID-19, approximately half of whom were seronegative at baseline [628].

Publication status

Both studies are only available as preprints (posted to medRxiv on 16 June 2021 [510] and 10 November 2021 [628]) and have therefore not been peer reviewed.

Study characteristics

Median age of participants was 62 years in both studies. Women comprised 37% of participants in RECOVERY and 47% in Somersan-Karakaya et al. Within RECOVERY, patients received a single intravenously administered 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab) or standard care. Twelve children (12–18 years) were included in RECOVERY but data were not reported separately. In Somersan-Karakaya et al patients received a single intravenously administered dose of 8000 mg REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab), 2400 mg REGEN-COV (1200 mg casirivimab plus 1200 mg imdevimab) or placebo. Children were ineligible for inclusion. Pregnant and breastfeeding women were ineligible in both trials.

Both trials separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming the appropriateness of this approach. The full ICEMAN analysis can be found here.

What are the main results?

Results demonstrate that casirivimab plus imdevimab reduces death in seronegative patients (50 fewer deaths per 1000; RR 0.82, CI 95% 0.73 to 0.91; 3673 patients in 2 studies). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.
For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in RECOVERY, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in administration.

**Our confidence in the results**

In seronegative patients certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is high for all-cause mortality, and moderate for mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

Although the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression, as of 19 November 2021 it is not approved for use in hospitalised patients.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention REGEN-COV</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 0.81 (CI 95% 0.56 — 1.17) Based on data from 10,982 participants in 2 studies.</td>
<td>201 per 1000</td>
<td>163 per 1000</td>
<td>High</td>
<td>Casirivimab plus imdevimab decreases all-cause mortality</td>
</tr>
<tr>
<td>Invasive mechanical ventilation [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 1 (CI 95% 0.89 — 1.13) Based on data from 9,198 participants in 1 studies.</td>
<td>105 per 1000</td>
<td>105 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients].</td>
</tr>
<tr>
<td>Discharged from hospital [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.98 — 1.04) Based on data from 9,785 participants in 1 studies.</td>
<td>690 per 1000</td>
<td>697 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably has little impact on discharge from hospital [total].</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
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<td>Standard care</td>
<td>REGEN-COV</td>
<td>Quality of evidence</td>
</tr>
<tr>
<td>Discharged from hospital [All patients]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 95% 0.98 — 1.08) Based on data from 10,982 participants in 2 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>High</td>
</tr>
<tr>
<td>All-cause mortality [seronegative]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.64 (CI 95% 0.36 — 1.15) Based on data from 3,673 participants in 2 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate Due to serious imprecision</td>
</tr>
<tr>
<td>Invasive mechanical ventilation [seronegative]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.73 — 1.06) Based on data from 3,083 participants in 1 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate Due to serious imprecision</td>
</tr>
<tr>
<td>Discharged from hospital [seropositive]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>High</td>
</tr>
<tr>
<td>Discharged from hospital [seronegative]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.11 (CI 95% 1.06 — 1.16) Based on data from 3,673 participants in 2 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate Due to serious imprecision</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
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<tr>
<td>All-cause mortality [seropositive] Within 28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.91 – 1.12) Based on data from 7,202 participants in 2 studies.</td>
<td>163 per 1000</td>
<td>165 per 1000</td>
<td>High</td>
<td>Casirivimab plus imdevimab has little or no difference on all-cause mortality [seropositive]</td>
</tr>
<tr>
<td>Invasive mechanical ventilation [seropositive] Within 28 days of commencing treatment</td>
<td>Relative risk 1.08 (CI 95% 0.92 – 1.26) Based on data from 6,702 participants in 1 studies.</td>
<td>83 per 1000</td>
<td>90 per 1000</td>
<td>Moderate</td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seropositive patients].</td>
</tr>
<tr>
<td>Discharged from hospital [seropositive] Within 28 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.95 – 1.01) Based on data from 6,632 participants in 1 studies.</td>
<td>740 per 1000</td>
<td>725 per 1000</td>
<td>Moderate</td>
<td>Casirivimab plus imdevimab probably has little impact on discharge from hospital [seropositive patients].</td>
</tr>
<tr>
<td>Serious Adverse Events Within 28 days of commencing treatment</td>
<td>Relative risk 0.85 (CI 95% 0.71 – 1.03) Based on data from 1,410 participants in 1 studies.</td>
<td>279 per 1000</td>
<td>237 per 1000</td>
<td>Low</td>
<td>Casirivimab plus imdevimab may decrease new serious adverse events</td>
</tr>
<tr>
<td>Duration of hospital stay [All patients] Days</td>
<td>Lower better Based on data from: 9,785 participants in 1 studies.</td>
<td>10 (Median)</td>
<td>10 (Median)</td>
<td>Moderate</td>
<td>Casirivimab plus imdevimab probably has little impact on duration of hospital stay [all patients].</td>
</tr>
<tr>
<td>Duration of hospital stay [seronegative] Days</td>
<td>Lower better Based on data from: 3,153 participants in 1 studies.</td>
<td>17 (Median)</td>
<td>13 (Median)</td>
<td>Low</td>
<td>Casirivimab plus imdevimab may decrease duration of hospital stay [seronegative patients].</td>
</tr>
</tbody>
</table>
Do not use casirivimab plus imdevimab in seropositive pregnant or breastfeeding women who are hospitalised with moderate to critical COVID-19.

In patients hospitalised with moderate to critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably has little impact on mortality, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
Clinical Question/ PICO

Population: Patients hospitalised with COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Standard care

Summary
Evidence indicates a reduction in death in seronegative patients hospitalised with mild-to-critical COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline [510], and one randomised trial that compared casirivimab plus imdevimab with placebo in 1336 patients hospitalised with mild-to-moderate COVID-19, approximately half of whom were seronegative at baseline [628].

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Both trials separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming the appropriateness of this approach. The full ICEMAN analysis can be found here.

What are the main results?
Results demonstrate that casirivimab plus imdevimab reduces death in seronegative patients (50 fewer deaths per 1000; RR 0.82, CI 95% 0.73 to 0.91; 3673 patients in 2 studies). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.

For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in RECOVERY, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in administration.

Our confidence in the results
In seronegative patients certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is high for all-cause mortality, and moderate for mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Although the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease...
progression, as of 19 November 2021 it is not approved for use in hospitalised patients.

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<td>REGEN-COV</td>
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<td>Invasive mechanical ventilation [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 1 (CI 95% 0.89 – 1.13) Based on data from 9,198 participants in 1 studies. ² (Randomized controlled)</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate Due to serious imprecision ³</td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients].</td>
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<td>Discharged from hospital [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.98 – 1.04) Based on data from 9,785 participants in 1 studies. ⁴ (Randomized controlled)</td>
<td>Standard care</td>
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<td>Relative risk 0.64 (CI 95% 0.36 – 1.15) Based on data from 3,673 participants in 2 studies. ⁷ (Randomized controlled)</td>
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<td>REGEN-COV</td>
<td>Moderate</td>
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<tr>
<td>Discharged from hospital [serononegative]</td>
<td>Within 28 days of commencing treatment</td>
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<td>Discharged from hospital [seropositive]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.11 (CI 95% 1.06 — 1.16) Based on data from 3,673 participants in 2 studies. <em>(Randomized controlled)</em></td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate</td>
</tr>
<tr>
<td>All-cause mortality [seropositive]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.91 — 1.12) Based on data from 7,202 participants in 2 studies. <em>(Randomized controlled)</em></td>
<td>Standard care</td>
<td>REGEN-COV</td>
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<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.08 (CI 95% 0.92 — 1.26) Based on data from 6,702 participants in 1 studies. <em>(Randomized controlled)</em></td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

9 Critical

6 Important

4 Important

3 Important
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention REGEN-COV</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>of commencing treatment</td>
<td>studies. 17 (Randomized controlled)</td>
<td>1000 (CI 95% 37 fewer – 7 more )</td>
<td>Low Due to very serious imprecision 20</td>
<td>Casirivimab plus imdevimab may decrease new serious adverse events</td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.85 (CI 95% 0.71 – 1.03) Based on data from 1,410 participants in 1 studies. 19 (Randomized controlled)</td>
<td>279 per 1000 Difference: 237 per 1000 42 fewer per 1000 (CI 95% 81 fewer – 8 more )</td>
<td>Low Due to very serious imprecision 20</td>
<td>Casirivimab plus imdevimab may decrease new serious adverse events</td>
</tr>
<tr>
<td>Duration of hospital stay [All patients] Days</td>
<td>Lower better Based on data from: 9,785 participants in 1 studies. 21 (Randomized controlled)</td>
<td>10 (Median)</td>
<td>10 (Median) CI 95%</td>
<td>Moderate Due to serious imprecision 22</td>
<td>Casirivimab plus imdevimab probably has little impact on duration of hospital stay [all patients].</td>
</tr>
<tr>
<td>Duration of hospital stay [seronegative] Days</td>
<td>Lower better Based on data from: 3,153 participants in 1 studies. 23 (Randomized controlled)</td>
<td>17 (Median)</td>
<td>13 (Median) CI 95%</td>
<td>Low Due to very serious imprecision 24</td>
<td>Casirivimab plus imdevimab may decrease duration of hospital stay [seronegative patients].</td>
</tr>
</tbody>
</table>

3. Imprecision: serious. Only data from one study.
5. Imprecision: serious. Only data from one study.
8. Imprecision: serious. Wide confidence intervals.
10. Imprecision: serious. Only data from one study.
Baseline/comparator: Control arm of reference used for intervention.

20. Imprecision: very serious. Only data from one study, Low number of patients, Wide confidence intervals.
22. Imprecision: serious. Only data from one study.
24. Imprecision: very serious. Only data from one study, Wide confidence intervals.

6.1.2.3 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for children and adolescents

Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce
Consider using, in exceptional circumstances, casirivimab plus imdevimab within 7 days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40 kg with mild COVID-19 who are at high risk of deterioration.

In adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.

Decisions to provide casirivimab plus imdevimab to a child or adolescent should be based on the individual’s combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Included data comes from the three-phase REGEN-COV trial [509][576] in which patients with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Available research does not currently provide enough evidence to determine the benefits of casirivimab plus imdevimab in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from casirivimab plus imdevimab. Based on international cohorts [580] potential factors to consider in mild patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity (above the 95th percentile on BMI for age growth chart)

As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms.

The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised children and adolescents with mild or asymptomatic COVID-19 is not known.

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

As of 29 October 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in adult outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Clinical Question/ PICO

- **Population:** Outpatients with mild COVID-19
- **Intervention:** Casirivimab plus imdevimab
- **Comparator:** Placebo

Summary

There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 adult outpatients with mild COVID-19 [509][576] and 207 asymptomatic outpatients [635]. Two trials are linked—one presents results from the phase I-II portion [509] and the second from the phase III portion of the study [576]. The third study included asymptomatic patients who had close contacts with confirmed COVID-19.
Publication status
One study is only available as a preprint (Weinreich et al. posted to medRxiv on 12 June 2021) and has therefore not been peer reviewed.

Study characteristics
Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 2400 mg or 8000 mg REGEN-COV (1:1 casirivimab:imdevimab). The larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose, revising their protocol midway to include one 1200 mg or 2400 mg dose. In O’Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding patients were ineligible.

What are the main results?
Casirivimab plus imdevimab decreases the incidence of adverse events (RR 0.74, CI 95% 0.64 to 0.86; 5842 patients in 2 studies) and serious adverse events (RR 0.34, CI 95% 0.25 to 0.48; 6622 patients in 3 studies), and probably decreases hospitalisation (RR 0.30, CI 95% 0.20 to 0.44; 4261 patients in 2 studies). We are unsure if casirivimab plus imdevimab has an impact on death, mechanical ventilation, ICU admission or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is low for the critical outcomes of death and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse events and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Taskforce notes that as of 15 October 2021, the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICU admission</strong></td>
<td>within 28 days of commencing treatment</td>
<td>Placebo</td>
<td>REGEN-COV</td>
<td>Low</td>
<td>Casirivimab plus imdevimab may have little impact on ICU admission (27 events).</td>
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<tr>
<td></td>
<td>Relative risk 0.32 (CI 95% 0.14 — 0.71)</td>
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<tr>
<td></td>
<td>Based on data from 3,432 participants in 1 studies.</td>
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<td>6 important</td>
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<td>13 per 1000</td>
<td>4 per 1000</td>
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<td>Difference: 9 fewer per 1000 (CI 95% 11 fewer — 4 fewer)</td>
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<tr>
<td><strong>Adverse events</strong></td>
<td>end of follow-up</td>
<td>Placebo</td>
<td></td>
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<tr>
<td></td>
<td>Relative risk 0.74 (CI 95% 0.64 — 0.86)</td>
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<tr>
<td></td>
<td>Based on data from 5,842 participants in 2 studies.</td>
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<td>6 important</td>
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<td>132 per 1000</td>
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<tr>
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<td>Difference: 34 fewer per 1000 (CI 95% 48 fewer — 18 fewer)</td>
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<tr>
<td><strong>Serious adverse event</strong></td>
<td>end of follow-up</td>
<td>Placebo</td>
<td></td>
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<tr>
<td></td>
<td>Relative risk 0.34 (CI 95% 0.25 — 0.48)</td>
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<tr>
<td></td>
<td>Based on data from 6,622 participants in 3 studies.</td>
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<td>6 important</td>
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<td>37 per 1000</td>
<td>13 per 1000</td>
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<td></td>
<td>Difference: 24 fewer per 1000 (CI 95% 28 fewer — 19 fewer)</td>
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<tr>
<td><strong>Discontinuation due to adverse event</strong></td>
<td>during treatment</td>
<td>Placebo</td>
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<td></td>
<td>Based on data from 780 participants in 1 studies.</td>
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<td>6 important</td>
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<td>45 per 1000</td>
<td>14 per 1000</td>
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<tr>
<td></td>
<td>Difference: 31 fewer per 1000 (CI 95% 36 fewer — 25 fewer)</td>
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<tr>
<td><strong>Hospitalisation</strong></td>
<td>within 28 days of commencing treatment</td>
<td>Placebo</td>
<td></td>
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<tr>
<td></td>
<td>Relative risk 0.3 (CI 95% 0.2 — 0.44)</td>
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<tr>
<td></td>
<td>Based on data from 4,261 participants in 2 studies.</td>
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<td></td>
<td>6 important</td>
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<td>45 per 1000</td>
<td>14 per 1000</td>
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<tr>
<td></td>
<td>Difference: 31 fewer per 1000 (CI 95% 36 fewer — 25 fewer)</td>
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</tbody>
</table>

2. **Imprecision:** very serious. due to low event numbers. Only data from one study.
4. **Imprecision:** very serious. Only data from one study, due to few events.
5. Systematic review [506] with included studies: Weinreich 2021 pIII. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: very serious.** Only data from one study, due to low event numbers.
10. **Imprecision: very serious.** due to few events. Only data from one study, Wide confidence intervals.
12. **Imprecision: serious.** majority of data comes from a single study.

---

Only in research settings

Do not use casirivimab plus imdevimab in children under 12 years of age without risk factors for deterioration who have **mild or asymptomatic COVID-19** outside of randomised trials with appropriate ethical approval.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

---

Clinical Question/ PICO

| Population: | Children or adolescents outpatients with mild or asymptomatic COVID-19 |
| Intervention: | Casirivimab plus imdevimab |
| Comparator: | Placebo |

Summary

There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 adult outpatients with mild COVID-19 [509][576] and 207 asymptomatic outpatients [635]. Two trials are linked—one presents results from the phase I-II portion [509] and the second from the phase III portion of the study [576]. The third study included asymptomatic patients who had close contacts with confirmed COVID-19 individuals [635].

Publication status

One study is only available as a preprint (Weinreich et al. posted to medRxiv on 12 June 2021 [509]) and has therefore not been peer reviewed.

Study characteristics

Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 1200 mg or 2400 mg REGEN-COV (1:1 casirivimab:imdevimab), however the larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose. In O’Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding patients were ineligible.

What are the main results?

There were too few patients who died or required mechanical ventilation to determine whether casirivimab plus imdevimab makes a difference. Casirivimab plus imdevimab may decrease the incidence of adverse events and number of patients requiring hospitalisation slightly, and may have little impact on incidence of serious adverse
events. We are uncertain if casirivimab plus imdevimab affects the incidence of ICU admission or discontinuation of treatment due to adverse events.

Our confidence in the results
Certainty of evidence is low for the critical outcomes of all-cause mortality and mechanical ventilation due to serious risk of bias (significant loss to follow-up) and serious imprecision (few events). Certainty is low for all other outcomes due to serious risk of bias, serious imprecision and serious publication bias (commercial funding), with the exception of discontinuation due to adverse events, which is very low certainty (due to very serious imprecision and serious publication bias).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As of 25 June 2021, REGN-COV2 (casirivimab plus imdevimab) is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 3.07 (CI 95% 0.87 — 10.85) Based on data from 5,347 participants in 2 studies.¹ (Randomized controlled)</td>
<td>1 per 1000</td>
<td>3 per 1000</td>
<td>Very low Due to serious risk of bias and serious imprecision, Due to serious indirectness ²</td>
<td>Casirivimab plus imdevimab may have little impact on death (10 events).</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies.³ (Randomized controlled)</td>
<td>4 per 1000</td>
<td>1 per 1000</td>
<td>Very low Due to serious risk of bias and serious imprecision, Due to very serious indirectness ⁴</td>
<td>Casirivimab plus imdevimab may have little impact on mechanical ventilation (8 events).</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.32 (CI 95% 0.14 — 0.71) Based on data from 3,432 participants in 1 studies.⁵ (Randomized controlled)</td>
<td>13 per 1000</td>
<td>4 per 1000</td>
<td>Very low Due to serious risk of bias and serious imprecision, Due to serious indirectness ⁶</td>
<td>Casirivimab plus imdevimab may have little impact on ICU admission (27 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 5,842 participants in 2 studies.⁷ (Randomized controlled)</td>
<td>132 per 1000</td>
<td>98 per 1000</td>
<td>Very low Due to serious risk of bias and serious publication bias, Due to serious indirectness ⁸</td>
<td>We are uncertain whether regen-cov improves or worsen adverse events</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td>Serious adverse event</td>
<td>Relative risk 0.34 (CI 95% 0.25 – 0.48) Based on data from 6,622 participants in 3 studies. (Randomized controlled)</td>
<td>Placebo</td>
<td>REGEN-COV</td>
<td>Very low Due to serious risk of bias and serious publication bias, Due to serious indirectness</td>
<td>Casirivimab plus imdevimab may have little impact on serious adverse events (140 events).</td>
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<tr>
<td>End of follow-up</td>
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<tr>
<td>Discontinuation due to</td>
<td>Based on data from 780</td>
<td>Control arm of reference used for intervention.</td>
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<tr>
<td>adverse event</td>
<td>participants in 1 study.</td>
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<tr>
<td>During treatment</td>
<td>(Randomized controlled)</td>
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<tr>
<td>Hospitalisation</td>
<td>Relative risk 0.3 (CI 95% 0.2 – 0.45) Based on data from 4,057 participants in 1 studies. (Randomized controlled)</td>
<td>Placebo</td>
<td>REGEN-COV</td>
<td>Very low Due to very serious imprecision and serious publication bias</td>
<td>We are uncertain whether casirivimab plus imdevimab increases or decreases discontinuation due to adverse events (1 event).</td>
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<tr>
<td>Within 28 days of</td>
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<tr>
<td>commencing treatment</td>
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</table>

2. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study, due to few events.
4. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Indirectness:** very serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study, due to few events.
5. Systematic review [506] with included studies: Weinreich 2021 p III. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
8. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Indirectness:** serious. Differences between the population of interest and those studied. **Publication bias:** serious. Mostly commercially funded studies.
10. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Indirectness:** serious. Differences between the population of interest and those studied. **Publication bias:** serious. Mostly commercially funded studies.
11. Systematic review [506] with included studies: Weinreich 2021 p I-II. **Baseline/comparator:** Control arm of
Consensus recommendation

Consider using, in exceptional circumstances, casirivimab plus imdevimab in seronegative children and adolescents aged 12 years and over and weighing at least 40 kg with moderate to critical COVID-19 who are at high risk of disease progression.

In adult patients hospitalised with moderate to critical COVID-19 who are seronegative (no detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably reduces the risk of death. The Taskforce notes that the RECOVERY trial administered a single intravenous 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab in 250 ml 0.9% saline) and assessed baseline serostatus using the Oxford immunoassay, the use of which has been supported by the UK National SARS-CoV-2-Serology Assay Evaluation Group [516]. No children or adolescents were included in this trial.

Available research does not currently provide enough evidence to determine the benefits of casirivimab plus imdevimab in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from casirivimab plus imdevimab. Based on international cohorts [580] potential factors to consider in moderate patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Practical Info

Following the US FDA Emergency Use Authorisation, the dosage in adult and paediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset [583].
Not recommended

Do not use casirivimab plus imdevimab in seropositive children and adolescents hospitalised with moderate to critical COVID-19.

In patients hospitalised with moderate to critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably has little impact on mortality, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Clinical Question/ PICO

Population: Children or adolescents hospitalised with moderate to critical COVID-19

Intervention: Casirivimab plus imdevimab

Comparator: Standard care

Summary

Evidence indicates a probable reduction in death in seronegative patients hospitalised with moderate-to-critical COVID-19.

What is the evidence informing this recommendation?

Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline [510].

Publication status

The study is only available as a preprint (posted to medRxiv on 16 June 2021) and has therefore not been peer reviewed.

Study characteristics

Median age of participants was 62 years and 37% were women (63 years and ~40% women in the seronegative cohort). Patients received a single intravenously administered 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab) or placebo. Pregnant and breastfeeding women were ineligible. Twelve children (12–18 years) were included in the trial but data were not reported separately.

The RECOVERY trial separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming that the appropriateness of this approach. The full ICEMAN analysis can be found here.

What are the main results?

Results demonstrate that casirivimab plus imdevimab probably reduces death in seronegative patients (53 fewer deaths per 1000; RR 0.82, CI 95% 0.73 to 0.92; 3153 patients from 1 study). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.

For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in the RECOVERY trial, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in administration.

Our confidence in the results
In seronegative patients certainty of the evidence is moderate for all-cause mortality and mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is moderate for all-cause mortality, mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As of 24 June 2021, REGEN-COV (casirivimab plus imdevimab) is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 0.94 (CI 95% 0.87 — 1.02) Based on data from 9,785 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Low Due to serious imprecision, Due to serious indirectness</td>
<td>Casirivimab plus imdevimab probably has little impact on death [all patients].</td>
</tr>
<tr>
<td>Invasive mechanical ventilation [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 1 (CI 95% 0.89 — 1.13) Based on data from 9,198 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious imprecision, Due to serious indirectness</td>
<td>Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients].</td>
</tr>
<tr>
<td>Discharged from hospital [All patients] Within 28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.98 — 1.04) Based on data from 9,785 participants in 1 studies. (Randomized controlled)</td>
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<td></td>
<td>Low Due to serious imprecision, Due to serious indirectness</td>
<td>Casirivimab plus imdevimab probably has little impact on discharge from hospital [total]</td>
</tr>
<tr>
<td>All-cause mortality [seronegative] Within 28 days of commencing treatment</td>
<td>Relative risk 0.82 (CI 95% 0.73 — 0.92) Based on data from 3,153 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious imprecision, Due to serious indirectness</td>
<td>Casirivimab plus imdevimab may reduce death [seronegative patients].</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
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<tr>
<td><strong>Invasive mechanical ventilation</strong></td>
<td><strong>seronegative</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.73 — 1.06) Based on data from 3,083 participants in 1 studies. 7 (Randomized controlled)</td>
<td>135 per 1000</td>
<td>119 per 1000</td>
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<tr>
<td><strong>Discharged from hospital</strong></td>
<td><strong>seronegative</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.11 (CI 95% 1.05 — 1.17) Based on data from 3,153 participants in 1 studies. 11 (Randomized controlled)</td>
<td>578 per 1000</td>
<td>642 per 1000</td>
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<tr>
<td><strong>All-cause mortality</strong></td>
<td><strong>seropositive</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.92 — 1.13) Based on data from 6,632 participants in 1 studies. 13 (Randomized controlled)</td>
<td>168 per 1000</td>
<td>171 per 1000</td>
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<tr>
<td><strong>Invasive mechanical ventilation</strong></td>
<td><strong>seropositive</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.08 (CI 95% 0.92 — 1.26) Based on data from 6,702 participants in 1 studies. 15 (Randomized controlled)</td>
<td>83 per 1000</td>
<td>90 per 1000</td>
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<tr>
<td><strong>Discharged from hospital</strong></td>
<td><strong>seropositive</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. 17 (Randomized controlled)</td>
<td>740 per 1000</td>
<td>725 per 1000</td>
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<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td>Duration of hospital stay [All patients] Days</td>
<td>Lower better based on data from: 9,785 participants in 1 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Low Due to serious imprecision, Due to serious indirectness</td>
<td>Casirivimab plus imdevimab probably has little impact on duration of hospital stay [all patients].</td>
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<tr>
<td>6 Important</td>
<td></td>
<td>10 (Median)</td>
<td>10 (Median) CI 95%</td>
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</tr>
<tr>
<td>Duration of hospital stay [seronegative] Days</td>
<td>Lower better based on data from: 3,153 participants in 1 studies.</td>
<td>Standard care</td>
<td>REGEN-COV</td>
<td>Very low Due to very serious imprecision, Due to serious indirectness</td>
<td>We are uncertain whether regen-cov improves or worsens duration of hospital stay [seronegative]</td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td>17 (Median)</td>
<td>13 (Median) CI 95%</td>
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</table>

2. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
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6. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
7. Systematic review [504] with included studies: RECOVERY 2021 seronegative. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
10. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
12. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, Wide confidence intervals.
14. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
15. Systematic review [504] with included studies: RECOVERY 2021 seropositive. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
17. Systematic review [504] with included studies: RECOVERY 2021 seropositive. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
19. Systematic review [504]. **Baseline/comparator:** Control arm of reference used for intervention.
6.1.3 Molnupiravir (Lagevrio)

The Taskforce notes the publication in the NEJM on 16 Dec 2021 from the MOVe-OUT Study Group that compared molnupiravir with placebo in 1433 non-hospitalised, unvaccinated adults with mild-to-moderate, laboratory-confirmed COVID-19 and at least one risk factor for severe COVID-19 illness. This study is under review by the Taskforce and a recommendation will be published in early 2022.

20. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
21. Systematic review [504]. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, Wide confidence intervals.
Consider using molnupirvir within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression, where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

Within the patient population for which molnupirvir is recommended for use (see Remark), decisions about the appropriateness of treatment with molnupirvir should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

* Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of molnupirvir is unclear in partially or fully vaccinated individuals. Additional recommendations for other patient groups are currently under development and will be included in a future version of the guideline.

Based on available data, molnupirvir may reduce hospitalisation or death in individuals with PCR-confirmed COVID-19 and mild illness when treated within 5 days of onset of symptoms, however the evidence is limited, effect sizes are small and there are limited safety data. Until further evidence is available, use of molnupirvir should only be considered where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

The Taskforce notes the high level of efficacy in reduction of the composite outcome of hospitalisation or death observed within the interim analysis (n=762; 68 fewer per 1000) and the subsequent reduction in efficacy within the final analysis (n=1408; 29 fewer per 1000) [643]. It is unclear whether or to what extent the significant proportional increase in patients infected with the Delta variant between the interim and final analyses contributes to the observed reduction in efficacy. The efficacy of molnupirvir against the Omicron variant is not known.

Results are based on a single trial in which non-vaccinated adults were treated with 800 mg of molnupirvir twice daily for 5 days. Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- Age ≥ 60 years
- Obesity (BMI ≥ 30 kg/m²)
- Chronic kidney disease (eGFR 30 - 60 mL/min/1.73m² by MDRD), excluding patients on dialysis
- Serious heart conditions such as heart failure, coronary artery disease or cardiomyopathies
- Chronic obstructive pulmonary disease
- Active cancer (excluding minor cancers not associated with immunosuppression, e.g. basal cell carcinomas)
- Immunocompromised state following solid organ transplant
- Sickle cell disease
- Diabetes mellitus

Pregnant & breastfeeding women and children & adolescents were not included in the trial. There are no clinical data for the use of molnupirvir in pregnant women, however animal reproductive studies indicate that molnupirvir may have embryolethal and teratogenic effects at high doses and may result in reduced fetal growth.

Contraception is recommended until 4 days after the final dose of molnupirvir in sexually active women of childbearing potential, and for 3 months in men who are sexually active with a partner of childbearing potential (TGA PI).

The efficacy of molnupirvir in vaccinated or immunocompromised patients is unknown.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.
Certainty of the Evidence

Certainty of the evidence is moderate for the composite outcome of hospitalisation or death, adverse events and serious adverse events (due to reliance on a single study) and low for all-cause mortality and discontinuation due to adverse events (due to reliance on a single study and few events). Certainty is low or very low for all subgroup analyses focused on SARS-CoV-2 variant.

Preference and values

We have no systematically collected information regarding patients' preferences and values.

Pregnant or breastfeeding patients

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Although there is uncertainty regarding the benefit to harm ratio for women and their babies, evidence demonstrates embryolethality and reduced fetal growth in rats when administered at seven and three times the therapeutic dose. As such, the panel believes most women would not opt for treatment.

Children and adolescents

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations

The limited availability of molnupiravir, as well as the cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of molnupiravir may affect equity based on geographic area and access to molnupiravir.

Acceptability

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

Feasibility

Oral molnupiravir (Lagevrio; Merck Sharp & Dohme) was granted provisional approval by the Therapeutic Goods Administration on 18 January 2022 for the treatment of COVID-19 under the Black Triangle Scheme.

Implementability could be affected by limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

General adult population

In adult outpatients with mild COVID-19, molnupiravir probably reduces the risk of hospitalisation or death slightly. Because of this, the Taskforce gives a consensus recommendation for molnupiravir both within and outside a randomised trial, only where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.
Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Molnupiravir
Comparator: Placebo

Summary
Evidence indicates that molnupiravir probably reduces the incidence of hospitalisation or death in adults with mild to moderate COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from a single clinical study report (MOVe-OUT) that compared molnupiravir with placebo in 1433 adult outpatients with mild to moderate COVID-19 [643]. Participants were randomised within five days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics
Median age of participants was 43 years and 51% were women. Two-thirds of participants were aged 18 to 49 years. Participants received four 200 mg tablets of molnupiravir or placebo twice daily for five days. Pregnant & breastfeeding women and children & adolescents were ineligible.

What are the main results?
Molnupiravir probably reduces the incidence of hospitalisation or death slightly (RR 0.70, CI 95% 0.49 to 0.99; 1408 patients in 1 study). Molnupiravir probably has little impact on incidence of adverse or serious adverse events, and may have little impact on discontinuation due to adverse events. We are unsure if molnupiravir has an impact on mortality.

Our confidence in the results
Certainty of the evidence is moderate for the composite outcome of hospitalisation or death, adverse events and serious adverse events (due to reliance on a single study) and low for all-cause mortality and discontinuation due to adverse events (due to reliance on a single study and few events). Certainty is low or very low for all subgroup analyses focused on SARS-CoV-2 variant.

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration provisionally approved the use of molnupiravir (Lagevrio) for the treatment of COVID-19 on 18 January 2022.

<table>
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<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Placebo</th>
<th>Intervention Molnupiravir</th>
<th>Certainty of Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 29 days of commencing treatment</td>
<td>Relative risk 0.11 (CI 95% 0.01 – 0.86) Based on data from 1,408 participants in 1 study. ¹ (Randomized controlled)</td>
<td>13 per 1000</td>
<td>1 per 1000</td>
<td>Low Due to very serious imprecision ²</td>
</tr>
<tr>
<td>All-cause mortality or hospitalisation [FINAL]</td>
<td>Within 29 days of commencing treatment</td>
<td>Relative risk 0.7 (CI 95% 0.49 – 0.99) Based on data from 1,408 participants in 1 study. ³ (Randomized controlled)</td>
<td>97 per 1000</td>
<td>68 per 1000</td>
<td>Moderate Due to serious imprecision ⁴</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
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<tr>
<td><strong>treatment</strong></td>
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<td>141 per 1000 fewer — 1 fewer)</td>
<td><strong>Moderate</strong> Due to serious imprecision</td>
<td>Molnupiravir probably reduces all-cause mortality or hospitalisation [interim] (81 events)</td>
</tr>
<tr>
<td><strong>All-cause mortality or hospitalisation [INTERIM]</strong></td>
<td>Relative risk 0.52 (CI 95% 0.33 — 0.8) Based on data from 762 participants in 1 studies. 5 (Randomized controlled)</td>
<td>73 per 1000</td>
<td>Difference: 68 fewer per 1000 ( CI 95% 94 fewer — 28 fewer )</td>
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<tr>
<td><strong>Mortality or hospitalisation [DELTA]</strong></td>
<td>Relative risk 0.76 (CI 95% 0.42 — 1.38) Based on data from 458 participants in 1 studies. 7 (Randomized controlled)</td>
<td>100 per 1000</td>
<td>Difference: 24 fewer per 1000 ( CI 95% 58 fewer — 38 more )</td>
<td><strong>Low</strong> Due to very serious imprecision</td>
<td>Molnupiravir may have little impact on mortality or hospitalisation [Delta variant] (40 events).</td>
</tr>
<tr>
<td><strong>Mortality or hospitalisation [GAMMA]</strong></td>
<td>Relative risk 0.07 (CI 95% 0 — 1.11) Based on data from 64 participants in 1 studies. 9 (Randomized controlled)</td>
<td>191 per 1000</td>
<td>Difference: 178 fewer per 1000 ( CI 95% 191 fewer — 21 more )</td>
<td><strong>Very low</strong> Due to extremely serious imprecision</td>
<td>We are uncertain whether molnupiravir increases or decreases mortality or hospitalisation [Gamma variant] (9 events).</td>
</tr>
<tr>
<td><strong>Mortality or hospitalisation [MU]</strong></td>
<td>Relative risk 0.5 (CI 95% 0.2 — 1.26) Based on data from 157 participants in 1 studies. 11 (Randomized controlled)</td>
<td>159 per 1000</td>
<td>Difference: 80 fewer per 1000 ( CI 95% 127 fewer — 41 more )</td>
<td><strong>Very low</strong> Due to extremely serious imprecision</td>
<td>We are uncertain whether molnupiravir increases or decreases mortality or hospitalisation [Mu variant] (19 events).</td>
</tr>
<tr>
<td><strong>Mortality or hospitalisation [OTHER]</strong></td>
<td>Relative risk 0.58 (CI 95% 0.2 — 1.68) Based on data from 85 participants in 1 studies. 13 (Randomized controlled)</td>
<td>184 per 1000</td>
<td>Difference: 77 fewer per 1000 ( CI 95% 147 fewer — 125 more )</td>
<td><strong>Very low</strong> Due to extremely serious imprecision</td>
<td>We are uncertain whether molnupiravir increases or decreases mortality or hospitalisation [other variants] (12 events).</td>
</tr>
<tr>
<td>Outcome</td>
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<td>Study results and measurements</td>
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<td></td>
<td>Placebo</td>
<td>Molnupiravir</td>
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<tr>
<td>Mortality or hospitalisation</td>
<td>Within 29 days of commencing treatment</td>
<td>Relative risk 1.18 (CI 95% 0.62 — 2.25) Based on data from 624 participants in 1 studies.</td>
<td>51 per 1000</td>
<td>60 per 1000</td>
<td>Low Due to very serious imprecision</td>
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<tr>
<td>Adverse events</td>
<td>Within 29 days of commencing treatment</td>
<td>Relative risk 0.92 (CI 95% 0.79 — 1.08) Based on data from 1,411 participants in 1 studies.</td>
<td>330 per 1000</td>
<td>304 per 1000</td>
<td>Moderate Due to serious imprecision</td>
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<tr>
<td>Serious adverse events</td>
<td>Within 29 days of commencing treatment</td>
<td>Relative risk 0.72 (CI 95% 0.51 — 1.03) Based on data from 1,411 participants in 1 studies.</td>
<td>96 per 1000</td>
<td>69 per 1000</td>
<td>Moderate Due to serious imprecision</td>
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<tr>
<td>Discontinuation due to AEs</td>
<td>Within 29 days of commencing treatment</td>
<td>Relative risk 0.49 (CI 95% 0.23 — 1.05) Based on data from 1,411 participants in 1 studies.</td>
<td>29 per 1000</td>
<td>14 per 1000</td>
<td>Low Due to very serious imprecision</td>
</tr>
</tbody>
</table>

2. **Imprecision:** very serious. Only data from one study, due to few events.
4. **Imprecision:** serious. Only data from one study.
6. **Imprecision:** serious. Only data from one study.
8. **Imprecision:** very serious. Only data from one study, Low number of patients.
10. **Imprecision:** extreme serious. Only data from one study, Low number of patients, Wide confidence intervals, due to few events.
11. Systematic review [636] with included studies: Bernal 2021. **Baseline/comparator:** Control arm of reference used...
for intervention.

12. **Imprecision: ~extreme_serious.** Only data from one study, Low number of patients, due to few events, Wide confidence intervals.


14. **Imprecision: ~extreme_serious.** Only data from one study, due to few events, Wide confidence intervals, Low number of patients.


16. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.


18. **Imprecision: serious.** Only data from one study.


20. **Imprecision: serious.** Only data from one study.


22. **Imprecision: very serious.** due to few events, Only data from one study.

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**Consensus recommendation**

In addition to at-risk unvaccinated adults, also consider using molnupiravir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunosuppressed or not immunocompetent regardless of vaccination status; or
- have received one or two doses of vaccine and who are at high risk of severe disease on the basis of age and multiple risk factors

**AND** where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

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Available research does not currently provide enough evidence to determine the benefits of molnupiravir in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from molnupiravir.

*There is no evidence evaluating the effectiveness of molnupiravir in partially or fully vaccinated patients. Given this, and the lower risk of deterioration in these patients, it is unlikely that molnupiravir will have a significant treatment benefit in patients who have received three doses of vaccine, unless the patient is immunosuppressed.*

*There is limited evidence on the effectiveness of molnupiravir in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that molnupiravir will be beneficial for immunosuppressed patients.*

**Immunocompromising conditions include:**

- **Primary or acquired immunodeficiency**
  - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
  - Other significantly immunocompromising conditions

- **Immunosuppressive therapy (current or recent)**
  - Chemotherapy, whole body radiotherapy or total lymphoid irradiation
  - High-dose corticosteroids ($\geq 20$ mg of prednisone per day, or equivalent) for $\geq 14$ days
  - All biological disease-modifying anti-rheumatic drugs (DMARDs) and most other (e.g. conventional synthetic) DMARDs [550]
Given the limited evidence of benefit or safety, small effect sizes and absence of evidence evaluating the effectiveness of molnupiravir for SARS-CoV-2 variants of concern, rigorous data collection should be undertaken on indications and key outcomes for patients who receive treatment with molnupiravir.

6.1.4 Nirmatrelvir plus ritonavir (Paxlovid)
Consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in unvaccinated adults* with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which nirmatrelvir plus ritonavir is conditionally recommended for use (see Remark), decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the patient’s individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

* Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of nirmatrelvir plus ritonavir is unclear in partially or fully vaccinated individuals. See consensus recommendation for guidance on use of nirmatrelvir plus ritonavir in vaccinated patients or in immunocompromised patients regardless of vaccination status.

In patients with confirmed COVID-19 who do not require oxygen, nirmatrelvir plus ritonavir probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on a single phase 2/3 trial comparing nirmatrelvir plus ritonavir with placebo in 1219 unvaccinated adults with PCR-confirmed COVID-19 and mild illness. Within this trial participants were treated with oral nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days.

The benefit of nirmatrelvir plus ritonavir is likely to be greatest in those with the greatest risk of severe disease. Based on the population included within the trial, evidence demonstrates a reduction in hospitalisation when used in individuals with one or more of the following risk factors for disease progression:

- Age ≥ 60 years
- Diabetes (requiring medication)
- BMI ≥ 25 kg/m2
- Cardiovascular disease
- Hypertension
- Chronic lung disease
- Chronic kidney disease (but where the eGFR ≥ 30 mL/min)*
- Immunosuppressed (e.g. bone marrow or organ transplantation, primary immune deficiencies, prolonged use of immune-weakening medications)
- Medical related technological dependence (e.g. CPAP not related to COVID-19)
- HIV positive (viral load < 400 copies/mL)
- Neurodevelopmental disorders (e.g. cerebral palsy, Down syndrome)
- Cancer (other than localised skin cancer)
- Sickle cell disease

* Individuals with an eGFR < 30 mL/min were excluded from the trial. In individuals with CKD and an eGFR of 30-60 mL/min, the dose of nirmatrelvir should be halved; i.e. nirmatrelvir/ritonavir 150/100 mg twice daily for 5 days (FDA EUA).

Pregnant & breastfeeding women and children & adolescents were not included in the trial.

Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of nirmatrelvir plus ritonavir is unclear in partially or fully vaccinated individuals.

The study was conducted before the Omicron variant was prevalent. As a result, there are no data regarding the effectiveness of nirmatrelvir plus ritonavir specific to the Omicron variant.

Ritonavir is an inhibitor, inducer and substrate of many enzymes and transporters involved in drug disposition and metabolism. It is a strong inhibitor of CYP3A, reducing the hepatic metabolism and increasing the concentration of nirmatrelvir and other CYP3A substrates. Coadministration of nirmatrelvir-ritonavir is contraindicated with drugs that are highly dependent upon CYP3A for clearance where an elevated concentration may be dangerous (e.g. anti-arrhythmics, antipsychotics, statins, anti-inflammatoryatories, anti-cancer drugs and anticoagulants. Coadministration is also contraindicated with potent CYP3A inducers (e.g. anti-epileptics, rifampin, St John’s wort), which can reduce concentrations of nirmatrelvir and/or ritonavir, reducing efficacy and increasing resistance. Induction persists many days after cessation due to time required for clearance of the inducing drug and of the induced CYP3A.
Evidence demonstrates a likely weak interaction between nirmatrelvir-ritonavir and budesonide, resulting in increased budesonide concentrations. There are no other expected interactions between nirmatrelvir-ritonavir and other therapeutics currently recommended for the treatment of COVID-19 within the Taskforce guidelines. It is crucial that consideration is given to the potential for complex, serious drug-drug interactions when prescribing and administering nirmatrelvir plus ritonavir with other medications (see Liverpool interaction checker and TGA PI).

As of 28 January 2022, the Taskforce has made conditional recommendations supporting the use of nirmatrelvir plus ritonavir, sotrovimab, and casirivimab plus imdevimab in adult outpatients with mild COVID-19. The relative effectiveness of these agents, or the effectiveness of these agents when used in combination, is unclear.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Nirmatrelvir plus ritonavir probably decreases the incidence of hospitalisation and serious adverse events and has little impact on incidence of adverse events and discontinuation due to adverse events. We are unsure if nirmatrelvir plus ritonavir has an impact on mortality.

Certainty of the Evidence

Certainty of the evidence is moderate for the composite outcomes of hospitalisation or death, hospitalisation, adverse or serious adverse events, and discontinuation due to adverse events (reliance on a single study). Certainty is low for all-cause mortality (reliance on a single study and few events).

Preference and values

We have no systematically collected information regarding patients' preferences and values.

Pregnant or breastfeeding patients

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Children and adolescents

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations

The limited availability of nirmatrelvir plus ritonavir, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of nirmatrelvir plus ritonavir may affect equity based on geographic area and access to nirmatrelvir plus ritonavir.
Acceptability

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

Feasibility

Oral nirmatrelvir plus ritonavir (Paxlovid; Pfizer Australia Pty Ltd) was granted provisional approval by the Therapeutic Goods Administration on 18 January 2022 for the treatment of COVID-19 under the Black Triangle Scheme (ARTG number: 377572).

Implementability could be affected by limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

General adult population

In adult outpatients with mild COVID-19, nirmatrelvir plus ritonavir probably reduces the risk of hospitalisation. Because of this, the Taskforce gives a conditional recommendation for nirmatrelvir plus ritonavir both within and outside a randomised trial.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Nirmatrelvir plus ritonavir
Comparator: Placebo

Summary

Evidence indicates that nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation or death in adults with mild to moderate COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?

Evidence comes from a single clinical study report that compared nirmatrelvir plus ritonavir (Paxlovid) with placebo in 1361 adult outpatients with mild to moderate COVID-19. Participants were randomised within five days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics

Mean age of participants was 45 years and 48% were women. Approximately half the patients were aged between 18 and 44 years (51%), 9% were aged 65–74 years, and 3% were aged over 70 years. Participants received three 100 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir twice daily for five days. Pregnant & breastfeeding women and children & adolescents were ineligible.

What are the main results?

Nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation or death (RR 0.15, CI 95% 0.06 to 0.34; 1219 patients in 1 study) and incidence of serious adverse events (RR 0.28, CI 95% 0.16 to 0.52; 1349 patients in 1 study). Nirmatrelvir plus ritonavir probably has little impact on incidence of adverse events or discontinuation due to adverse events. We are unsure if nirmatrelvir plus ritonavir impacts all-cause mortality.

Our confidence in the results

Certainty of the evidence is moderate for the composite outcomes of hospitalisation or death, hospitalisation, adverse or serious adverse events, and discontinuation due to adverse events (reliance on a single study). Certainty is low for all-cause mortality (reliance on a single study and few events).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information

The Therapeutic Goods Administration provisionally approved the use of nirmatrelvir plus ritonavir (Paxlovid) for the treatment of COVID-19 on 18 January 2022.

Important issues, or potential issues not investigated
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation or death</td>
<td>Day 28, ≤ 5 days symptom onset</td>
<td>Relative risk 0.15 (CI 95% 0.06 — 0.34) Based on data from 1,219 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>Placebo</td>
<td>Paxlovid</td>
<td>Moderate</td>
<td>Paxlovid probably decreases hospitalisation or death (47 events).</td>
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<td>67 per 1000</td>
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<td>Difference: 57 fewer per 1000 (CI 95% 63 fewer — 44 fewer)</td>
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<tr>
<td>All-cause mortality</td>
<td>Day 28, ≤ 5 days symptom onset</td>
<td>Relative risk 0.05 (CI 95% 0 — 0.82) Based on data from 1,219 participants in 1 studies. ² (Randomized controlled)</td>
<td>Placebo</td>
<td>Paxlovid</td>
<td>Low</td>
<td>Paxlovid may decrease all-cause mortality slightly (10 events).</td>
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<td>16 per 1000</td>
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<td>Difference: 15 fewer per 1000 (CI 95% 16 fewer — 3 fewer)</td>
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<tr>
<td>Hospitalisation</td>
<td>Day 28, ≤ 5 days symptom onset</td>
<td>Relative risk 0.15 (CI 95% 0.06 — 0.34) Based on data from 1,219 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Placebo</td>
<td>Paxlovid</td>
<td>Moderate</td>
<td>Paxlovid probably decreases hospitalisation (47 events).</td>
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<td>Difference: 57 fewer per 1000 (CI 95% 63 fewer — 44 fewer)</td>
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<tr>
<td>Adverse events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.89 (CI 95% 0.72 — 1.09) Based on data from 1,349 participants in 1 studies. ⁴ (Randomized controlled)</td>
<td>Placebo</td>
<td>Paxlovid</td>
<td>Moderate</td>
<td>Paxlovid probably has little impact on adverse events (284 events).</td>
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<td>223 per 1000</td>
<td>198 per 1000</td>
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<td>Difference: 25 fewer per 1000 (CI 95% 62 fewer — 20 more)</td>
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<tr>
<td>Serious adverse events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.28 (CI 95% 0.16 — 0.52) Based on data from 1,349 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td>Placebo</td>
<td>Paxlovid</td>
<td>Moderate</td>
<td>Paxlovid probably decreases serious adverse events slightly (59 events).</td>
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<td>68 per 1000</td>
<td>19 per 1000</td>
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<td>Difference: 49 fewer per 1000 (CI 95% 57 fewer — 33 fewer)</td>
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<tr>
<td>Discontinuation due to adverse events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.56 (CI 95% 0.3 — 1.01) Based on data from 1,361 participants in 1 studies. ⁶ (Randomized controlled)</td>
<td>Placebo</td>
<td>Paxlovid</td>
<td>Moderate</td>
<td>Paxlovid probably has little impact on discontinuation due to adverse events (45 events).</td>
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<td>42 per 1000</td>
<td>24 per 1000</td>
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<td>Difference: 18 fewer per 1000 (CI 95% 29 fewer — 0 fewer)</td>
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</table>
2. **Imprecision:** Serious. Only data from one study.
4. **Imprecision:** Very serious. Only data from one study, due to few events.
6. **Imprecision:** Serious. Only data from one study.
7. Systematic review [634] with included studies: Paxlovid interim CSR 12-21. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision:** Serious. Only data from one study.
10. **Imprecision:** Serious. Only data from one study.
12. **Imprecision:** Serious. Only data from one study.

**Consensus recommendation**

In addition to at-risk unvaccinated adults, also consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunosuppressed or not immunocompetent regardless of vaccination status; or
- have received one or two doses of vaccine and who are at high risk of severe disease on the basis of age and multiple risk factors.

The available research does not currently provide enough evidence to determine the benefits of nirmatrelvir plus ritonavir in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from nirmatrelvir plus ritonavir.

There is no evidence evaluating the effectiveness of nirmatrelvir plus ritonavir in partially or fully vaccinated patients. Given this and the lower risk of deterioration in these patients, it is unlikely that nirmatrelvir plus ritonavir will be particularly valuable in patients who have received three doses of vaccine, unless the patient is immunosuppressed.

There is limited evidence on the effectiveness of nirmatrelvir plus ritonavir in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that nirmatrelvir plus ritonavir will be beneficial for immunosuppressed patients.

**Immunocompromising conditions include:**

- **Primary or acquired immunodeficiency**
  - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - Immunosuppressed due to primary or acquired (HIV/AIDS) immunodeficiency
  - Other significantly immunocompromising conditions

- **Immunosuppressive therapy (current or recent)**
  - Chemotherapy, whole body radiotherapy or total lymphoid irradiation
  - High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - All biological disease-modifying anti-rheumatic drugs (DMARDs) and most other (e.g. conventional synthetic) DMARDs [550]
6.1.5 Systemic corticosteroids

6.1.5.1 Corticosteroids for adults

Use dexamethasone 6 mg daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days
- prednisolone: oral (50 mg), daily for up to 10 days
- methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain

It is unclear whether older people living with frailty or cognitive impairment, or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

In patients receiving oxygen or invasive mechanical ventilation, death is reduced with corticosteroids. Although indirect evidence suggests that corticosteroids may increase the risk of hyperglycaemia, the panel believes the mortality benefit outweighs any potential harms associated with corticosteroid use.

Older people living with frailty or cognitive impairment

People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

People requiring palliative care

In addition to the concerns in the general adult population, there is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

Certainty of the Evidence

In patients with severe or critical illness, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect), mechanical ventilation or death and discharge from hospital (due to serious imprecision).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Preference and values

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that since there are mortality benefits most informed patients would agree with the recommendation and opt for corticosteroids.
People requiring palliative care and older people living with frailty or cognitive impairment
Additional variability may be expected in these populations given the potentially different preferences and values placed on outcomes and goals of care, such as symptom relief.

Resources and other considerations
Corticosteroids are widely available and affordable. Use of corticosteroids in adults with COVID-19 who are receiving supplementary oxygen or invasive ventilation is unlikely to have an impact on availability of these drugs for other indications.

Equity
We have no systematically collected evidence regarding impact on equity. Since corticosteroids are widely available and affordable, no negative impact is expected.

Acceptability
Although we have no systematically collected evidence regarding acceptability, corticosteroids are likely to be acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Acceptability may vary in these populations due to individual decision-making around goals of care.

Feasibility
Intravenous dexamethasone (Pfizer Australia Pty Ltd; Alphapharm Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers 178774, 16374, 163200; [AusPAR]). As of 3 December 2021, dexamethasone is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Corticosteroids are likely to be feasible because they are already widely used for other indications. There are no known issues with availability of these drugs.

Rationale
Due to a reduction in death, along with no important resource implications and the likely acceptability of these drugs, we recommend corticosteroids for adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Clinical Question/ PICO
Population: Patients with COVID-19
Intervention: Corticosteroids
Comparator: Standard care

Summary
Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.
What is the evidence informing this recommendation?

Evidence comes from a meta-analysis and associated living guidance [27] of seven randomised trials of patients with critical COVID-19 [31][32][33][34][36][37][500], one study of patients with moderate, severe or critical COVID-19 [38], and one study of patients with severe COVID-19 [39]. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress [28] and sepsis [29]—provided indirect evidence for serious adverse events.

We have found three new studies comparing corticosteroids with standard care (Corral-Gudino et al. (GLUCOCOVID) Wien Klin Wochenschr doi: 10.1007/s00508-020-01805-8, Tang et al. Respiration doi: 10.1159/000512063 and Jamaati et al. Eur J Pharmacol doi: 10.1016/j.ejphar.2021.173947). These studies are currently under review and, although not expected to change the recommendation, an updated recommendation will be included in a future version of the guideline.

Study characteristics

Three studies compared dexamethasone with standard care [34][36][38], three compared hydrocortisone with standard care [31][33][500] and three compared methylprednisolone with standard care [32][37][39].

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?

Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications possibly shows no difference in the incidence of gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was probably associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results

In patients with severe or critical illness, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect) and invasive mechanical ventilation or death, and discharge from hospital (due to serious imprecision).

In patients with moderate illness, certainty is low for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to very serious imprecision (reliance on a single study and wide confidence intervals).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), certainty is low due to serious indirectness (evidence from non-COVID-19 patients) and serious imprecision.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. 5 (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Moderate Due to some inconsistency 2</td>
<td>Corticosteroids probably decrease death at day 28 in adults who require oxygen.</td>
</tr>
<tr>
<td>Serious adverse events [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies. 3 (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Moderate Due to serious inconsistency 4</td>
<td>Corticosteroids probably have little impact on serious adverse events in adults who require oxygen.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. 7 (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Moderate Due to only one study 7</td>
<td>Corticosteroids probably decrease invasive mechanical ventilation or death in adults who require oxygen.</td>
</tr>
<tr>
<td>Discharge from hospital [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. 8 (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Moderate Due to serious inconsistency 9</td>
<td>Corticosteroids probably increases discharge from hospital in adults who require oxygen.</td>
</tr>
<tr>
<td>All-cause mortality [adults not requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1.1 — 1.61) Based on data from 1,535 participants in 1 studies. 10 (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Moderate Due to only one study 11</td>
<td>Corticosteroids probably increase death in adults who do not require oxygen.</td>
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<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Corticosteroids</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td><em>Critical</em> Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days of commencing treatment</td>
<td>Relative risk 1.25 (CI 95% 1.01 — 1.57) Based on data from 1,535 participants in 1 studies. (&lt;sup&gt;12&lt;/sup&gt; Randomized controlled)</td>
<td>155 per 1000</td>
<td>194 per 1000</td>
<td>Moderate</td>
<td>Due to only one study (&lt;sup&gt;13&lt;/sup&gt;) Corticosteroids probably increase invasive mechanical ventilation or death in adults who do not require oxygen.</td>
<td></td>
</tr>
<tr>
<td><em>Critical</em> Discharge from hospital [adults not requiring oxygen] Within 28 days of commencing treatment</td>
<td>Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. (&lt;sup&gt;14&lt;/sup&gt; Randomized controlled)</td>
<td>804 per 1000</td>
<td>772 per 1000</td>
<td>Moderate</td>
<td>Due to only one study (&lt;sup&gt;15&lt;/sup&gt;) Corticosteroids may have little impact on discharge from hospital in adults who do not require oxygen.</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding End of treatment</td>
<td>Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies. (&lt;sup&gt;16&lt;/sup&gt;)</td>
<td>48 per 1000</td>
<td>51 per 1000</td>
<td>Low</td>
<td>Due to serious indirectness and imprecision Corticosteroids may have little impact on gastrointestinal bleeding.</td>
<td></td>
</tr>
<tr>
<td>Super infections End of treatment</td>
<td>Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies. (&lt;sup&gt;17&lt;/sup&gt;)</td>
<td>186 per 1000</td>
<td>188 per 1000</td>
<td>Low</td>
<td>Due to serious indirectness and imprecision Corticosteroids may have little impact on number of patients with super infections.</td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia End of treatment</td>
<td>Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies. (&lt;sup&gt;18&lt;/sup&gt;)</td>
<td>286 per 1000</td>
<td>332 per 1000</td>
<td>Moderate</td>
<td>Due to serious indirectness Corticosteroids probably increase the risk of hyperglycaemia.</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Relative risk 1.09 (CI 95% 0.86 — 1.39)</td>
<td>69</td>
<td>75</td>
<td>Low</td>
<td>Corticosteroids may have little impact on</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>weakness End of treatment</td>
<td>Based on data from 6,358 participants in 8 studies.</td>
<td>Standard care</td>
<td>Steroids per 1000</td>
<td>Due to serious indirectness and imprecision</td>
<td>neuromuscular weakness.</td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td>Difference: 6 more per 1000 (CI 95% 10 fewer — 27 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric effects End of treatment</td>
<td>Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies.</td>
<td>Control arm of reference used for intervention.</td>
<td>Steroids per 1000</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on neuropsychiatric effects.</td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td>Difference: 7 fewer per 1000 (CI 95% 21 fewer — 22 more)</td>
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</tr>
</tbody>
</table>


2. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies.


4. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies.

5. The number of patients with severe illness (i.e. who do not require mechanical ventilation at enrolment) that progress to requiring invasive mechanical ventilation or death within 28 days

6. Systematic review [26] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.

7. **Imprecision:** serious. Only data from one study.


9. **Inconsistency:** serious. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.

10. Systematic review [26] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.

11. **Imprecision:** serious. Only data from one study.

12. Systematic review [26] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.

13. **Imprecision:** serious. Only data from one study.


15. **Imprecision:** serious. Only data from one study.

16. Systematic review [27] . **Baseline/comparator:** Control arm of reference used for intervention.

17. Systematic review [27] . **Baseline/comparator:** Control arm of reference used for intervention.

18. Systematic review [27] . **Baseline/comparator:** Control arm of reference used for intervention.

19. Systematic review [27] . **Baseline/comparator:** Control arm of reference used for intervention.

20. Systematic review [27] . **Baseline/comparator:** Control arm of reference used for intervention.
Conditional recommendation against

Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19 in **adults who do not require oxygen**.

*Corticosteroids may still be considered for other evidence-based indications in people who have COVID-19.*

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

**Benefits and harms**

In patients who do not require oxygen, death and risk of hypoglycaemia may be higher with dexamethasone and other corticosteroids.

**Certainty of the Evidence**

In patients who do not require oxygen, certainty of the evidence is moderate for all outcomes (mortality, mechanical ventilation or death, and discharge from hospital) due to serious imprecision (reliance on a single study).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values.

Based on the available evidence, the Consumer Panel believes that informed patients would not agree to this treatment for COVID-19.

**Resources and other considerations**

There are no identified resource issues as the recommendation reflects usual care.

**Equity**

There are no identified equity issues as the recommendation reflects usual care.

**Acceptability**

We have no systematically collected evidence regarding acceptability.

**Feasibility**

There are no identified feasibility issues as the recommendation reflects usual care.
Rationale
Evidence suggests that dexamethasone in patients with COVID-19 who do not require oxygen may increase the risk of death. We therefore recommend against dexamethasone and other corticosteroids in this population unless there is an alternative evidence-based indication for its use.

Clinical Question/ PICO

| Population: | Patients with COVID-19 |
| Intervention: | Corticosteroids |
| Comparator: | Standard care |

Summary
Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance [27] of seven randomised trials of patients with critical COVID-19 [31][32][33][34][36][37][500], one study of patients with moderate, severe or critical COVID-19 [38], and one study of patients with severe COVID-19 [39]. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress [28] and sepsis [29]—provided indirect evidence for serious adverse events.

We have found three new studies comparing corticosteroids with standard care (Corral-Gudino et al. (GLUCOCOVID) Wien Klin Wochenschr doi: 10.1007/s00508-020-01805-8, Tang et al. Respiration doi: 10.1159/000512063 and Jamaati et al. Eur J Pharmacol doi: 10.1016/j.ejphar.2021.173947). These studies are currently under review and, although not expected to change the recommendation, an updated recommendation will be included in a future version of the guideline.

Study characteristics
Three studies compared dexamethasone with standard care [34][36][38], three compared hydrocortisone with standard care [31][33][500] and three compared methylprednisolone with standard care [32][37][39].

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications possibly shows no difference in the incidence of gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was probably associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
In patients with severe or critical illness, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect) and invasive mechanical ventilation or death, and discharge from hospital (due to serious imprecision).
In patients with moderate illness, certainty is low for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to very serious imprecision (reliance on a single study and wide confidence intervals).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), certainty is low due to serious indirectness (evidence from non-COVID-19 patients) and serious imprecision.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Corticosteroid</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. 9 (Randomized controlled)</td>
<td>316 per 1000</td>
<td>265 per 1000</td>
<td>Moderate Due to some inconsistency 2</td>
<td>Corticosteroids probably decrease death at day 28 in adults who require oxygen.</td>
</tr>
<tr>
<td>Serious adverse events [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies. 6 (Randomized controlled)</td>
<td>234 per 1000</td>
<td>187 per 1000</td>
<td>Moderate Due to serious inconsistency 4</td>
<td>Corticosteroids probably have little impact on serious adverse events in adults who require oxygen.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. 5 (Randomized controlled)</td>
<td>320 per 1000</td>
<td>282 per 1000</td>
<td>Moderate Due to only one study 7</td>
<td>Corticosteroids probably decrease invasive mechanical ventilation or death in adults who require oxygen.</td>
</tr>
<tr>
<td>Discharge from hospital [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. 8 (Randomized controlled)</td>
<td>582 per 1000</td>
<td>640 per 1000</td>
<td>Moderate Due to serious inconsistency 9</td>
<td>Corticosteroids probably increases discharge from hospital in adults who require oxygen.</td>
</tr>
</tbody>
</table>
### Outcome

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence: Quality of evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Important</td>
<td>All-cause mortality (adults not requiring oxygen) Within 28 days of commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1.1 – 1.61) Based on data from 1,535 participants in 1 studies.</td>
<td>140 per 1000</td>
<td>Moderate Due to only one study</td>
<td>Corticosteroids probably increase death in adults who do not require oxygen.</td>
</tr>
<tr>
<td>9 Critical</td>
<td>Invasive mechanical ventilation or death [adults not requiring oxygen]</td>
<td>Relative risk 1.25 (CI 95% 1.1 – 1.57) Based on data from 1,535 participants in 1 studies.</td>
<td>155 per 1000</td>
<td>Moderate Due to only one study</td>
<td>Corticosteroids probably increase invasive mechanical ventilation or death in adults who do not require oxygen.</td>
</tr>
<tr>
<td>6 Important</td>
<td>Discharge from hospital [adults not requiring oxygen] Within 28 days of commencing treatment</td>
<td>Relative risk 0.96 (CI 95% 0.9 – 1.01) Based on data from 1,535 participants in 1 studies.</td>
<td>804 per 1000</td>
<td>Moderate Due to only one study</td>
<td>Corticosteroids may have little impact on discharge from hospital in adults who do not require oxygen.</td>
</tr>
<tr>
<td>6 Important</td>
<td>Gastrointestinal bleeding End of treatment</td>
<td>Relative risk 1.06 (CI 95% 0.85 – 1.33) Based on data from 5,403 participants in 30 studies.</td>
<td>48 per 1000</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on gastrointestinal bleeding.</td>
</tr>
<tr>
<td>6 Important</td>
<td>Super infections End of treatment</td>
<td>Relative risk 1.01 (CI 95% 0.9 – 1.13) Based on data from 6,027 participants in 32 studies.</td>
<td>186 per 1000</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on number of patients with super infections.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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</tr>
<tr>
<td>Hyperglycaemia</td>
<td>End of treatment</td>
<td>Relative risk 1.16 (CI 95% 1.08 – 1.25) Based on data from 8,938 participants in 24 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Moderate Due to serious indirectness</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuromuscular weakness</td>
<td>End of treatment</td>
<td>Relative risk 1.09 (CI 95% 0.86 – 1.39) Based on data from 6,358 participants in 8 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric effects</td>
<td>End of treatment</td>
<td>Relative risk 0.81 (CI 95% 0.41 – 1.63) Based on data from 1,813 participants in 7 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
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</tr>
</tbody>
</table>


2. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies.


4. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies.

5. The number of patients with severe illness (i.e. who do not require mechanical ventilation at enrolment) that progress to requiring invasive mechanical ventilation or death within 28 days.

6. Systematic review [26] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.

7. **Imprecision:** serious. Only data from one study.


9. **Inconsistency:** serious. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.

10. Systematic review [26] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.

11. **Imprecision:** serious. Only data from one study, Wide confidence intervals.

12. Systematic review [26] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.

13. **Imprecision:** serious. Only data from one study.


15. **Imprecision:** serious. Only data from one study.
6.1.5.2 Corticosteroids for pregnant or breastfeeding women

Use dexamethasone 6 mg daily intravenously or orally for up to 10 days in pregnant or breastfeeding women with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

If steroids are indicated for fetal lung maturity in women at risk of preterm birth, a standard antenatal corticosteroid regimen should be used (e.g. intramuscular dexamethasone 6 mg every 12 hours for four doses), followed by 6 mg dexamethasone daily until 10 days has been reached (see 13.1 - Antenatal Corticosteroids).

If steroids are not indicated for fetal lung maturity, use dexamethasone 6 mg daily intravenously or orally for up to 10 days.

The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days
- prednisolone: oral (50 mg), daily for up to 10 days

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

### Evidence To Decision

#### Benefits and harms

In patients receiving oxygen or invasive mechanical ventilation, death is reduced with dexamethasone. Although indirect evidence suggests that corticosteroids may increase the risk of hyperglycaemia, the panel believes the mortality benefit outweighs any potential harms associated with corticosteroid use.

Dexamethasone is used for other clinical indications during pregnancy and is considered safe to use when indicated.

#### Certainty of the Evidence

In patients with severe or critical illness, certainty of the evidence is low for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect and serious indirectness), mechanical ventilation or death and discharge from hospital (due to serious imprecision and serious indirectness).

For adverse events (gastrointestinal bleeding, super-infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.
Rationale
Due to a reduction in death, along with no important resource implications, and the likely acceptability of corticosteroids and applicability of the evidence to pregnant and breastfeeding women, we recommend corticosteroids for pregnant and breastfeeding women with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

The recommended corticosteroid regimen (dexamethasone 6 mg daily intravenously or orally) reflects the regimen used in the RECOVERY trial, which is the largest trial available and demonstrated a significant reduction in all-cause mortality. The acceptable alternative regimens (hydrocortisone, prednisolone) were informed by the range of corticosteroid regimens used in other available trials, as well as a pharmacological assessment to ensure that an alternative regimen has equivalent bioavailability.

Preference and values
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women. The Consumer Panel believes that since there are mortality benefits most informed pregnant or breastfeeding women would agree with the recommendation and opt for corticosteroids.

Resources and other considerations
Corticosteroids are widely available and affordable. Use of corticosteroids in pregnant and breastfeeding women with COVID-19 who are receiving supplementary oxygen or invasive ventilation is unlikely to have an impact on availability of these drugs for other indications.

Equity
We have no systematically collected evidence regarding impact on equity. Since corticosteroids are widely available and affordable, no negative impact is expected.

Acceptability
Although we have no systematically collected evidence regarding acceptability, corticosteroids are likely to be acceptable to both patients and clinicians.

Feasibility
Intravenous dexamethasone (Pfizer Australia Pty Ltd; Alphapharm Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers 178774, 16374, 163200; [AusPAR](https://auspar.gov.au)). As of 3 December 2021, dexamethasone is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Corticosteroids are likely to be feasible because they are already widely used for other indications. There are no known issues with availability of these drugs.

Clinical Question/ PICO
- **Population:** Special populations with COVID-19 [adapted from general adult population]
- **Intervention:** Corticosteroids
- **Comparator:** Standard care
Summary
Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance [27] of seven randomised trials of patients with critical COVID-19 [31][32][33][34][36][37][500], one study of patients with moderate, severe and critical COVID-19 [38] and one study of patients with severe COVID-19 [39]. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress [28] and sepsis [29]—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care [34][36][38], three compared hydrocortisone with standard care [31][33][500] and three compared methylprednisolone with standard care [32][37][39].

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or NIV, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications shows no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
Certainty of the evidence for all outcomes is judged to be low for pregnant and breastfeeding women, and children and adolescents due to serious indirectness. This is in addition to concerns in the adult population about inconsistency in direction of effect and serious imprecision.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment</td>
<td>Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. 1 (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious inconsistency and serious indirectness 2</td>
<td>Corticosteroids may decrease death at day 28 in patients who require oxygen.</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Corticosteroids</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td>9 Critical</td>
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<tr>
<td>Serious adverse events [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies.</td>
<td>234 per 1000</td>
<td>Low Due to serious inconsistency and indirectness</td>
<td>Corticosteroids may have little impact on serious adverse events in patients who require oxygen.</td>
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<td></td>
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<td>187 per 1000</td>
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<td>47 fewer per 1000 (CI 95% 0.53 — 0.84)</td>
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<tr>
<td>6 Important</td>
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<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies.</td>
<td>320 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.</td>
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<td>282 per 1000</td>
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<td></td>
<td></td>
<td>38 fewer per 1000 (CI 95% 0.79 — 0.97)</td>
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<tr>
<td>9 Critical</td>
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</tr>
<tr>
<td>All-cause mortality [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1.01 — 1.43) Based on data from 1,535 participants in 1 studies.</td>
<td>140 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may increase death in patients who do not require oxygen.</td>
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<td>178 per 1000</td>
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<td></td>
<td>38 more per 1000 (CI 95% 1.01 — 1.43)</td>
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<tr>
<td>9 Critical</td>
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<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 1.25 (CI 95% 1.01 — 1.57) Based on data from 1,535 participants in 1 studies.</td>
<td>155 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.</td>
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<td></td>
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<td>194 per 1000</td>
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<td>39 more per 1000 (CI 95% 1.01 — 1.57)</td>
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<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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</tr>
<tr>
<td>Discharge from hospital [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>End of treatment</td>
<td>Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies.</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Super infections</td>
<td>End of treatment</td>
<td>Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies.</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>End of treatment</td>
<td>Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies.</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Neuromuscular weakness</td>
<td>End of treatment</td>
<td>Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies.</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Neuropsychiatric effects</td>
<td>End of treatment</td>
<td>Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies.</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
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</tr>
<tr>
<td>Discharge from hospital [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies.</td>
<td>Standard care; Control arm of reference used for intervention.</td>
<td>Corticosteroids</td>
<td>Low Due to serious inconsistency and serious indirectness.</td>
</tr>
</tbody>
</table>

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4. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Indirectness:** serious. Differences between the population of interest and those studied.
5. The number of patients with severe illness (i.e. who do not require mechanical ventilation at enrolment) that progress to requiring invasive mechanical ventilation or death within 28 days
6. Systematic review [26] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
8. Systematic review [26] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
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16. Systematic review [27]. **Baseline/comparator:** Control arm of reference used for intervention.
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20. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Indirectness:** serious. Differences between the population of interest and those studied.
Conditional recommendation against

Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19 in pregnant or breastfeeding women who do not require oxygen.

Antenatal corticosteroids should still be used for fetal lung maturation in pregnant women at risk of preterm birth who also have COVID-19. Dexamethasone and other corticosteroids should still be used for other evidence-based indications in pregnant and breastfeeding women who have COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

In pregnant or breastfeeding women who do not require oxygen, there may be more deaths with dexamethasone and other corticosteroids.

Certainty of the Evidence

In pregnant or breastfeeding women who do not require oxygen, certainty of the evidence is judged to be low for all outcomes (mortality, mechanical ventilation or death, and discharge from hospital) due to serious imprecision (reliance on a single study and wide confidence intervals) and serious indirectness (results based on the general adult population).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Preference and values

We have no systematically collected information regarding preferences and values of pregnant or breastfeeding women. The Consumer Panel believes that most informed pregnant or breastfeeding women may prefer to wait until the available evidence is clearer, and would not agree to this treatment for COVID-19.

Resources and other considerations

There are no identified resource issues as the recommendation reflects usual care.

Equity

There are no identified equity issues as the recommendation reflects usual care.

Acceptability

We have no systematically collected evidence regarding acceptability.
Rationale
Evidence suggests that dexamethasone in pregnant and breastfeeding women with COVID-19 who do not require oxygen may increase the risk of death. We therefore recommend against dexamethasone and other corticosteroids in this population unless there is an alternative evidence-based indication for their use.

Clinical Question/ PICO
- **Population:** Special populations with COVID-19 [adapted from general adult population]
- **Intervention:** Corticosteroids
- **Comparator:** Standard care

Summary
Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance [27] of seven randomised trials of patients with critical COVID-19 [31][32][33][34][36][37][500], one study of patients with moderate, severe and critical COVID-19 [38] and one study of patients with severe COVID-19 [39]. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress [28] and sepsis [29]—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care [34][36][38], three compared hydrocortisone with standard care [31][33][500] and three compared methylprednisolone with standard care [32][37][39].

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or NIV, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications shows no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
Certainty of the evidence for all outcomes is judged to be low for pregnant and breastfeeding women, and children and adolescents due to serious indirectness. This is in addition to concerns in the adult population about inconsistency in direction of effect and serious imprecision.
<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Timeframe</th>
<th>Study Results and Measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of Evidence (Quality of Evidence)</th>
<th>Plain Language Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. 1 (Randomized controlled)</td>
<td>316 per 1000</td>
<td>265 per 1000</td>
<td>Low Due to serious inconsistency and serious indirectness 2</td>
<td>Corticosteroids may decrease death at day 28 in patients who require oxygen.</td>
</tr>
<tr>
<td>Serious adverse events [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies. 3 (Randomized controlled)</td>
<td>234 per 1000</td>
<td>187 per 1000</td>
<td>Low Due to serious inconsistency and indirectness 4</td>
<td>Corticosteroids may have little impact on serious adverse events in patients who require oxygen.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. 5 (Randomized controlled)</td>
<td>320 per 1000</td>
<td>282 per 1000</td>
<td>Low Due to only one study and serious indirectness 7</td>
<td>Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.</td>
</tr>
<tr>
<td>All-cause mortality [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies. 8 (Randomized controlled)</td>
<td>140 per 1000</td>
<td>178 per 1000</td>
<td>Low Due to only one study and serious indirectness 9</td>
<td>Corticosteroids may increase death in patients who do not require oxygen.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults not requiring oxygen]</td>
<td></td>
<td>Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. 10</td>
<td>155 per 1000</td>
<td>194 per 1000</td>
<td>Low Due to only one study and serious indirectness 11</td>
<td>Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
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<tr>
<td>Oxygen</td>
<td>Within 28 days after</td>
<td>(Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low</td>
<td>Discharge from hospital [adults not requiring oxygen]</td>
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<td></td>
<td>commencing treatment</td>
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</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>End of treatment</td>
<td>Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 study.</td>
<td>Standard care</td>
<td></td>
<td>Low</td>
<td>Corticosteroids may have little impact on gastrointestinal bleeding.</td>
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<td>Low</td>
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<tr>
<td>Super infections</td>
<td>End of treatment</td>
<td>Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies.</td>
<td>Standard care</td>
<td></td>
<td>Low</td>
<td>Corticosteroids may have little impact on number of patients with super infections.</td>
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<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
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<tr>
<td>Hyperglycaemia</td>
<td>End of treatment</td>
<td>Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies.</td>
<td>Standard care</td>
<td></td>
<td>Moderate</td>
<td>Corticosteroids probably increase the risk of hyperglycaemia.</td>
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<td></td>
<td>(Randomized controlled)</td>
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</tr>
<tr>
<td>Neuromuscular weakness</td>
<td>End of treatment</td>
<td>Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies.</td>
<td>Standard care</td>
<td></td>
<td>Low</td>
<td>Corticosteroids may have little impact on neuromuscular weakness.</td>
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<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td>Low</td>
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<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
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</tr>
<tr>
<td>Discharge from hospital [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious inconsistency and serious indirectness</td>
<td>Corticosteroids may increase discharge from hospital in patients who require oxygen.</td>
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### 6.1.5.3 Corticosteroids for children and adolescents

#### Conditional recommendation

Consider using dexamethasone daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in **children and adolescents with acute COVID-19 who are receiving oxygen** (including mechanically ventilated patients).

A dose of 6 mg daily is recommended in adults. The RECOVERY trial protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children but it is unclear whether any children were included in the trial. If dexamethasone is not available, an acceptable alternative regimen would be:

- hydrocortisone: intravenous or intramuscular 1 mg/kg/dose, every 6 hours for up to 10 days (to a maximum dose of 50 mg every 6 hours)
- methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain

For specific recommendations on the use of corticosteroids for PIMS-TS see section.

This is a **moderate priority** recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

#### Evidence To Decision

**Benefits and harms**

In patients receiving oxygen or invasive mechanical ventilation, death is reduced with corticosteroids. Although indirect evidence suggests that corticosteroids may increase the risk of hypoglycaemia, the panel believes the mortality benefit outweighs any potential harms associated with corticosteroid use.

**Certainty of the Evidence**

In patients with severe or critical illness, certainty of the evidence is low for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect and serious indirectness), mechanical ventilation or death, and discharge from hospital (due to serious imprecision and serious indirectness).

For adverse events (gastrointestinal bleeding, super-infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

**Preference and values**

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians.
The Consumer Panel believes that some informed patients (and their parents, carers, families or guardians) may prefer to wait until the available evidence is clearer, but most informed patients (and their parents, carers, families or guardians) would agree to this treatment for COVID-19.

**Rationale**

Due to a reduction in death, along with no important resource implications and the likely acceptability of these drugs, we recommend considering using corticosteroids in children and adolescents with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

**Resources and other considerations**

Corticosteroids are widely available and affordable. Use of corticosteroids in adults with COVID-19 who are receiving supplementary oxygen or invasive ventilation is unlikely to have an impact on availability of these drugs for other indications.

**Equity**

We have no systematically collected evidence regarding impact on equity. Since corticosteroids are widely available and affordable, no negative impact is expected.

**Acceptability**

Although we have no systematically collected evidence regarding acceptability, corticosteroids are likely to be acceptable to both patients and clinicians.

**Feasibility**

Intravenous dexamethasone (Pfizer Australia Pty Ltd; Alphapharm Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers 178774, 16374, 163200; [AusPAR](https://auspar.gov.au)). As of 3 December 2021, dexamethasone is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Corticosteroids are likely to be feasible because they are already widely used for other indications. There are no known issues with availability of these drugs.

**Clinical Question/ PICO**

**Population:** Special populations with COVID-19 [adapted from general adult population]

**Intervention:** Corticosteroids

**Comparator:** Standard care

**Summary**

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from a meta-analysis and associated living guidance [27] of seven randomised trials of patients with critical COVID-19 [31][32][33][34][36][37][500], one study of patients with moderate, severe and critical COVID-19 [38] and one study of patients with severe COVID-19 [39]. Over 5700 patients are included in the
meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress [28] and sepsis [29]—provided indirect evidence for serious adverse events.

**Study characteristics**

Three studies compared dexamethasone with standard care [34][36][38], three compared hydrocortisone with standard care [31][33][500] and three compared methylprednisolone with standard care [32][37][39].

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or NIV, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

**What are the main results?**

Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications shows no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

**Our confidence in the results**

Certainty of the evidence for all outcomes is judged to be low for pregnant and breastfeeding women, and children and adolescents due to serious indirectness. This is in addition to concerns in the adult population about inconsistency in direction of effect and serious imprecision.

---

### Outcome Timeframe | Study results and measurements | Comparator | Intervention | Certainty of the Evidence | Plain language summary
---|---|---|---|---|---
**All-cause mortality [adults requiring oxygen]**  
Within 28 days of commencing treatment | Relative risk 0.84  
(CI 95% 0.73 — 0.98)  
Based on data from 5,789 participants in 9 studies.  
1 (Randomized controlled) | Standard care  
316 per 1000  
Difference:  
51 fewer per 1000  
(CI 95% 85 fewer — 6 fewer) | Corticosteroids may decrease death at day 28 in patients who require oxygen.  
**Low**  
Due to serious inconsistency and serious indirectness | 265 per 1000

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### Serious adverse events [adults requiring]

Relative risk 0.8  
(CI 95% 0.53 — 1.19)  
Based on data from 696 participants in 6 studies.  
2 (Randomized controlled)  
| Standard care  
234 per 1000  
Difference:  
47 fewer per 1000 | Corticosteroids may have little impact on serious adverse events in patients who require oxygen.  
**Low**  
Due to serious inconsistency and indirectness | 187 per 1000
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator (Standard care)</th>
<th>Intervention (Corticosteroids)</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation or death [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. (Randomized controlled)</td>
<td>1000 (CI 95% 110 fewer — 44 more)</td>
<td>320 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.</td>
</tr>
<tr>
<td>All-cause mortality [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies. (Randomized controlled)</td>
<td>140 per 1000</td>
<td>178 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may increase death in patients who do not require oxygen.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. (Randomized controlled)</td>
<td>155 per 1000</td>
<td>194 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.</td>
</tr>
<tr>
<td>Discharge from hospital [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. (Randomized controlled)</td>
<td>804 per 1000</td>
<td>772 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>End of treatment</td>
<td>Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on gastrointestinal bleeding.</td>
</tr>
<tr>
<td>Super infections</td>
<td>End of treatment</td>
<td>Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on number of patients with super infections.</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>End of treatment</td>
<td>Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Moderate Due to serious indirectness</td>
<td>Corticosteroids probably increase the risk of hyperglycaemia.</td>
</tr>
<tr>
<td>Neuromuscular weakness</td>
<td>End of treatment</td>
<td>Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on neuromuscular weakness.</td>
</tr>
<tr>
<td>Neuropsychiatric effects</td>
<td>End of treatment</td>
<td>Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on neuropsychiatric effects.</td>
</tr>
<tr>
<td>Discharge from hospital [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious inconsistency and serious indirectness</td>
<td>Corticosteroids may increase discharge from hospital in patients who require oxygen.</td>
</tr>
</tbody>
</table>

2. Inconsistency: serious. The direction of the effect is not consistent between the included studies. Indirectness: serious. Differences between the population of interest and those studied.


4. Inconsistency: serious. The direction of the effect is not consistent between the included studies. Indirectness: serious. Differences between the population of interest and those studied.

5. The number of patients with severe illness (i.e. who do not require mechanical ventilation at enrolment) that progress to requiring invasive mechanical ventilation or death within 28 days


11. Indirectness: serious. Differences between the population of interest and those studied. Imprecision: serious. Only data from one study.


17. Systematic review [27]. Baseline/comparator: Control arm of reference used for intervention.


20. Inconsistency: serious. The direction of the effect is not consistent between the included studies. Indirectness: serious. Differences between the population of interest and those studied.
Conditional recommendation against

Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19 in children and adolescents who do not require oxygen.

Dexamethasone and other corticosteroids should still be used for other evidence-based indications in children and adolescents who have COVID-19.

For specific recommendations on the use of corticosteroids for PIMS-TS see section.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

In adult patients who do not require oxygen, there may be more deaths with dexamethasone and other corticosteroids. It is unclear if any children were included in the trials, therefore there is uncertainty regarding the benefits in this population but there are known potential adverse effects.

Certainty of the Evidence

In children and adolescents who do not require oxygen, certainty of the evidence is judged to be low for all outcomes (mortality, mechanical ventilation or death, and discharge from hospital) due to serious imprecision (reliance on a single study and wide confidence intervals) and serious indirectness (results based on the general adult population).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Preference and values

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians.

The Consumer Panel believes that most informed patients (and their parents, carers, families and guardians) may prefer to wait until the available evidence is clearer, and would not agree to this treatment for COVID-19.

Resources and other considerations

There are no identified resource issues as the recommendation reflects usual care.

Equity

There are no identified equity issues as the recommendation reflects usual care.
**Rationale**

Evidence from an adult population suggests that dexamethasone and other corticosteroids in people with COVID-19 who do not require oxygen may increase the risk of death. We therefore recommend against dexamethasone and other corticosteroids in children or adolescents unless there is an alternative evidence-based indication for its use.

**Clinical Question/ PICO**

- **Population:** Special populations with COVID-19 [adapted from general adult population]
- **Intervention:** Corticosteroids
- **Comparator:** Standard care

**Summary**

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from a meta-analysis and associated living guidance [27] of seven randomised trials of patients with critical COVID-19 [31][32][33][34][36][37][500], one study of patients with moderate, severe and critical COVID-19 [38] and one study of patients with severe COVID-19 [39]. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress [28] and sepsis [29]—provided indirect evidence for serious adverse events.

**Study characteristics**

Three studies compared dexamethasone with standard care [34][36][38], three compared hydrocortisone with standard care [31][33][500] and three compared methylprednisolone with standard care [32][37][39].

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or NIV, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

**What are the main results?**

Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications shows no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).
Our confidence in the results
Certainty of the evidence for all outcomes is judged to be low for pregnant and breastfeeding women, and children and adolescents due to serious indirectness. This is in addition to concerns in the adult population about inconsistency in direction of effect and serious imprecision.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Corticosteroids</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies.</td>
<td>316 per 1000</td>
<td>265 per 1000</td>
<td>Low Due to serious inconsistency and serious indirectness</td>
<td>Corticosteroids may decrease death at day 28 in patients who require oxygen.</td>
</tr>
<tr>
<td>Serious adverse events [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies.</td>
<td>234 per 1000</td>
<td>187 per 1000</td>
<td>Low Due to serious inconsistency and serious indirectness</td>
<td>Corticosteroids may have little impact on serious adverse events in patients who require oxygen.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies.</td>
<td>320 per 1000</td>
<td>282 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.</td>
</tr>
<tr>
<td>All-cause mortality [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1.1 — 1.61) Based on data from 1,535 participants in 1 studies.</td>
<td>140 per 1000</td>
<td>178 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may increase death in patients who do not require oxygen.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<td>Invasive mechanical ventilation or death [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.</td>
</tr>
<tr>
<td>Discharge from hospital [adults not requiring oxygen]</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>End of treatment</td>
<td>Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on gastrointestinal bleeding.</td>
</tr>
<tr>
<td>Super infections</td>
<td>End of treatment</td>
<td>Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on number of patients with super infections.</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>End of treatment</td>
<td>Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies.</td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td>Moderate Due to serious indirectness</td>
<td>Corticosteroids probably increase the risk of hyperglycaemia.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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</tr>
<tr>
<td>Neuromuscular weakness</td>
<td>End of treatment</td>
<td>Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies. 17</td>
<td>Standard care</td>
<td>Corticosteroids 5</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on neuromuscular weakness.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>69 per 1000</td>
<td>75 per 1000 (CI 95% 10 fewer — 27 more)</td>
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<tr>
<td></td>
<td></td>
<td>Difference: 6 more per 1000 (CI 95% 10 fewer — 27 more)</td>
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<tr>
<td>Neuropsychiatric effects</td>
<td>End of treatment</td>
<td>Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies. 18</td>
<td>Standard care</td>
<td>Corticosteroids 4</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Corticosteroids may have little impact on neuropsychiatric effects.</td>
</tr>
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<td></td>
<td>35 per 1000</td>
<td>28 per 1000 (CI 95% 21 fewer — 22 more)</td>
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<tr>
<td></td>
<td></td>
<td>Difference: 7 fewer per 1000 (CI 95% 21 fewer — 22 more)</td>
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</tr>
<tr>
<td>Discharge from hospital</td>
<td>[adults requiring oxygen]</td>
<td>Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. 19</td>
<td>Standard care</td>
<td>Corticosteroids 3</td>
<td>Low Due to serious inconsistency and serious indirectness</td>
<td>Corticosteroids may increase discharge from hospital in patients who require oxygen.</td>
</tr>
<tr>
<td></td>
<td>Within 28 days of commencing treatment</td>
<td></td>
<td></td>
<td>582 per 1000</td>
<td>640 per 1000 (CI 95% 35 more — 87 more)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 58 more per 1000 (CI 95% 35 more — 87 more)</td>
<td></td>
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</tbody>
</table>

2. Inconsistency: serious. The direction of the effect is not consistent between the included studies. Indirectness: serious. Differences between the population of interest and those studied.
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5. The number of patients with severe illness (i.e. who do not require mechanical ventilation at enrolment) that progress to requiring invasive mechanical ventilation or death within 28 days
9. Indirectness: serious. Differences between the population of interest and those studied. Imprecision: serious. Only data from one study, Wide confidence intervals.
11. Indirectness: serious. Differences between the population of interest and those studied. Imprecision: serious. Only data from one study.
12. Systematic review [26] with included studies: RECOVERY. Baseline/comparator: Control arm of reference used
for intervention.

13. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.

14. Systematic review [27]. **Baseline/comparator:** Control arm of reference used for intervention.

15. Systematic review [27]. **Baseline/comparator:** Control arm of reference used for intervention.

16. Systematic review [27]. **Baseline/comparator:** Control arm of reference used for intervention.

17. Systematic review [27]. **Baseline/comparator:** Control arm of reference used for intervention.

18. Systematic review [27]. **Baseline/comparator:** Control arm of reference used for intervention.


20. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Indirectness:** serious. Differences between the population of interest and those studied.

### 6.1.6 Other immunomodulating drugs

**Info Box**

As of 3 June 2021, the Taskforce has developed conditional recommendations supporting the use of three non-steroidal immunomodulatory agents for the treatment of COVID-19 in hospitalised patients requiring supplemental oxygen. All three treatments demonstrate a mortality benefit when used in this patient population (moderate certainty of evidence), however the Taskforce cautions against the concomitant use of two or more of these immunomodulatory agents due to increased risk of side effects such as opportunistic infection.

All studies that contribute data to analyses underpinning these recommendations compare the treatment of interest with either standard care or placebo. In the absence of data directly comparing one agent to another, it is unclear which of these agents is clinically superior, and thus it is not possible to promote the use of one treatment over another based on clinical evidence alone.

The Taskforce acknowledges the importance of other factors in deciding which treatment is administered, such as availability (e.g. sarilumab has not been approved by the TGA), route of administration and cost. A table providing a comparison of clinical and non-clinical factors between the three recommended immunomodulators can be found [here](#).

It is important to note that as of 17 August 2021, there is a significant shortage of tocilizumab within Australia (TGA statement). As a result, in patients who are receiving supplemental oxygen but are not mechanically ventilated, baricitinib should be considered instead of tocilizumab, unless contraindicated.

### 6.1.6.1 Baricitinib

#### 6.1.6.1.1 Baricitinib for adults
Consider using baricitinib in adults hospitalised with COVID-19 who require supplemental oxygen.

In patients hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for baricitinib both within and outside the context of a randomised trial.

In accordance with the ACTT-2 and COV-BARRIER studies, baricitinib should be administered as a 4 mg oral daily dose for up to 14 days. In patients receiving more intensive oxygen delivery where oral administration is not feasible, administer via nasogastric tube. Consider using a reduced dose of 2 mg daily in patients with an eGFR of between 30 and 60 mL/min/1.73m2.

The Taskforce previously recommended baricitinib for use in patients who required supplemental oxygen but not mechanical ventilation or ECMO due to the absence of direct evidence within this population. Data from the COV-BARRIER extension study suggests baricitinib is safe and effective in patients hospitalised with COVID-19 who require mechanical ventilation or ECMO. The Taskforce has subsequently revised the recommendation to include these patients.

The Taskforce notes the current critical shortage of tocilizumab. Therefore, in patients who are receiving supplemental oxygen, baricitinib should be considered as an alternative to tocilizumab, unless contraindicated. For the TGA and Medicine Availability Working Group statements regarding the shortage, click here.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

### Evidence To Decision

#### Benefits and harms

In patients hospitalised with moderate or severe COVID-19 who require supplemental oxygen, baricitinib probably decreases the incidence of death and the need for invasive mechanical ventilation.

Evidence from randomised trials versus standard care demonstrates that baricitinib has an acceptable safety profile and probably reduces the incidence of serious adverse events. Consideration should be given when administering baricitinib to patients already on other immunosuppressant or immunomodulatory drugs.

#### Older people living with frailty or cognitive impairment

People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

#### People requiring palliative care

There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

#### Pregnant or breastfeeding women

There is uncertainty around the benefits and harms of baricitinib for pregnant or breastfeeding women with COVID-19 as no details were reported in the trials for these populations.

#### Children or adolescents

As the included trials are based on adults, there remains uncertainty around the benefits and harms of baricitinib for children and adolescents with COVID-19.

### Certainty of the Evidence

Certainty of the evidence is moderate for mortality and low for invasive mechanical ventilation. Certainty is high.
for serious adverse events, moderate for adverse events and clinical recovery, and low for all other outcomes (patients requiring non-invasive ventilation or high-flow oxygen, discontinuation due to adverse events, time to recovery, and duration of hospitalisation).

**Preference and values**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that since there are probable mortality benefits most informed patients with COVID-19 who require supplemental oxygen would agree with the recommendation and opt for treatment with baricitinib.

**Pregnant or breastfeeding patients**
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

**Children and adolescents**
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**
We have no systematically collected evidence regarding impact on equity, however this may be affected by geographic area and access to baricitinib.

**Acceptability**
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**Feasibility**
Oral baricitinib (Olumiant; Eli Lilly Australia Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers: 277917, 277905; AusPAR). As of 3 December 2021, baricitinib is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

**Rationale**
**General adult population**
In patients hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for baricitinib both within and outside a randomised trial.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Baricitinib</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary

Evidence indicates that baricitinib probably reduces the risk of death in hospitalised adults who require supplemental oxygen, and may reduce the need for invasive mechanical ventilation, non-invasive ventilation and/or high-flow oxygen.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials—one that compared baricitinib plus remdesivir with remdesivir alone in 1033 adults hospitalised with suspected COVID-19 (ACTT-2) [22], one that compared baricitinib with standard care in 1525 adults with mild-to-severe COVID-19 (COV-BARRIER) [559], and one that compared baricitinib with standard care in 101 adults with severe-to-critical COVID-19 (COV-BARRIER) [604].

Study characteristics

Mean age of participants was 57 years and 38% were women. In the ACTT-2 trial, patients received either 4 mg baricitinib plus remdesivir (200 mg on day one, 100 mg a day until day 10 or hospital discharge) or remdesivir alone (same regimen as treatment arm). In the COV-BARRIER trial, patients also received 4 mg baricitinib. Pregnant and breastfeeding women were ineligible.

What are the main results?

Baricitinib increases the risk of serious adverse events (49 fewer SAEs per 1000; RR 0.77, CI 95% 0.66 to 0.9; 2617 patients in 3 studies) and probably decreases death (45 fewer deaths per 1000; RR 0.64, CI 95% 0.51 to 0.8; 2659 patients in 3 studies) and clinical recovery (59 more per 1000; RR 1.08, CI 95% 1.01 to 1.14; 1134 patients in 2 studies).

Baricitinib may decrease the need for invasive mechanical ventilation, non-invasive ventilation and high-flow nasal oxygen therapy. Baricitinib probably has little impact on incidence of adverse events. We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events, duration of hospitalisation or time to recovery.

Our confidence in the results

Certainty of the evidence is high for serious adverse events and moderate for death, adverse events and clinical recovery due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information

According to the Therapeutic Goods Administration, known harms associated with baricitinib include an increased risk of serious infections, gastrointestinal disorders, thrombosis and headaches [24].
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>of commencing treatment</td>
<td>2,659 participants in 3 studies. (Randomized controlled)</td>
<td>Difference: 45 fewer per 1000 (CI 95% 61 fewer — 25 fewer)</td>
<td>Standard care</td>
<td>Baricitinib</td>
<td>Low</td>
<td>Baricitinib may decrease requirement for invasive mechanical ventilation or ECMO slightly (116 events).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Relative risk 0.66 (CI 95% 0.46 — 0.93) Based on data from 922 participants in 1 studies. (Randomized controlled)</td>
<td>Difference: 52 fewer per 1000 (CI 95% 82 fewer — 11 fewer)</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision 4</td>
</tr>
<tr>
<td>Non-invasive ventilation or HFNO</td>
<td>Relative risk 0.83 (CI 95% 0.63 — 1.1) Based on data from 706 participants in 1 studies. (Randomized controlled)</td>
<td>Difference: 40 fewer per 1000 (CI 95% 87 fewer — 24 more)</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision 6</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.77 (CI 95% 0.66 — 0.9) Based on data from 2,617 participants in 3 studies. (Randomized controlled)</td>
<td>Difference: 49 fewer per 1000 (CI 95% 72 fewer — 21 fewer)</td>
<td></td>
<td></td>
<td>High</td>
<td>Baricitinib decreases serious adverse events.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 0.94 (CI 95% 0.87 — 1.01) Based on data from 2,634 participants in 3 studies. (Randomized controlled)</td>
<td>Difference: 28 fewer per 1000 (CI 95% 61 fewer — 5 more)</td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Baricitinib probably decreases adverse events slightly.</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>Relative risk 0.8 (CI 95% 0.57 — 1.12) Based on data from 1,502 participants in 1 studies. (Randomized controlled)</td>
<td>Difference: 19 fewer per 1000 (CI 95% 40 fewer — 11 more)</td>
<td></td>
<td></td>
<td>Low</td>
<td>Baricitinib may have little or no difference on discontinuation due to adverse events (126 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>------------------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
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<td>---------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>End of follow-up</td>
<td>Relative risk 1.08 (CI 95% 1.01 — 1.14) Based on data from 1,134 participants in 2 studies.</td>
<td>Standard care</td>
<td>Baricitinib</td>
<td>Moderate</td>
<td>Baricitinib probably improves clinical recovery.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td>738 per 1000</td>
<td>797 per 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Difference:</td>
<td>59 more per 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(CI 95% 7 more — 103 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalisation</td>
<td>Mean (days)</td>
<td>Lower better (Randomized controlled)</td>
<td></td>
<td>13.7 (Mean)</td>
<td>12.9 (Mean)</td>
<td>Low Due to very serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Difference:</td>
<td>MD 0.8 lower CI 95%</td>
<td>We are uncertain whether baricitinib increases or decreases duration of hospitalisation.</td>
</tr>
<tr>
<td>Time to recovery</td>
<td>Median (days)</td>
<td>Lower better (Randomized controlled)</td>
<td></td>
<td>11 (Median)</td>
<td>10 (Median)</td>
<td>Low Due to very serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CI 95%</td>
<td>We are uncertain whether baricitinib increases or decreases time to recovery.</td>
</tr>
</tbody>
</table>

2. **Publication bias:** serious. Mostly commercially funded studies.
4. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.
6. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.
9. **Imprecision:** serious. Wide confidence intervals.
11. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
13. **Imprecision:** serious. Wide confidence intervals.
14. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
15. **Imprecision:** very serious. Only data from one study, Wide confidence intervals.

**6.1.6.1.2 Baricitinib for pregnant or breastfeeding women**
Evidence To Decision

Benefits and harms

There is uncertainty around the benefits and harms of baricitinib for pregnant or breastfeeding women with COVID-19.

In non-pregnant adult patients hospitalised with moderate or severe COVID-19 who require supplemental oxygen, baricitinib probably decreases the incidence of death and the need for invasive mechanical ventilation.

Evidence from randomised trials versus standard care demonstrates that baricitinib has an acceptable safety profile for non-pregnant adults and probably reduces the incidence of serious adverse events. Consideration should be given when administering baricitinib to patients already on other immunosuppressant or immunomodulatory drugs.

Information on use of baricitinib in pregnancy in humans is limited and insufficient (single case report) to assess the drug-associated risks for birth anomalies or pregnancy loss, though placental transfer is expected based on molecular weight [487][488]. However, teratogenic effects has been observed in animal studies when used in high doses [489]. It is also unknown whether baricitinib is excreted in human milk, though animal data have shown excretion of baricitinib in milk [489].

Decisions about baricitinib administration in pregnancy need to be made with consideration of the potential maternal benefit and the theoretical fetal risks. Factors that may weigh into shared decision-making include severity of maternal status, underlying risk factors and gestational age. Placental transfer of baricitinib may be expected based on molecular weight.

Certainty of the Evidence

Certainty of the evidence is moderate for mortality and low for patients requiring invasive mechanical ventilation. Certainty is moderate for adverse and serious adverse events and low for all other outcomes (patients requiring non-invasive ventilation or high-flow oxygen, discontinuation due to adverse events, clinical recovery and time to recovery, and duration of hospitalisation).

Preference and values

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to
Rationale

In non-pregnant adults hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death.

Information on baricitinib in pregnancy in humans is insufficient to assess the drug-associated risks for birth anomalies or pregnancy loss, though teratogenic effects have been observed in animal studies when used in high doses. It is also unknown whether baricitinib is excreted in human milk, however animal data have shown excretion of baricitinib in milk.

Clinical Question/ PICO

Population: Special Populations with COVID-19
Intervention: Baricitinib
Comparator: Standard care

Summary

Evidence indicates that baricitinib probably reduces the risk of death in hospitalised adults who require supplemental oxygen, and may reduce the need for invasive mechanical ventilation, non-invasive ventilation and/or high-flow oxygen.

What is the evidence informing this recommendation?

Evidence comes from two randomised trials—one that compared baricitinib plus remdesivir with remdesivir alone in 1033 adults hospitalised with suspected COVID-19 (ACTT-2) [22], and one that compared baricitinib with standard care in 1525 adults with mild to severe COVID-19 (COV-BARRIER) [559].

Study characteristics

In both studies, mean age of participants was 57 years and 38% were women. In the ACTT-2 trial, patients received either 4 mg baricitinib plus remdesivir (200 mg on day one, 100 mg a day until day 10 or hospital discharge) or remdesivir alone (same regimen as treatment arm). In the COV-BARRIER trial, patients also received 4 mg baricitinib. Pregnant and breastfeeding women were ineligible.

What are the main results?

Baricitinib probably decreases death (40 fewer deaths per 1000; RR 0.63, CI 95% 0.48 to 0.81; 2558 patients in 2 studies) and serious adverse events (40 fewer SAEs per 1000; RR 0.79, CI 95% 0.67 to 0.94; 2518 patients in 2 studies).
Baricitinib may decrease the need for invasive mechanical ventilation, non-invasive ventilation and high-flow nasal oxygen therapy, and may increase clinical recovery. Baricitinib probably has little impact on incidence of adverse events. We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events, duration of hospitalisation or time to recovery.

Our confidence in the results
Certainty of the evidence is moderate for mortality, adverse events and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known harms associated with baricitinib include an increased risk of serious infections, gastrointestinal disorders, thrombosis and headaches [24].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.63 (CI 95% 0.48 — 0.81) Based on data from 2,558 participants in 2 studies. (Randomized controlled)</td>
<td>9 Critical</td>
<td>107 per 1000</td>
<td>67 per 1000</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>End of follow-up</td>
<td>Relative risk 0.66 (CI 95% 0.46 — 0.93) Based on data from 922 participants in 1 studies. (Randomized controlled)</td>
<td>9 Critical</td>
<td>152 per 1000</td>
<td>100 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Non-invasive ventilation or HFNO</td>
<td>End of follow-up</td>
<td>Relative risk 0.83 (CI 95% 0.63 — 1.1) Based on data from 706 participants in 1 studies. (Randomized controlled)</td>
<td>6 Important</td>
<td>236 per 1000</td>
<td>196 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.79 (CI 95% 0.67 — 0.94) Based on data from 2,518 participants in 2 studies. (Randomized controlled)</td>
<td>192 per 1000</td>
<td>192 per 1000</td>
<td>152 per 1000</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Baricitinib</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6 Important</td>
<td>Adverse events End of follow-up</td>
<td>Relative risk 0.95 (CI 95% 0.87 — 1.04) Based on data from 2,535 participants in 2 studies. (Randomized controlled)</td>
<td>451 fewer per 1000</td>
<td>Low Due to serious imprecision and serious indirectness</td>
<td>Baricitinib may make little or no difference to adverse events.</td>
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<tr>
<td></td>
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<td></td>
<td>428 fewer per 1000</td>
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<td></td>
<td></td>
<td></td>
<td>Difference: 23 fewer per 1000 (CI 95% 59 fewer — 18 more)</td>
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<tr>
<td></td>
<td>Discontinuation due to adverse events During treatment</td>
<td>Relative risk 0.8 (CI 95% 0.57 — 1.12) Based on data from 1,502 participants in 1 study. (Randomized controlled)</td>
<td>93 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events.</td>
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<tr>
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<td>74 per 1000</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 19 fewer per 1000 (CI 95% 40 fewer — 11 more)</td>
<td></td>
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<tr>
<td></td>
<td>Clinical recovery End of follow-up</td>
<td>Relative risk 1.07 (CI 95% 1.01 — 1.14) Based on data from 1,033 participants in 1 study. (Randomized controlled)</td>
<td>784 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether baricitinib improves or worsens clinical recovery.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>839 per 1000</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 55 more per 1000 (CI 95% 8 more — 110 more)</td>
<td></td>
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<tr>
<td></td>
<td>Duration of hospitalisation Mean (Days)</td>
<td>Lower better (Randomized controlled)</td>
<td>13.7 (Mean)</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether baricitinib increases or decreases duration of hospitalisation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.9 (Mean)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: MD 0.8 lower CI 95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to recovery Median (Days)</td>
<td>Lower better (Randomized controlled)</td>
<td>11 (Median)</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether baricitinib increases or decreases time to recovery.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 (Median)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CI 95%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. due to only 2 studies.
4. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those
studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.


6. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.


8. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious due to 2 studies.


10. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


12. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals. Only data from one study.


14. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.

15. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals. Only data from one study.

16. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, Wide confidence intervals.

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**6.1.6.1.3 Baricitinib for children and adolescents**

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**Only in research settings**

Do not use baricitinib for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

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*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

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**Evidence To Decision**

**Benefits and harms**

There is uncertainty around the benefits and harms of baricitinib for children and adolescents with COVID-19.

In adult patients hospitalised with moderate or severe COVID-19 who require supplemental oxygen, baricitinib probably decreases the incidence of death and the need for invasive mechanical ventilation.

Evidence from randomised trials versus standard care demonstrates that baricitinib has an acceptable safety profile for adults and probably reduces the incidence of serious adverse events. Consideration should be given
Currently baricitinib is not approved in children or adolescents for any other indication. Given this, uncertainties remain regarding the potential benefits and harms of this drug in this population.

Certainty of the Evidence
In adult patients, certainty of the evidence is moderate for mortality and low for patients requiring invasive mechanical ventilation. Certainty is moderate for adverse and serious adverse events and low for all other outcomes (patients requiring non-invasive ventilation or high-flow oxygen, discontinuation due to adverse events, clinical recovery and time to recovery, and duration of hospitalisation).

For children and adolescents, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Preference and values
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity
We have no systematically collected evidence regarding impact on equity, however this may be affected by geographic area and access to baricitinib.

Acceptability
We have no systematically collected evidence regarding acceptability.

Feasibility
Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale
Currently baricitinib is not approved in children or adolescents for any other indication. Given this, uncertainties remain regarding the potential benefits and harms of this drug in this population.
Clinical Question/ PICO
Population: Special Populations with COVID-19
Intervention: Baricitinib
Comparator: Standard care

Summary
Evidence indicates that baricitinib probably reduces the risk of death in hospitalised adults who require supplemental oxygen, and may reduce the need for invasive mechanical ventilation, non-invasive ventilation and/or high-flow oxygen.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials—one that compared baricitinib plus remdesivir with remdesivir alone in 1033 adults hospitalised with suspected COVID-19 (ACTT-2) [22], and one that compared baricitinib with standard care in 1525 adults with mild to severe COVID-19 (COV-BARRIER) [559].

Study characteristics
In both studies, mean age of participants was 57 years and 38% were women. In the ACTT-2 trial, patients received either 4 mg baricitinib plus remdesivir (200 mg on day one, 100 mg a day until day 10 or hospital discharge) or remdesivir alone (same regimen as treatment arm). In the COV-BARRIER trial, patients also received 4 mg baricitinib. Pregnant and breastfeeding women were ineligible.

What are the main results?
Baricitinib probably decreases death (40 fewer deaths per 1000; RR 0.63, CI 95% 0.48 to 0.81; 2558 patients in 2 studies) and serious adverse events (40 fewer SAEs per 1000; RR 0.79, CI 95% 0.67 to 0.94; 2518 patients in 2 studies).

Baricitinib may decrease the need for invasive mechanical ventilation, non-invasive ventilation and high-flow nasal oxygen therapy, and may increase clinical recovery. Baricitinib probably has little impact on incidence of adverse events. We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events, duration of hospitalisation or time to recovery.

Our confidence in the results
Certainty of the evidence is moderate for mortality, adverse events and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known harms associated with baricitinib include an increased risk of serious infections, gastrointestinal disorders, thrombosis and headaches [24].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Baricitinib</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.63 (CI 95% 0.48 — 0.81) Based on data from 2,558 participants in 2 studies. [2] (Randomized controlled)</td>
<td>107 per 1000</td>
<td>67 per 1000</td>
<td>Low Due to serious imprecision and serious indirectness [2] Baricitinib may decrease incidence of death.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparator Standard care</td>
<td>Intervention Baricitinib</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
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<td>----------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Relative risk 0.66 (CI 0.46 — 0.93) Based on data from 922 participants in 1 studies. ³ (Randomized controlled)</td>
<td>152 per 1000</td>
<td>100 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness ⁴</td>
<td>We are uncertain whether baricitinib improves or worsens invasive mechanical ventilation or ECMO.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>Relative risk 0.83 (CI 0.63 — 1.1) Based on data from 706 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td>236 per 1000</td>
<td>196 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness ⁶</td>
<td>We are uncertain whether baricitinib improves or worsens NIV / HFNO.</td>
</tr>
<tr>
<td>Non-invasive ventilation or HFNO</td>
<td>Relative risk 0.79 (CI 0.67 — 0.94) Based on data from 2,518 participants in 2 studies. ⁷ (Randomized controlled)</td>
<td>192 per 1000</td>
<td>152 per 1000</td>
<td>Low Baricitinib may decrease serious adverse events slightly.</td>
<td></td>
</tr>
<tr>
<td>End of follow-up</td>
<td>Relative risk 0.95 (CI 0.87 — 1.04) Based on data from 2,535 participants in 2 studies. ⁷ (Randomized controlled)</td>
<td>451 per 1000</td>
<td>428 per 1000</td>
<td>Low Baricitinib may make little or no difference to adverse events.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.8 (CI 0.57 — 1.12) Based on data from 1,502 participants in 1 studies. ¹¹ (Randomized controlled)</td>
<td>93 per 1000</td>
<td>74 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness ¹²</td>
<td>We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 1.07 (CI 1.01 — 1.14) Based on data from 1,033 participants in 1 studies. ¹³ (Randomized controlled)</td>
<td>784 per 1000</td>
<td>839 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness ¹⁴</td>
<td>We are uncertain whether baricitinib improves or worsens clinical recovery.</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>Relative risk 0.8 (CI 0.57 — 1.12) Based on data from 1,502 participants in 1 studies. ¹¹ (Randomized controlled)</td>
<td>93 per 1000</td>
<td>74 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness ¹²</td>
<td>We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events.</td>
</tr>
<tr>
<td>During treatment</td>
<td>Relative risk 1.07 (CI 1.01 — 1.14) Based on data from 1,033 participants in 1 studies. ¹³ (Randomized controlled)</td>
<td>784 per 1000</td>
<td>839 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness ¹⁴</td>
<td>We are uncertain whether baricitinib improves or worsens clinical recovery.</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Relative risk 1.07 (CI 1.01 — 1.14) Based on data from 1,033 participants in 1 studies. ¹³ (Randomized controlled)</td>
<td>784 per 1000</td>
<td>839 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness ¹⁴</td>
<td>We are uncertain whether baricitinib improves or worsens clinical recovery.</td>
</tr>
</tbody>
</table>

² Critical
³ Important
⁴ Very low
⁵ Important
⁶ Very low
⁷ Important
⁸ Low
⁹ Important
¹⁰ Low
¹¹ Important
¹² Very low
¹³ Important
¹⁴ Very low
## Outcome Timeframe | Study results and measurements | Comparator | Intervention | Certainty of the Evidence (Quality of evidence) | Plain language summary
---|---|---|---|---|---
### Duration of hospitalisation
Mean (Days)
6 Important
| Lower better (Randomized controlled) | **13.7** (Mean) | **12.9** (Mean) | Very low Due to very serious imprecision and serious indirectness | We are uncertain whether baricitinib increases or decreases duration of hospitalisation.

**Difference:** MD 0.8 lower CI 95%

### Time to recovery
Median (Days)
6 Important
| Lower better (Randomized controlled) | **11** (Median) | **10** (Median) | Very low Due to very serious imprecision and serious indirectness | We are uncertain whether baricitinib increases or decreases time to recovery.

**CI 95%** Very low Due to very serious imprecision and serious indirectness

---

2. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. due to only 2 studies.
4. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.
6. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.
8. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. due to 2 studies.
10. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.
12. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
14. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.
15. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
16. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, Wide confidence intervals.
6.1.6.2 Sarilumab

6.1.6.2.1 Sarilumab for adults

**Conditional recommendation**

Consider using sarilumab for the treatment of COVID-19 in adults who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation.

In patients hospitalised with COVID-19 who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation, sarilumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for sarilumab both within and outside the context of a randomised trial.

Uncertainty remains whether sarilumab impacts mortality in patients who require no ventilatory support or low-flow oxygen.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

**Evidence To Decision**

**Benefits and harms**

**General adult population**

In patients hospitalised with critical COVID-19 who require supplemental oxygen, sarilumab probably decreases the incidence of death.

Evidence from randomised trials versus standard care demonstrates that sarilumab does not increase the risk of serious adverse events, however it probably increases the risk of non-serious adverse events. According to the Therapeutic Goods Administration, common side effects and harms associated with sarilumab include upper respiratory tract infections, neutropenia and injection site reactions [312].

**Children and adolescents**

The safety profile in children and adolescents with COVID-19 has not been established.

**Certainty of the Evidence**

Certainty of the evidence is moderate for mortality, adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that since there are probable mortality benefits most informed patients with COVID-19 who require supplemental oxygen would agree with the recommendation and opt for sarilumab.

**Pregnant or breastfeeding patients**

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for...
Rationale

**General adult population**

In patients hospitalised with COVID-19 who require supplemental oxygen, sarilumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for sarilumab both within and outside the context of a randomised trial.

**Children and adolescents**

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit.

Equity

We have no systematically collected evidence regarding impact on equity; however potential limitations on availability may affect equity based on geographic area and access to sarilumab.

Acceptability

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians, unless contraindicated (e.g. in patients with bacterial, fungal or mycobacterial infections).

Feasibility

Subcutaneous sarilumab (Kevzara; Sanofi-Aventis Australia Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers: 293333, 293334, 293335, 293336; AusPAR). As of 3 December 2021, sarilumab is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Rationale

**General adult population**

In patients hospitalised with COVID-19 who require supplemental oxygen, sarilumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for sarilumab both within and outside the context of a randomised trial.

Clinical Question/ PICO

- **Population:** Patients with COVID-19
- **Intervention:** Sarilumab
- **Comparator:** Standard care

Summary

Evidence indicates that sarilumab probably reduces the risk of death in hospitalised adults who require high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.

**What is the evidence informing this recommendation?**

Evidence comes from three randomised trials that compared sarilumab with standard care in 450 adults hospitalised with critical COVID-19 requiring organ support (48 received sarilumab) [85] and 2238 patients...
hospitalised with severe–critical COVID-19 \[314]\[475].

Additional data from the REMAP-CAP investigators were published in medRxiv on 22 Jun 2021 (485 randomised to sarilumab). These new data will be added to the existing study and an updated recommendation will be included in a future version of the guideline. Results of the SARTRE study (200 patients) were published in Infect Dis Ther on 17 Oct 2021 and the CORIMUNO-SARI-1 study (144 patients) in Lancet Rheumatol on 17 Nov 2021.

**Study characteristics**
Mean age of participants ranged from 58 to 63 years, and the proportion of women ranged from 19 to 36%. Pregnant and breastfeeding women were ineligible.

In REMAP-CAP and Lescure et al. there was a disproportionate number of patients between arms. In REMAP-CAP the intervention arm consisted primarily of patients receiving tocilizumab—only 48 of the 865 patients in the study received sarilumab. Conversely, Lescure et al. used a 2:2:1 randomisation ratio (200 mg sarilumab, 400 mg sarilumab, placebo) and only 84 of the 416 patients received placebo. In REMAP-CAP there was a higher proportion of patients with diabetes (37% vs 27%) and severe cardiovascular disease (12% vs 2%) in the standard care arm compared with the sarilumab arm.

Consideration was given to separating data based on severity of illness (severe and critical subgroups); however it was considered inappropriate to do so due to limited data and a non-significant test for subgroup differences (P=0.08).

**What are the main results?**
Sarilumab probably decreases death slightly (29 fewer deaths per 1000; RR 0.90, CI 95% 0.73 to 1.10; 2303 patients in 3 studies). Sarilumab probably has little impact on serious adverse events or discharge from hospital, but probably increases adverse events slightly (43 more per 1000; RR 1.08, CI 95% 0.98 to 1.19; 1865 patients in 2 studies). We are unsure whether sarilumab increases or decreases the requirement for ventilation, admission to ICU, clinical improvement or clinical recovery.

**Our confidence in the results**
Certainty of the evidence is moderate for death, serious adverse events and adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness \[312\].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [all patients]</td>
<td>Relative risk 0.9 (CI 95% 0.73 — 1.1) Based on data from 2,303 participants in 3 studies. ¹ (Randomized controlled)</td>
<td>294 per 1000</td>
<td>265 per 1000</td>
<td>Moderate Due to serious imprecision ² Sarilumab probably decreases death slightly.</td>
<td></td>
</tr>
<tr>
<td>Within 21–29 days of commencing treatment</td>
<td>Difference: 29 fewer per 1000 (CI 95% 79 fewer — 29 more)</td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

² Critical
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requiring ventilation (HFNO, NIV, MV)</td>
<td>End of follow-up</td>
<td>Relative risk 1.15 (CI 95% 0.66 — 1.99) Based on data from 416 participants in 1 study.</td>
<td>Standard care</td>
<td>Sarilumab</td>
<td>Low</td>
<td>Sarilumab may have little impact on number of patients requiring ventilation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.02 (CI 95% 0.89 — 1.18) Based on data from 2,315 participants in 3 studies.</td>
<td>Standard care</td>
<td>Sarilumab</td>
<td>Moderate</td>
<td>Sarilumab probably has little impact on serious adverse events.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.08 (CI 95% 0.98 — 1.19) Based on data from 1,865 participants in 2 studies.</td>
<td>Standard care</td>
<td>Sarilumab</td>
<td>Moderate</td>
<td>Sarilumab probably increases adverse events slightly.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>During treatment</td>
<td>Relative risk 1.06 (CI 95% 0.49 — 2.29) Based on data from 268 participants in 1 study.</td>
<td>Standard care</td>
<td>Sarilumab</td>
<td>Low</td>
<td>We are uncertain whether sarilumab increases or decreases admission to ICU (35 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Within 22 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.87 — 1.1) Based on data from 1,097 participants in 1 study.</td>
<td>Standard care</td>
<td>Sarilumab</td>
<td>Low</td>
<td>Sarilumab may have little impact on clinical improvement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 22 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.89 — 1.1) Based on data from 1,449 participants in 1 study.</td>
<td>Standard care</td>
<td>Sarilumab</td>
<td>Low</td>
<td>Sarilumab may have little impact on clinical recovery.</td>
</tr>
</tbody>
</table>
### 6.1.6.2.2 Sarilumab for pregnant or breastfeeding women

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Sarilumab</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge from hospital</td>
<td>Relative risk 0.99 (CI 95% 0.92 – 1.07) Based on data from 1,513 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Moderate Due to serious imprecision 16</td>
<td>Sarilumab probably has little impact on discharge from hospital.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>590 per 1000</td>
<td>584 per 1000</td>
<td>6 fewer per 1000 (CI 95% 47 fewer – 41 more)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision:** serious. Wide confidence intervals.
4. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
6. **Imprecision:** serious. Wide confidence intervals.
8. **Imprecision:** serious. Wide confidence intervals.
10. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
12. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
14. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
16. **Imprecision:** serious. Wide confidence intervals.

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**6.1.6.2.2 Sarilumab for pregnant or breastfeeding women**

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**Only in research settings**

Do not use sarilumab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*
Evidence To Decision

<table>
<thead>
<tr>
<th>Benefits and harms</th>
<th>Small net benefit, or little difference between alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is uncertainty around the benefits and harms of sarilumab for pregnant or breastfeeding women with COVID-19.</td>
<td></td>
</tr>
<tr>
<td>In non-pregnant adult patients hospitalised with critical COVID-19 who require supplemental oxygen, sarilumab probably decreases the incidence of death.</td>
<td></td>
</tr>
<tr>
<td>Evidence from randomised trials versus standard care in non-pregnant adults demonstrates that sarilumab does not increase the risk of serious adverse events, however it probably increases the risk of non-serious adverse events. According to the Therapeutic Goods Administration, common side effects and harms associated with sarilumab include upper respiratory tract infections, neutropaenia and injection site reactions [312].</td>
<td></td>
</tr>
</tbody>
</table>

Certainty of the Evidence

- Certainty of the evidence is moderate for mortality, adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

- For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Preference and values

- Substantial variability is expected or uncertain

- We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations

- Important issues, or potential issues not investigated

- We have no systematically collected evidence regarding cost-benefit.

Equity

- Important issues, or potential issues not investigated

- We have no systematically collected evidence regarding impact on equity; however potential limitations on availability may affect equity based on geographic area and access to sarilumab.

Acceptability

- Important issues, or potential issues not investigated

- We have no systematically collected evidence regarding acceptability by pregnant or breastfeeding women.

Feasibility

- Important issues, or potential issues not investigated

- Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

- There is no information on the use of sarilumab during pregnancy and breastfeeding in humans. Limited data are
available from animal studies, where the possibility that sarilumab increases stillbirth or pregnancy loss rates cannot be ruled out. It is not known if sarilumab is present in breast milk.

In non-pregnant adult patients hospitalised with COVID-19 who require supplemental oxygen, sarilumab probably reduces the risk of death. Because of this, the Taskforce has given a conditional recommendation for sarilumab in non-pregnant adult patients both within and outside the context of a randomised trial.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Sarilumab</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary

Evidence indicates that sarilumab probably reduces the risk of death in hospitalised adults who require high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials that compared sarilumab with standard care in 450 adults hospitalised with critical COVID-19 requiring organ support (48 received sarilumab) [85] and 2238 patients hospitalised with severe–critical COVID-19 [314][475].

Additional data from the REMAP-CAP investigators were published in medRxiv on 22 Jun 2021 (485 randomised to sarilumab). These new data will be added to the existing study and an updated recommendation will be included in a future version of the guideline. Results of the SARTRE study (200 patients) were published in Infect Dis Ther on 17 Oct 2021 and the CORIMUNO-SARI-1 study (144 patients) in Lancet Rheumatol on 17 Nov 2021.

Study characteristics

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Consideration was given to separating data based on severity of illness (severe and critical subgroups); however it was considered inappropriate to do so due to limited data and a non-significant test for subgroup differences (P=0.08).

What are the main results?

Sarilumab probably decreases death slightly (29 fewer deaths per 1000; RR 0.90, CI 95% 0.73 to 1.10; 2303 patients in 3 studies). Sarilumab probably has little impact on serious adverse events or discharge from hospital, but probably increases adverse events slightly (43 more per 1000; RR 1.08, CI 95% 0.98 to 1.19; 1865 patients in 2 studies). We are unsure whether sarilumab increases or decreases the requirement for ventilation, admission to ICU, clinical improvement or clinical recovery.

Our confidence in the results

Certainty of the evidence is moderate for death, serious adverse events and adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information

According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness [312].
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Sarilumab</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [all patients]</td>
<td>Within 21-29 days of commencing treatment</td>
<td>Relative risk 0.9 (CI 95% 0.73 — 1.1) Based on data from 2,303 participants in 3 studies. 2 (Randomized controlled)</td>
<td>294 per 1000</td>
<td>265 per 1000</td>
<td>Moderate Due to serious imprecision 2</td>
<td>Sarilumab probably decreases death slightly.</td>
</tr>
<tr>
<td>Requiring ventilation (HFNO, NIV, MV)</td>
<td>End of follow-up</td>
<td>Relative risk 1.15 (CI 95% 0.66 — 1.99) Based on data from 416 participants in 1 studies. 3 (Randomized controlled)</td>
<td>155 per 1000</td>
<td>178 per 1000</td>
<td>Low Due to very serious imprecision 4</td>
<td>Sarilumab may have little impact on number of patients requiring ventilation.</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.02 (CI 95% 0.89 — 1.18) Based on data from 2,315 participants in 3 studies. 5 (Randomized controlled)</td>
<td>199 per 1000</td>
<td>203 per 1000</td>
<td>Moderate Due to serious imprecision 6</td>
<td>Sarilumab probably has little impact on serious adverse events.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.08 (CI 95% 0.98 — 1.19) Based on data from 1,865 participants in 2 studies. 7 (Randomized controlled)</td>
<td>539 per 1000</td>
<td>582 per 1000</td>
<td>Moderate Due to serious imprecision 8</td>
<td>Sarilumab probably increases adverse events slightly.</td>
</tr>
<tr>
<td>Admission to ICU During treatment</td>
<td>6 Important</td>
<td>Relative risk 1.06 (CI 95% 0.49 — 2.29) Based on data from 268 participants in 1 studies. 9 (Randomized controlled)</td>
<td>125 per 1000</td>
<td>132 per 1000</td>
<td>Low Due to very serious imprecision 10</td>
<td>We are uncertain whether sarilumab increases or decreases admission to ICU (35 events).</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Within 22 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.87 — 1.1) Based on data from 1,097 participants in 1 studies. 11 (Randomized controlled)</td>
<td>608 per 1000</td>
<td>596 per 1000</td>
<td>Low Due to very serious imprecision 12</td>
<td>Sarilumab may have little impact on clinical improvement.</td>
</tr>
</tbody>
</table>
### Outcome

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical recovery</td>
<td>Within 22 days of commencing treatment</td>
<td>6 Important</td>
<td>Relative risk 0.99 (CI 95% 0.89 – 1.1) Based on data from 1,449 participants in 1 study.</td>
<td>589 per 1000</td>
<td>Low&lt;br&gt;Due to very serious imprecision&lt;br&gt;Sarilumab may have little impact on clinical recovery.</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>End of follow-up</td>
<td>6 Important</td>
<td>Relative risk 0.99 (CI 95% 0.92 – 1.07) Based on data from 1,513 participants in 2 studies.</td>
<td>590 per 1000</td>
<td>Moderate&lt;br&gt;Due to serious imprecision&lt;br&gt;Sarilumab probably has little impact on discharge from hospital.</td>
</tr>
</tbody>
</table>

2. **Imprecision:** serious. Wide confidence intervals.
4. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
6. **Imprecision:** serious. Wide confidence intervals.
8. **Imprecision:** serious. Wide confidence intervals.
10. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
12. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
14. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
16. **Imprecision:** serious. Wide confidence intervals.

### 6.1.6.2.3 Sarilumab for children and adolescents
Only in research settings

Do not use sarilumab for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

**Benefits and harms**

In adult patients hospitalised with critical COVID-19 who require supplemental oxygen, sarilumab probably decreases the incidence of death.

Evidence from randomised trials versus standard care in adult patients demonstrates that sarilumab does not increase the risk of serious adverse events, however it probably increases the risk of non-serious adverse events. According to the Therapeutic Goods Administration, common side effects and harms associated with sarilumab include upper respiratory tract infections, neutropaenia and injection site reactions.

Currently there is insufficient evidence for the safety of sarilumab in children and adolescents, as it has not been approved previously for any other indication. Phase II trials are currently being conducted to assess this in children and adolescents for other indications.

**Certainty of the Evidence**

Certainty of the evidence is moderate for mortality, adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Preference and values**

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit.

**Equity**

We have no systematically collected evidence regarding impact on equity; however potential limitations on availability may affect equity based on geographic area and access to sarilumab.
Currently, sarilumab is not approved in children or adolescents for any other indication. Given this, uncertainties remain regarding the potential benefits and harms of this drug in this population.

Clinical Question/ PICO

| Population: | Special Populations with COVID-19 |
| Intervention: | Sarilumab |
| Comparator: | Standard care |

Summary

Evidence indicates that sarilumab probably reduces the risk of death in hospitalised adults who require high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials that compared sarilumab with standard care in 450 adults hospitalised with critical COVID-19 requiring organ support (48 received sarilumab) [85] and 2238 patients hospitalised with severe–critical COVID-19 [314][475].

Study characteristics

Mean age of participants ranged from 58 to 63 years, and the proportion of women ranged from 19 to 36%. Pregnant and breastfeeding women were ineligible.

In REMAP-CAP there was a higher proportion of patients with diabetes (37% vs 27%) and severe cardiovascular disease (12% vs 2%) in the standard care arm compared with the sarilumab arm.

In REMAP-CAP and Lescure et al. there was a disproportionate number of patients between arms. In REMAP-CAP the intervention arm consisted primarily of patients receiving tocilizumab—only 48 of the 865 patients in the study received sarilumab. Conversely, Lescure et al. used a 2:2:1 randomisation ratio (200 mg sarilumab, 400 mg sarilumab, placebo) and only 84 of the 416 patients received placebo.

Consideration was given to separating data based on severity of illness (severe and critical subgroups); however it was considered inappropriate to do so due to limited data and a non-significant test for subgroup differences (P=0.08).

What are the main results?

Sarilumab probably decreases death slightly (29 fewer deaths per 1000; RR 0.90, CI 95% 0.73 to 1.10; 2303 patients in 3 studies). Sarilumab probably has little impact on serious adverse events or discharge from hospital, but probably increases adverse events slightly (43 more per 1000; RR 1.08, CI 95% 0.98 to 1.19; 1865 patients in 2 studies). We are unsure whether sarilumab increases or decreases the requirement for ventilation, admission to ICU, clinical improvement or clinical recovery.

Our confidence in the results

Certainty of the evidence is moderate for death, serious adverse events and adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).
### Additional information

According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness [312].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Sarilumab</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [all patients] Within 21-29 days of commencing treatment</td>
<td>Relative risk 0.9 (CI 95% 0.73 — 1.1) Based on data from 2,303 participants in 3 studies.</td>
<td>294 per 1000</td>
<td>265 per 1000</td>
<td>Low</td>
<td>Due to serious imprecision and serious indirectness 2 Sarilumab may decrease incidence of death slightly.</td>
</tr>
<tr>
<td>Requiring ventilation (HFNO, NIV, MV) End of follow-up</td>
<td>Relative risk 1.15 (CI 95% 0.66 — 1.99) Based on data from 416 participants in 1 study.</td>
<td>155 per 1000</td>
<td>178 per 1000</td>
<td>Very low</td>
<td>Due to very serious imprecision and serious indirectness 4 We are uncertain whether sarilumab improves or worsens requirement for ventilation.</td>
</tr>
<tr>
<td>Serious adverse events End of follow-up</td>
<td>Relative risk 1.02 (CI 95% 0.89 — 1.18) Based on data from 2,315 participants in 3 studies.</td>
<td>199 per 1000</td>
<td>203 per 1000</td>
<td>Low</td>
<td>Due to serious imprecision and serious indirectness 6 Sarilumab may make little or no difference to serious adverse events.</td>
</tr>
<tr>
<td>Adverse events End of follow-up</td>
<td>Relative risk 1.08 (CI 95% 0.98 — 1.19) Based on data from 1,865 participants in 2 studies.</td>
<td>539 per 1000</td>
<td>582 per 1000</td>
<td>Low</td>
<td>Due to serious imprecision and serious indirectness 8 Sarilumab may increase adverse events slightly.</td>
</tr>
<tr>
<td>Admission to ICU During treatment</td>
<td>Relative risk 1.06 (CI 95% 0.49 — 2.29) Based on data from 268 participants in 1 study.</td>
<td>125 per 1000</td>
<td>132 per 1000</td>
<td>Very low</td>
<td>Due to very serious imprecision and serious We are uncertain whether sarilumab increases or decreases admission to ICU.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>---------</td>
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<td>------------------------------------------------</td>
</tr>
<tr>
<td>6 Important</td>
<td>Controlled)</td>
<td>Relative risk 0.98 (CI 95% 0.87 – 1.1) Based on data from 1,097 participants in 1 studies.</td>
<td>Standard care</td>
<td>Sarilumab</td>
<td>1,000 (CI 95% 64 fewer – 161 more)</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Within 22 days of commencing treatment</td>
<td>608 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether sarilumab increases or decreases clinical improvement.</td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td>Relative risk 0.99 (CI 95% 0.89 – 1.1) Based on data from 1,449 participants in 1 studies.</td>
<td>596 per 1000</td>
<td>12 fewer per 1000 (CI 95% 79 fewer – 61 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 22 days of commencing treatment</td>
<td>589 per 1000</td>
<td>Very low Due to very serious imprecision and very serious indirectness</td>
<td>We are uncertain whether sarilumab increases or decreases clinical recovery.</td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td>Relative risk 0.99 (CI 95% 0.92 – 1.07) Based on data from 1,513 participants in 2 studies.</td>
<td>583 per 1000</td>
<td>6 fewer per 1000 (CI 95% 65 fewer – 59 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>End of follow-up</td>
<td>584 per 1000</td>
<td>6 fewer per 1000 (CI 95% 47 fewer – 41 more)</td>
<td>Low Due to serious imprecision and serious indirectness</td>
<td>Sarilumab may make little or no difference to discharge from hospital.</td>
</tr>
<tr>
<td>6 Important</td>
<td>Relative risk 0.99 (CI 95% 0.96 – 1.04) Based on data from 1,513 participants in 2 studies.</td>
<td>584 per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.
4. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
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8. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.
10. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.

11. Clinical improvement
12. Clinical recovery
13. Discharge from hospital
6.1.6.3 Tocilizumab

6.1.6.3.1 Tocilizumab for adults

**Conditional recommendation**

Consider using tocilizumab for the treatment of COVID-19 in adults who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

The Taskforce notes the current critical shortage of tocilizumab. Therefore, in patients who are receiving supplemental oxygen, baricitinib should be considered as an alternative to tocilizumab, unless contraindicated. For the TGA and Medicine Availability Working Group statements regarding the shortage, click here.

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- Patients > 90 kg: 800 mg tocilizumab
- Patients 66–90 kg: 600 mg tocilizumab
- Patients 41–65 kg: 400 mg tocilizumab
- Patients ≤ 40 kg: 8 mg/kg tocilizumab

In the RECOVERY trial, 29% of patients received a second dose 12-24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.
Evidence To Decision

**Benefits and harms**

In patients hospitalised with moderate to critical COVID-19 who require supplemental oxygen, tocilizumab decreases the need for invasive mechanical ventilation and probably reduces the incidence of death.

Evidence from randomised trials versus standard care demonstrates that tocilizumab has an acceptable safety profile and may reduce the incidence of serious adverse events. Consideration should be given when administering tocilizumab to patients already on other immunosuppressant or immunomodulatory drugs. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab [84].

**Older people living with frailty or cognitive impairment**

People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

**People requiring palliative care**

There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

For the critical outcomes, certainty of the evidence is high for mortality and patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay, all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that since there are probable mortality benefits most informed patients with COVID-19 who require supplemental oxygen would agree with the recommendation and opt for tocilizumab.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Additional variability may be expected in these populations given the potentially different preferences and values placed on outcomes and goals of care, such as symptom relief.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit, however there are significant costs associated with tocilizumab use (approximately AU$400 per 400 mg vial).

**Equity**

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of tocilizumab may affect equity based on geographic area and access to tocilizumab.

**Acceptability**

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable.
Rationale

General adult population
In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial.

Feasibility

Intravenous tocilizumab (Actemra; Roche Products Pty Ltd) was granted provisional approval for the treatment of COVID-19 on 1 December 2021 (ARTG numbers: 370315, 370314, 296808, 234034, 149404, 149403, 149402; AusPAR unpublished as of 3 December 2021)

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Clinical Question/ PICO

| Population: | Patients with COVID-19 |
| Intervention: | Tocilizumab |
| Comparator: | Standard care |

Summary

Evidence indicates that tocilizumab probably reduces the risk of death in hospitalised adults who require supplemental oxygen, as well as reducing the need for invasive mechanical ventilation and admission to ICU.

What is the evidence informing this recommendation?

Evidence comes from 11 randomised trials that compared tocilizumab with standard care in over 7200 adults hospitalised with COVID-19 [68][69][71][72][81][85][86][87][90][92][605]. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate-to-critical COVID-19 [90]. There was variability in disease severity among patients included in the trials (Table 1).

Results from the tocilizumab arm of the REMAP-CAP trial showed a strong mortality benefit in patients with critical illness who were receiving organ support [85]. These data contrasted with the existing meta-analysis of randomised trials conducted by the Taskforce, in which a mortality benefit was not observed in patients using tocilizumab. However, the vast majority of relevant data published before REMAP-CAP was of patients with moderate to severe illness (Table 1), with the exception of the COVACTA trial [86], which included 108 patients with critical illness.

To determine whether differences in observed effect on death might be explained by differences in disease severity, the Taskforce assessed the credibility of these subgroups using the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN). Results from this analysis suggest that it is inappropriate to separate data based on disease severity. More specifically:

- the majority of data included in the comparison came from between trials rather than within trials
- only a single between-trial publication (REMAP-CAP) provided data for the smallest subgroup (patients with critical illness)
- the test for subgroup differences suggests that chance may be a likely explanation (P = 0.74), and that the data are largely homogenous ($I^2 = 0\%$)
- results from the COVACTA trial conflict with those of the REMAP-CAP trial, showing no mortality benefit in critical patients treated with tocilizumab.

Following publication of the tocilizumab arm of the RECOVERY trial, the Taskforce updated the ICEMAN
analysis to determine whether the inclusion of the RECOVERY data affected the appropriateness of subgroup analyses. Results from the updated analysis suggest that it is still likely to be inappropriate to separate data based on disease severity. This is because:

- There remained limited within-trial (COVACTA and RECOVERY) and between-trial publications (REMAP-CAP, COVACTA and RECOVERY) that provide data for the smallest subgroup (patients with critical illness).
- The test for subgroup differences continues to suggest that chance may be a likely explanation, with the P value increasing to 0.78 following inclusion of the RECOVERY trial. Data remains sufficiently homogenous between data points ($I^2 = 0\%$).

It should be noted that the ICEMAN analysis did not include the trial by Veiga et al. [81], as this study pooled mortality results for patients with moderate to critical illness, and thus did not contribute data to either of the proposed subgroups. The full ICEMAN analysis can be found here.

Additional data from the REMAP-CAP investigators were published in medRxiv on 22 Jun 2021 (972 randomised to tocilizumab). These new data will be added to the existing study and an updated recommendation will be included in a future version of the guideline.

We have found two new studies comparing tocilizumab with standard care (Rutgers et al. SSRN doi: 10.2139/ssrn.3834311 and Talaschian et al. Res Sq doi: 10.21203/rs.3.rs-463921/v1). These studies are currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

**Study characteristics**

Mean or median age ranged from 55 to 64 years and women comprised 26 to 50% of patients across the studies. Pregnant and breastfeeding women were generally ineligible, with the exception of RECOVERY which included three pregnant patients. Studies included patients with moderate, severe and critical COVID-19 (Table 1).

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Number of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate–Severe</td>
<td>1132</td>
<td>[68][69][71][72][87][92]</td>
</tr>
<tr>
<td>Moderate–Critical</td>
<td>5323</td>
<td>[81][86][90][605]</td>
</tr>
<tr>
<td>Critical</td>
<td>755</td>
<td>[85]</td>
</tr>
</tbody>
</table>

All included trials reported high levels of the inflammatory marker C-reactive protein (CRP) (Table 2). Thresholds for CRP or other biomarkers of inflammation to guide use of tocilizumab within included trials were variable; however these should be considered where there is evidence of systemic inflammation.

**Table 2: Baseline levels of CRP within included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Tocilizumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMAP-CAP</td>
<td>Median (IQR): 150 (85–221)</td>
<td>Median (IQR): 130 (71–208)</td>
</tr>
<tr>
<td>Hermine 2020</td>
<td>Median (IQR): 120 (75–220)</td>
<td>Median (IQR): 127 (84–171)</td>
</tr>
<tr>
<td>Rosas 2021</td>
<td>Mean (SD): 168 (101)</td>
<td>Mean (SD): 173 (114)</td>
</tr>
<tr>
<td>Salama 2020</td>
<td>Mean (SD): 152 (177)</td>
<td>Mean (SD): 203 (405)</td>
</tr>
<tr>
<td>Veiga 2021</td>
<td>Mean (SD): 160 (104)</td>
<td>Mean (SD): 193 (283)</td>
</tr>
</tbody>
</table>

What are the main results?

Tocilizumab probably decreases death slightly (39 fewer per 1000; RR 0.87, CI 95% 0.8 to 0.93; 7121 patients in 10 studies) and the need for invasive mechanical ventilation (41 fewer per 1000; RR 0.79, CI 95% 0.70 to 0.9; 4248 patients in 4 studies). In addition, tocilizumab probably decreases the number of patients admitted to ICU (76 fewer per 1000; RR 0.82, CI 95% 0.54 to 1.23; 699 patients in 4 studies), and decreases duration of hospital stay.

Tocilizumab probably has little impact on adverse or serious adverse events, septic shock, number of patients discharged from hospital or clinical progression. The effect of tocilizumab on other outcomes is uncertain.
Our confidence in the results
For the critical outcomes, certainty of the evidence is high for death and patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay (RECOVERY), all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, common adverse effects related to tocilizumab are generally mild and include headache, dizziness, infections and injection site reactions [66]. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab.

According to the Therapeutic Goods Administration, the safety and efficacy of intravenous tocilizumab in children under 18 years of age with conditions other than polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA) or cytokine release syndrome (CRS) have not been established. The use of tocilizumab in children under two years of age has not been studied.

According to the Therapeutic Goods Administration, tocilizumab should not be used during pregnancy unless clearly necessary. There are no adequate data from the use of tocilizumab in pregnant women. The potential risk for humans is unknown. Women of childbearing potential should be advised to use adequate contraception during and for several months after therapy with tocilizumab. It is unknown whether tocilizumab is excreted in human breast milk, and its efficacy and safety in lactating women has not been established.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Day 21-28 after commencing treatment</td>
<td>Relative risk 0.87 (CI 95% 0.8 — 0.93) Based on data from 7,121 participants in 10 studies. ¹</td>
<td>302 per 1000</td>
<td>263 per 1000</td>
<td>High</td>
<td>Tocilizumab decreases death slightly.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>End of follow-up</td>
<td>Relative risk 0.79 (CI 95% 0.7 — 0.9) Based on data from 4,246 participants in 4 studies. ²</td>
<td>193 per 1000</td>
<td>152 per 1000</td>
<td>High</td>
<td>Tocilizumab decreases the need for invasive mechanical ventilation.</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Within 14 days</td>
<td>Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from 130 participants in 1 studies. ³</td>
<td>284 per 1000</td>
<td>142 per 1000</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>We are uncertain whether tocilizumab increases or decreases respiratory failure or ARDS (28 events).</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>of commencing treatment</td>
<td>9 Critical</td>
<td></td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>1000 (CI 95% 213 fewer — 9 more)</td>
<td>Tocilizumab probably decreases admission to ICU (12 events).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td>Relative risk 0.89 (CI 95% 0.77 — 1.02)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>193 per 1000</td>
<td>Tocilizumab probably has little impact on serious adverse events</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>6 Important</td>
<td>Based on data from 2,951 participants in 9 studies.</td>
<td>(Randomized controlled)</td>
<td>(Randomized controlled)</td>
<td>172 per 1000</td>
<td>Tocilizumab probably has little impact on serious adverse events</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td>Relative risk 1.04 (CI 95% 0.9 — 1.21)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>525 per 1000</td>
<td>Tocilizumab probably has little impact on adverse events</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>6 Important</td>
<td>Based on data from 2,204 participants in 8 studies.</td>
<td>(Randomized controlled)</td>
<td>(Randomized controlled)</td>
<td>546 per 1000</td>
<td>Tocilizumab probably has little impact on adverse events</td>
</tr>
<tr>
<td>Septic shock</td>
<td></td>
<td>Relative risk 0.76 (CI 95% 0.44 — 1.33)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>41 per 1000</td>
<td>Tocilizumab probably has little impact on septic shock (51 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>6 Important</td>
<td>Based on data from 1,457 participants in 3 studies.</td>
<td>(Randomized controlled)</td>
<td>(Randomized controlled)</td>
<td>31 per 1000</td>
<td>Tocilizumab probably has little impact on septic shock (51 events).</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td></td>
<td>Relative risk 0.82 (CI 95% 0.54 — 1.23)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>423 per 1000</td>
<td>Tocilizumab probably decreases admission to ICU.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>6 Important</td>
<td>Based on data from 699 participants in 4 studies.</td>
<td>(Randomized controlled)</td>
<td>(Randomized controlled)</td>
<td>347 per 1000</td>
<td>Tocilizumab probably decreases admission to ICU.</td>
</tr>
<tr>
<td>Discharged from hospital</td>
<td></td>
<td>Relative risk 1.05 (CI 95% 0.98 — 1.13)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>542 per 1000</td>
<td>Tocilizumab probably decreases discharged from hospital</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>6 Important</td>
<td>Based on data from 5,251 participants in 5 studies.</td>
<td>(Randomized controlled)</td>
<td>(Randomized controlled)</td>
<td>569 per 1000</td>
<td>Tocilizumab probably decreases discharged from hospital</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td>Relative risk 1.08 (CI 95% 0.92 — 1.27)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>871 941</td>
<td>We are uncertain whether tocilizumab</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
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<td>---------</td>
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<td>-----------------------------------------------</td>
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</tr>
<tr>
<td><strong>recovery</strong></td>
<td>End of follow-up</td>
<td>Based on data from 65 participants in 1 studies. 15 (Randomized controlled)</td>
<td>Standard care per 1000</td>
<td>Tocilizumab per 1000</td>
<td>Due to very serious imprecision 16 increases or decreases clinical recovery.</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 95% 0.94 – 1.12) Based on data from 242 participants in 1 studies. 17 (Randomized controlled)</td>
<td>889 per 1000</td>
<td>916 per 1000</td>
<td>Low</td>
<td>We are uncertain whether tocilizumab increases or decreases clinical improvement.</td>
</tr>
<tr>
<td><strong>Clinical progression</strong></td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.08 (CI 95% 0.72 – 1.62) Based on data from 365 participants in 2 studies. 19 (Randomized controlled)</td>
<td>215 per 1000</td>
<td>232 per 1000</td>
<td>Moderate Due to serious imprecision 18 Tocilizumab probably has little impact on clinical progression.</td>
<td></td>
</tr>
<tr>
<td><strong>Time to deterioration</strong></td>
<td>Days</td>
<td>Hazard Ratio 1.11 (CI 95% 0.59 – 2.1) Based on data from 45 participants in 1 studies. (Randomized controlled)</td>
<td>27.9 (Median)</td>
<td>15 (Median)</td>
<td>Low Due to very serious imprecision 21 We are uncertain whether tocilizumab increases or decreases time to discharge.</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of mechanical ventilation</strong></td>
<td>Days</td>
<td>Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from: 19 participants in 1 studies. 22 (Randomized controlled)</td>
<td>5 (Median)</td>
<td>6 (Median)</td>
<td>Low Due to very serious imprecision 23 We are uncertain whether tocilizumab decreases duration of mechanical ventilation.</td>
<td></td>
</tr>
<tr>
<td><strong>Time to improvement</strong></td>
<td>Days</td>
<td>Based on data from: 219 participants in 1 studies. 24 (Randomized controlled)</td>
<td>5 (Median)</td>
<td>6 (Median)</td>
<td>Low Due to very serious imprecision 25 We are uncertain whether tocilizumab increases or decreases time to improvement.</td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Tocilizumab</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------</td>
<td>---------------------------</td>
<td>--------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay (mean) Days 6 Important</td>
<td>Based on data from: 129 participants in 1 studies.</td>
<td>14.7 (Mean)</td>
<td>11.3 (Mean)</td>
<td>Low</td>
<td>We are uncertain whether tocilizumab decreases duration of hospital stay.</td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay (median) Days 6 Important</td>
<td>Lower better Based on data from: 4,116 participants in 1 studies. (Randomized controlled)</td>
<td>28 (Median)</td>
<td>20 (Median)</td>
<td>Moderate</td>
<td>Tocilizumab probably decreases duration of hospital stay.</td>
<td></td>
</tr>
</tbody>
</table>

2. Baseline/comparator: Control arm of reference used for intervention.
4. Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study.
8. Imprecision: serious. Wide confidence intervals.
10. Imprecision: serious. Wide confidence intervals.
16. Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study.
18. Imprecision: very serious. Wide confidence intervals, Only data from one study, Low number of patients.
21. Imprecision: very serious. Low number of patients, Only data from one study.
6.1.6.3.2 Tocilizumab for pregnant or breastfeeding women

**Conditional recommendation**

Consider using tocilizumab for the treatment of COVID-19 in pregnant or breastfeeding women who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- Patients > 90 kg: 800 mg tocilizumab
- Patients 66–90 kg: 600 mg tocilizumab
- Patients 41–65 kg: 400 mg tocilizumab
- Patients ≤ 40 kg: 8 mg/kg tocilizumab

In pregnant and breastfeeding women, dosing should be based on body weight at time of clinical need.

In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

For the babies of women who received tocilizumab during pregnancy (after 20 weeks of gestation), live vaccines (rotavirus and BCG) should be avoided in the first six months of life. All non-live vaccinations are safe and should be undertaken (see factsheet).

In women who receive tocilizumab while breastfeeding only, live vaccines (rotavirus and BCG) can be given to the baby (see factsheet).

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.
Evidence To Decision

**Benefits and harms**

In patients hospitalised with moderate to critical COVID-19 who require supplemental oxygen, tocilizumab decreases the need for invasive mechanical ventilation and probably reduces the incidence of death.

Evidence from randomised trials in non-pregnant patients demonstrates that tocilizumab when compared with standard care has an acceptable safety profile and may reduce the incidence of serious adverse events. Consideration should be given when administering tocilizumab to patients already on other immunosuppressant or immunomodulatory drugs. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab [88].

The safety profile of tocilizumab has not been described for pregnant and breastfeeding women. Limited observational data on the effects of tocilizumab in pregnant and breastfeeding women reported in the literature suggest that rates of congenital anomaly, pregnancy loss and other adverse outcomes are not higher than the general population [93]. A 2021 review of available safety data on tocilizumab in pregnant and breastfeeding people did not identify a serious safety signal, however there are currently insufficient data available, particularly on tocilizumab exposure in the second or third trimester of pregnancy [558].

The RECOVERY trial protocol specified that pregnant and breastfeeding women were eligible for the tocilizumab arm. The trial specified that, for pregnant women treated with tocilizumab after 20 weeks’ gestation, their infant should not be immunised with live vaccines (such as rotavirus and BCG) for the first six months of life [96]. The Australian Immunisation Handbook specifies that BCG can be administered up to 12 months of age [97].

A small observational study of 12 pregnant women with severe COVID-19 in Spain described the use of tocilizumab, though most also received other treatments (such as lopinavir- ritonavir, azithromycin, hydroxychloroquine, corticosteroids and interferon β-1b [94]. All 12 pregnancies resulted in live births, though hepatotoxicity was observed in two women (which had resolved by discharge) and cytomegalovirus reactivation was detected in one woman.

In breastfeeding women, available evidence shows that very low concentrations of tocilizumab are identified in breast milk and no drug is transferred into the serum of breastfed infants [98][99][558]. Hence, the Pregnancy and Perinatal Care Panel considered that live vaccines (rotavirus and BCG) can still be used in babies of women who received tocilizumab during breastfeeding only.

**Certainty of the Evidence**

For the critical outcomes, certainty of the evidence in non-pregnant patients is moderate for mortality, high for patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay, all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Preference and values**

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.
Rationale
In non-pregnant patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Limited observational data are available on the use of tocilizumab in pregnant and breastfeeding women with severe COVID-19. While there is currently no evidence to suggest additional harms to mother or baby due to tocilizumab, further studies are needed in this population. Considering the decreased risk of death, tocilizumab’s use should be considered in this population for the treatment of COVID-19 requiring supplemental oxygen. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial.

Clinical Question/ PICO
Population: Children and adolescents, pregnant or breastfeeding women with COVID-19
Intervention: Tocilizumab
Comparator: Standard care

Summary
Evidence indicates that tocilizumab probably reduces the risk of death in hospitalised adults who require supplemental oxygen, as well as reducing the need for invasive mechanical ventilation and admission to ICU.

What is the evidence informing this recommendation?
Evidence comes from nine randomised trials that compared tocilizumab with standard care in 6390 adults hospitalised with COVID-19 [68][69][71][72][81][85][86][87][90]. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate to critical COVID-19 [90]. There was variability in disease severity among patients included in the trials (Table 1).

Results from the tocilizumab arm of the REMAP-CAP trial showed a strong mortality benefit in patients with critical illness who were receiving organ support [85]. These data contrasted with the existing meta-analysis of randomised trials conducted by the Taskforce, in which a mortality benefit was not observed in patients using tocilizumab. However the vast majority of relevant data published before REMAP-CAP was of patients with moderate-to-severe illness (Table 1), with the exception of the COVACTA trial [86], which included 108
patients with critical illness.

To determine whether differences in observed effect on death might be explained by differences in disease severity, the Taskforce assessed the credibility of these subgroups using the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN). Results from this analysis suggest that it is inappropriate to separate data based on disease severity. More specifically:

- the majority of data included in the comparison came from between trials rather than within trials
- only a single between-trial publication (REMAP-CAP) provided data for the smallest subgroup (patients with critical illness)
- the test for subgroup differences suggests that chance may be a likely explanation (P = 0.74), and that the data are largely homogenous ($I^2 = 0\%$)
- results from the COVACTA trial conflict with those of the REMAP-CAP trial, showing no mortality benefit in critical patients treated with tocilizumab.

Following publication of the tocilizumab arm of the RECOVERY trial, the Taskforce updated the ICEMAN analysis to determine whether the inclusion of the RECOVERY data affected the appropriateness of subgroup analyses. Results from the updated analysis suggest that it is still likely to be inappropriate to separate data based on disease severity. This is because:

- There remained limited within-trial (COVACTA and RECOVERY) and between-trial publications (REMAP-CAP, COVACTA and RECOVERY) that provide data for the smallest subgroup (patients with critical illness).
- The test for subgroup differences continues to suggest that chance may be a likely explanation, with the P value increasing to 0.78 following inclusion of the RECOVERY trial. Data remains sufficiently homogenous between data points ($I^2 = 0\%$).

It should be noted that the ICEMAN analysis did not include the trial by Veiga et al. [81], as this study pooled mortality results for patients with moderate-to-critical illness, and thus did not contribute data to either of the proposed subgroups. The full ICEMAN analysis can be found here.

We have found two new studies comparing tocilizumab with standard care (Soin et al. Lancet Respir Med doi: 10.1016/S2213-2600(21)00081-3 and Rutgers et al. SSRN doi: 10.2139/ssrn.3834311). These studies are currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

### Study characteristics

Mean or median age ranged from 55 to 64 years and women comprised 26 to 50% of patients across the studies. Pregnant and breastfeeding women were generally ineligible, with the exception of RECOVERY which included three pregnant patients. Studies included patients with moderate, severe and critical COVID-19 (Table 1).

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Number of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate–Severe</td>
<td>952</td>
<td>[68][69][71][72][87]</td>
</tr>
<tr>
<td>Moderate–Critical</td>
<td>4683</td>
<td>[81][86][90]</td>
</tr>
<tr>
<td>Critical</td>
<td>755</td>
<td>[85]</td>
</tr>
</tbody>
</table>

All included trials reported high levels of the inflammatory marker C-reactive protein (CRP) (Table 2). Thresholds for CRP or other biomarkers of inflammation to guide use of tocilizumab within included trials were variable; however these should be considered where there is evidence of systemic inflammation.

### Table 1: Disease severity of patients within included trials

### Table 2: Baseline levels of CRP within included studies
What are the main results?
Tocilizumab probably decreases death slightly (26 fewer per 1000 patients; RR 0.91, CI 95% 0.80 to 1.03; 6302 patients in 8 studies), the need for invasive mechanical ventilation (32 fewer per 1000; RR 0.80, CI 95% 0.69 to 0.92; 4069 patients in 3 studies) and the number of patients admitted to ICU (96 fewer per 1000; RR 0.68, CI 95% 0.51 to 0.90; 520 patients in 3 studies). In addition, tocilizumab probably increases the number of patients discharged from hospital (35 more per 1000; RR 1.07, CI 95% 0.99 to 1.16; 4611 patients in 4 studies) and decreases duration of hospital stay.

Tocilizumab probably has little impact on adverse or serious adverse events, septic shock, discharge from hospital or clinical progression. The effect of tocilizumab on other outcomes is uncertain.

Our confidence in the results
For the critical outcomes, certainty of the evidence is moderate for death, high for patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay (RECOVERY), all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, common adverse effects related to tocilizumab are generally mild and include headache, dizziness, infections and injection site reactions [66]. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab.

According to the Therapeutic Goods Administration, the safety and efficacy of intravenous tocilizumab in children under 18 years of age with conditions other than polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA) or cytokine release syndrome (CRS) have not been established. The use of tocilizumab in children under two years of age has not been studied.

Limited observational data are available on the use of tocilizumab in pregnant and breastfeeding women with severe COVID-19, and while there is no evidence to suggest additional harms to mother or baby due to tocilizumab, further studies are needed in this population. For breastfeeding women, limited evidence suggests that very low concentrations of tocilizumab are identified in breast milk, and no drug is transferred into the serum of breastfed infants.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [All patients]</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Moderate</td>
<td>Tocilizumab may decrease death.</td>
</tr>
<tr>
<td>Day 21-28 after commencing treatment</td>
<td>Relative risk 0.91 (CI 95% 0.8 — 1.03) Based on data from 6,302 participants in 8 studies. ¹ (Randomized controlled)</td>
<td>294 per 1000</td>
<td>268 per 1000</td>
<td>Due to serious inconsistency and serious indirectness ²</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Relative risk 0.8 (CI 95% 0.69 — 0.92) Based on data from 4,069 participants in 3 studies</td>
<td>159 per 1000</td>
<td>127 per 1000</td>
<td>Due to serious indirectness ⁴</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>End of follow-up</strong></td>
<td></td>
<td>studies. 3 (Randomized controlled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong></td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from 130 participants in 1 studies. 7 (Randomized controlled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 0.88 (CI 95% 0.74 — 1.05) Based on data from 2,129 participants in 7 studies. 7 (Randomized controlled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.03 (CI 95% 0.82 — 1.28) Based on data from 1,382 participants in 6 studies. 9 (Randomized controlled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Septic shock</strong></td>
<td>End of follow-up</td>
<td>Relative risk 0.59 (CI 95% 0.26 — 1.35) Based on data from 815 participants in 2 studies. 11 (Randomized controlled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Admission to ICU</strong></td>
<td>End of follow-up</td>
<td>Relative risk 0.68 (CI 95% 0.51 — 0.9) Based on data from 520 participants in 3 studies. 13 (Randomized controlled)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The table provides a summary of study results, comparator, intervention, and certainty of evidence for various outcomes related to respiratory failure or ARDS, serious adverse events, and septic shock in the context of tocilizumab treatment. The certainty of the evidence ranges from very low to low, indicating varying levels of confidence in the study findings due to factors such as serious indirectness and imprecision.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge from hospital</td>
<td>End of follow-up</td>
<td>Relative risk 1.07 (CI 95% 0.99 — 1.16) Based on data from 4,611 participants in 4 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Low Due to serious imprecision and serious indirectness</td>
<td>Tocilizumab may increase discharge from hospital.</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>End of follow-up</td>
<td>Relative risk 1.08 (CI 95% 0.92 — 1.27) Based on data from 65 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Very low Due to very serious imprecision, very serious indirectness and serious indirectness</td>
<td>We are uncertain whether tocilizumab increases or decreases clinical recovery.</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 95% 0.94 — 1.12) Based on data from 242 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether tocilizumab increases or decreases clinical improvement.</td>
</tr>
<tr>
<td>Clinical progression</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.08 (CI 95% 0.72 — 1.62) Based on data from 365 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Low Due to serious imprecision and serious indirectness</td>
<td>Tocilizumab may have little or no impact on clinical progression.</td>
</tr>
<tr>
<td>Time to deterioration</td>
<td>Days</td>
<td>Hazard Ratio 1.11 (CI 95% 0.59 — 2.1) Based on data from 45 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether tocilizumab increases or decreases time to discharge.</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>Days</td>
<td>Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from: 19 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether tocilizumab decreases duration of mechanical ventilation.</td>
</tr>
</tbody>
</table>
Time to improvement

Days

6 Important

Based on data from: 219 participants in 1 study. 26 (Randomized controlled)

5 (Median)

Difference: 1 more CI 95%

Very low

Due to very serious imprecision and serious indirectness

We are uncertain whether tocilizumab increases or decreases time to improvement.

Duration of hospital stay

(mean) Days

6 Important

Based on data from: 129 participants in 1 study. 28 (Randomized controlled)

14.7 (Mean)

Difference: MD 3.4 lower ( CI 95% 6.2 lower — 0.6 lower )

Low

Due to very serious imprecision

We are uncertain whether tocilizumab decreases duration of hospital stay.

Duration of hospital stay

(median) Days

6 Important

Lower better Based on data from: 4,116 participants in 1 studies. (Randomized controlled)

28 (Median)

20 (Median)

Low

Due to very serious imprecision and serious indirectness

Tocilizumab may decrease duration of hospital stay.


2. **Inconsistency:** serious. **Indirectness:** serious. Differences between the population of interest and those studied.


4. **Indirectness:** serious. Differences between the population of interest and those studied.


6. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals. Low number of patients. Only data from one study.


8. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


10. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


12. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. due to few events.

**6.1.6.3.3 Tocilizumab for children and adolescents**

**comparator:** Control arm of reference used for intervention.

14. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


16. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


18. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study.


20. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, Low number of patients.


22. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.

23. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.

24. Systematic review [67]. **Baseline/comparator:** Control arm of reference used for intervention.

25. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.

26. Systematic review [67]. **Baseline/comparator:** Control arm of reference used for intervention.

27. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.


29. **Imprecision:** very serious. Low number of patients, Only data from one study.

30. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

In adult patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections). No children were enrolled in any of the trials included.

There is no established dose for tocilizumab for the treatment of acute COVID-19 in children or adolescents. (The Taskforce notes that RECOVERY is recruiting children and adolescents with PIMS-TS for their trial of tocilizumab [89].) Tocilizumab should be administered as a single intravenous infusion over 60 minutes. Following protocol information in the RECOVERY trial, as well as previous literature on the use of tocilizumab for other indications, the suggested dose is dependent on body weight:

- Infants < 1 year (excluded from RECOVERY trial): dosing from other uses 12 mg/kg [88]
- < 30 kg: 12 mg/kg
- ≥ 30 kg: 8 mg/kg (max 800 mg)

In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab in adults. Use of combined tocilizumab and corticosteroids should be considered in children and adolescents hospitalised with COVID-19 who require oxygen, however, the optimal sequencing of tocilizumab and corticosteroid use is unclear in all populations.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

In adults hospitalised with moderate to critical COVID-19 who require supplemental oxygen, tocilizumab decreases the need for invasive mechanical ventilation and probably reduces the incidence of death.

Evidence from randomised trials versus standard care demonstrates that tocilizumab has an acceptable safety profile and may reduce the incidence of serious adverse events in adults. Consideration should be given when administering tocilizumab to patients already on other immunosuppressant or immunomodulatory drugs. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab [84].

Older people living with frailty or cognitive impairment

People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

People requiring palliative care

There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

Pregnant or breastfeeding women

There is uncertainty around the benefits and harms of tocilizumab for pregnant or breastfeeding women with...
COVID-19 as no details were reported in the trials for these populations.

Children or adolescents
As included trials are all based on adult patients, there remains uncertainty around the benefits and harms of tocilizumab use in children and adolescents with COVID-19.

Certainty of the Evidence
For the critical outcomes, certainty of the evidence is moderate for mortality, high for patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay, all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Preference and values
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there are probable mortality benefits most patients with COVID-19 who require supplemental oxygen would opt for tocilizumab.

Pregnant or breastfeeding patients
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit, however there are significant costs associated with tocilizumab use (approximately AU$400 per 400 mg vial).

Equity
We have no systematically collected evidence regarding impact on equity; however the any limitations on availability and the significant cost of tocilizumab may affect equity based on geographic area and access to tocilizumab.

Acceptability
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable.
Rationale

**General adult population**

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial.

Feasibility

Intravenous tocilizumab (Actemra; Roche Products Pty Ltd) was granted provisional approval for the treatment of COVID-19 on 1 December 2021 (ARTG numbers: 370315, 370314, 296808, 234034, 149404, 149403, 149402; AusPAR unpublished as of 3 December 2021)

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Clinical Question/ PICO

**Population:** Children and adolescents, pregnant or breastfeeding women with COVID-19

**Intervention:** Tocilizumab

**Comparator:** Standard care

Summary

Evidence indicates that tocilizumab probably reduces the risk of death in hospitalised adults who require supplemental oxygen, as well as reducing the need for invasive mechanical ventilation and admission to ICU.

**What is the evidence informing this recommendation?**

Evidence comes from nine randomised trials that compared tocilizumab with standard care in 6390 adults hospitalised with COVID-19 [68][69][71][72][81][85][86][87][90]. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate to critical COVID-19 [90]. There was variability in disease severity among patients included in the trials (Table 1).

Results from the tocilizumab arm of the REMAP-CAP trial showed a strong mortality benefit in patients with critical illness who were receiving organ support [85]. These data contrasted with the existing meta-analysis of randomised trials conducted by the Taskforce, in which a mortality benefit was not observed in patients using tocilizumab. However the vast majority of relevant data published before REMAP-CAP was of patients with moderate-to-severe illness (Table 1), with the exception of the COVACTA trial [86], which included 108 patients with critical illness.

To determine whether differences in observed effect on death might be explained by differences in disease severity, the Taskforce assessed the credibility of these subgroups using the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN). Results from this analysis suggest that it is inappropriate to separate data based on disease severity. More specifically:

- the majority of data included in the comparison came from between trials rather than within trials
- only a single between-trial publication (REMAP-CAP) provided data for the smallest subgroup (patients with critical illness)
- the test for subgroup differences suggests that chance may be a likely explanation (P = 0.74), and that the data are largely homogenous ($I^2 = 0\%$)
- results from the COVACTA trial conflict with those of the REMAP-CAP trial, showing no mortality benefit in critical patients treated with tocilizumab.

Following publication of the tocilizumab arm of the RECOVERY trial, the Taskforce updated the ICEMAN
analysis to determine whether the inclusion of the RECOVERY data affected the appropriateness of subgroup analyses. Results from the updated analysis suggest that it is still likely to be inappropriate to separate data based on disease severity. This is because:

- There remained limited within-trial (COVACTA and RECOVERY) and between-trial publications (REMAP-CAP, COVACTA and RECOVERY) that provide data for the smallest subgroup (patients with critical illness).
- The test for subgroup differences continues to suggest that chance may be a likely explanation, with the P value increasing to 0.78 following inclusion of the RECOVERY trial. Data remains sufficiently homogenous between data points ($I^2 = 0\%$).

It should be noted that the ICEMAN analysis did not include the trial by Veiga et al. [81], as this study pooled mortality results for patients with moderate-to-critical illness, and thus did not contribute data to either of the proposed subgroups. The full ICEMAN analysis can be found here.

We have found two new studies comparing tocilizumab with standard care (Soin et al. Lancet Respir Med doi: 10.1016/S2213-2600(21)00081-3 and Rutgers et al. SSRN doi: 10.2139/ssrn.3834311). These studies are currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

**Study characteristics**

Mean or median age ranged from 55 to 64 years and women comprised 26 to 50% of patients across the studies. Pregnant and breastfeeding women were generally ineligible, with the exception of RECOVERY which included three pregnant patients. Studies included patients with moderate, severe and critical COVID-19 (Table 1).

**Table 1:** Disease severity of patients within included trials

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Number of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate–Severe</td>
<td>952</td>
<td>[68][69][71][72][87]</td>
</tr>
<tr>
<td>Moderate–Critical</td>
<td>4683</td>
<td>[81][86][90]</td>
</tr>
<tr>
<td>Critical</td>
<td>755</td>
<td>[85]</td>
</tr>
</tbody>
</table>

All included trials reported high levels of the inflammatory marker C-reactive protein (CRP) (Table 2). Thresholds for CRP or other biomarkers of inflammation to guide use of tocilizumab within included trials were variable; however these should be considered where there is evidence of systemic inflammation.

**Table 2:** Baseline levels of CRP within included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Tocilizumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMAP-CAP</td>
<td>Median (IQR): 150 (85–221)</td>
<td>Median (IQR): 130 (71–208)</td>
</tr>
<tr>
<td>Hermine 2020</td>
<td>Median (IQR): 120 (75–220)</td>
<td>Median (IQR): 127 (84–171)</td>
</tr>
<tr>
<td>Rosas 2021</td>
<td>Mean (SD): 168 (101)</td>
<td>Mean (SD): 173 (114)</td>
</tr>
<tr>
<td>Salama 2020</td>
<td>Mean (SD): 152 (177)</td>
<td>Mean (SD): 203 (405)</td>
</tr>
<tr>
<td>Veiga 2021</td>
<td>Mean (SD): 160 (104)</td>
<td>Mean (SD): 193 (283)</td>
</tr>
</tbody>
</table>

**What are the main results?**

Tocilizumab probably decreases death slightly (26 fewer per 1000 patients; RR 0.91, CI 95% 0.80 to 1.03; 6302 patients in 8 studies), the need for invasive mechanical ventilation (32 fewer per 1000; RR 0.80, CI 95% 0.69 to 0.92; 4069 patients in 3 studies) and the number of patients admitted to ICU (96 fewer per 1000; RR 0.68, CI 95% 0.51 to 0.90; 520 patients in 3 studies). In addition, tocilizumab probably increases the number of patients discharged from hospital (35 more per 1000; RR 1.07, CI 95% 0.99 to 1.16; 4611 patients in 4 studies) and decreases duration of hospital stay.

Tocilizumab probably has little impact on adverse or serious adverse events, septic shock, discharge from hospital or clinical progression. The effect of tocilizumab on other outcomes is uncertain.

**Our confidence in the results**

For the critical outcomes, certainty of the evidence is moderate for death, high for patients requiring invasive
mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay (RECOVERY), all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, common adverse effects related to tocilizumab are generally mild and include headache, dizziness, infections and injection site reactions. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab.

According to the Therapeutic Goods Administration, the safety and efficacy of intravenous tocilizumab in children under 18 years of age with conditions other than polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA) or cytokine release syndrome (CRS) have not been established. The use of tocilizumab in children under two years of age has not been studied.

Limited observational data are available on the use of tocilizumab in pregnant and breastfeeding women with severe COVID-19, and while there is no evidence to suggest additional harms to mother or baby due to tocilizumab, further studies are needed in this population. For breastfeeding women, limited evidence suggests that very low concentrations of tocilizumab are identified in breast milk, and no drug is transferred into the serum of breastfed infants.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Tocilizumab</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [All patients]</td>
<td>Day 21-28 after commencing treatment</td>
<td>Relative risk 0.91 (CI 95% 0.8 — 1.03) Based on data from 6,302 participants in 8 studies. ¹ (Randomized controlled)</td>
<td>294 per 1000</td>
<td>268 per 1000</td>
<td>Low Due to serious inconsistency and serious indirectness ²</td>
<td>Tocilizumab may decrease death.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>End of follow-up</td>
<td>Relative risk 0.8 (CI 95% 0.69 — 0.92) Based on data from 4,069 participants in 3 studies. ³ (Randomized controlled)</td>
<td>159 per 1000</td>
<td>127 per 1000</td>
<td>Moderate Due to serious indirectness ⁴</td>
<td>Tocilizumab probably decreases need for invasive mechanical ventilation</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from 130 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td>284 per 1000</td>
<td>142 per 1000</td>
<td>Very low Due to very serious imprecision and serious indirectness ⁶</td>
<td>We are uncertain whether tocilizumab increases or decreases respiratory failure or ARDS (28 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td>Critical</td>
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<td></td>
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<tr>
<td>Serious adverse events</td>
<td></td>
<td>Relative risk 0.88 (CI 95% 0.74 – 1.05) Based on data from 2,129 participants in 7 studies.</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Low</td>
<td>Tocilizumab may make little or no difference to serious adverse events (366 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Important</td>
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<tr>
<td>Relative risk 1.03 (CI 95% 0.82 – 1.28) Based on data from 1,382 participants in 6 studies.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td></td>
<td>Relative risk 0.59 (CI 95% 0.26 – 1.35) Based on data from 815 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Tocilizumab may have little impact on septic shock (22 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Important</td>
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<td></td>
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<tr>
<td>Relative risk 0.68 (CI 95% 0.51 – 0.9) Based on data from 520 participants in 3 studies.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Admission to ICU</td>
<td></td>
<td>Relative risk 1.07 (CI 95% 0.99 – 1.16) Based on data from 4,611 participants in 4 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Tocilizumab may decrease admission to ICU (135 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Important</td>
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<td></td>
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<tr>
<td>Relative risk 1.08 (CI 95% 0.92 – 1.27) Based on data from 65 participants in 1 study.</td>
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<tr>
<td>Discharge from hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td>Tocilizumab may increase discharge from hospital.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Important</td>
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</tr>
<tr>
<td>Relative risk 1.07 (CI 95% 0.99 – 1.16) Based on data from 4,611 participants in 4 studies.</td>
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<td></td>
</tr>
<tr>
<td>Clinical recovery</td>
<td></td>
<td>Relative risk 1.08 (CI 95% 0.92 – 1.27) Based on data from 65 participants in 1 study.</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether tocilizumab increases or decreases clinical recovery.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 0.94 — 1.2) Based on data from 242 participants in 1 studies.</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>Imprecision, very serious indirectness and serious indirectness</td>
<td>889 more per 1000 (CI 95% 70 fewer — 235 more) Very low Due to very serious imprecision and serious indirectness. We are uncertain whether tocilizumab increases or decreases clinical improvement.</td>
</tr>
<tr>
<td>Time to deterioration</td>
<td>Days</td>
<td>Hazard Ratio 1.11 (CI 0.59 — 2.1) Based on data from 45 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious imprecision and serious indirectness</td>
<td>215 more per 1000 (CI 95% 60 fewer — 133 more) Low Tocilizumab may have little or no impact on clinical progression.</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>Days</td>
<td>Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from: 19 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>27.9 (Median) 12.9 fewer CI 95% Very low We are uncertain whether tocilizumab decreases duration of mechanical ventilation.</td>
</tr>
<tr>
<td>Time to improvement</td>
<td>Days</td>
<td>Based on data from: 219 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>5 (Median) 1 more CI 95% Very low We are uncertain whether tocilizumab increases or decreases time to improvement.</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>Based on data from:</td>
<td></td>
<td></td>
<td></td>
<td>Low Due to very</td>
<td>14.7 (Mean) 11.3 (Mean) Low We are uncertain whether tocilizumab decreases duration of hospital stay.</td>
</tr>
</tbody>
</table>
### Tocilizumab for Duration of Hospital Stay

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of hospital stay (median)</td>
<td>Days</td>
<td>Lower better (Randomized controlled)</td>
<td>Standard care</td>
<td>Tocilizumab</td>
<td>MD 3.4 lower (CI 95% 6.2 lower – 0.6 lower)</td>
<td>Tocilizumab may decrease duration of hospital stay.</td>
</tr>
<tr>
<td>(mean)</td>
<td>Days</td>
<td>129 participants in 1 study. (Randomized controlled)</td>
<td>Difference:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


2. **Inconsistency:** serious. **Indirectness:** serious. Differences between the population of interest and those studied.


4. **Indirectness:** serious. Differences between the population of interest and those studied.


6. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study.


8. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


10. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


12. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. due to few events.


14. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


16. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.


18. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study.


---

Based on data from: 4,116 participants in 1 studies. (Randomized controlled)
used for intervention.

20. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, Low number of patients.


22. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Wide confidence intervals.

23. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.

24. Systematic review [67]. **Baseline/comparator:** Control arm of reference used for intervention.

25. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.

26. Systematic review [67]. **Baseline/comparator:** Control arm of reference used for intervention.

27. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.


29. **Imprecision:** very serious. Low number of patients, Only data from one study.

30. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.

### 6.1.7 Remdesivir

#### 6.1.7.1 Remdesivir for adults

**Conditional recommendation**

Consider using remdesivir in adults with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation.

In patients hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [51]. For a full description of the rationale underpinning this decision please see here.

It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.
Evidence To Decision

**Benefits and harms**

In patients who are hospitalised with moderate COVID-19 and who do not require ventilation (non-invasive ventilation, mechanical ventilation or ECMO), remdesivir probably reduces the incidence of death.

Evidence from randomised trials versus standard care demonstrates that remdesivir has an acceptable safety profile and may reduce the incidence of serious adverse events. Based on the results of two studies that compared 10-day to 5-day courses of remdesivir, it is unclear which of these regimens provide the optimal duration of treatment—current evidence does not suggest a clear benefit for 10 days over 5 days.

**Older people living with frailty or cognitive impairment**

People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

**People requiring palliative care**

In addition to the concerns in the general adult population, there is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

Certainty of the evidence is moderate for death at day 28 in patients who do not require ventilation and in patients who require ventilation. Certainty is also moderate for discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is low for all other outcomes.

**People requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, there is more uncertainty due to lack of information on whether these populations were included in the trials.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that since there are probable mortality benefits most informed patients with COVID-19 who do not require ventilation would opt for remdesivir.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Additional variability may be expected in these populations given the potentially different preferences and values placed on outcomes and goals for care, such as symptom relief.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Criteria for accessing remdesivir from the National Medical Stockpile, released by the Australian Government on 31 July, limits the treatment course to 5 days for eligible patients.

**Equity**

We have no systematically collected evidence regarding impact on equity; however as remdesivir is only accessible through special arrangements with the Australian Government, this may affect equity based on geographic area and access to remdesivir.
Acceptability

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment

Because the benefit to harm ratio is uncertain, the acceptability may vary in these populations due to individual decision making around goals of care.

Feasibility

Intravenous remdesivir (Veklury; Gilead Sciences Pty Ltd) was granted provisional approval for the treatment of COVID-19 by the Therapeutic Goods Administration on 10 July 2020 under the Black Triangle Scheme (ARTG numbers: 338419, 338420; AusPAR).

Treatment with remdesivir is not feasible in patients who do not meet eligibility for clinical treatment specified by the Australian Government Department of Health. Implementability may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and more general criteria (such as geographic area).

Rationale

In patients hospitalised with COVID-19 who do not require ventilation remdesivir probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [51]. For a full description of the rationale underpinning this decision please see here.

It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.

Clinical Question/ PICO

**Population:** Remdesivir dosage for COVID-19  
**Intervention:** 5 days’ treatment  
**Comparator:** Up to 10 days’ treatment  

Summary

There remains uncertainty whether a 5-day course of remdesivir is more effective and safer than a 10-day course.

What is the evidence informing this recommendation?

Evidence comes from two randomised trials that compared 5-day to 10-day treatment with remdesivir in 781 hospitalised patients with severe COVID-19 [45][47].

Study characteristics

For a comprehensive description, see the study characteristics table.

What are the main results?

There is a lower risk of death within 14 days of treatment with a 5-day versus a 10-day course of remdesivir (16 fewer per 1000; RR 0.73, CI 95% 0.40 to 1.33; 781 patients in 2 studies). The evidence is more uncertain for death within 28 days of treatment (5 fewer per 1000; RR 0.67, CI 95% 0.11 to 3.99; 384 patients in 1 study).

There is probably little difference between a 5-day and 10-day course of remdesivir regarding adverse events, discontinuation of treatment due to adverse events and discharge from hospital.
Our confidence in the results
Certainty of the evidence is moderate for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is low for death within 28 days, acute respiratory failure or ARDS, clinical recovery within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation [45], lack of blinding), serious imprecision (too few events) and very serious imprecision (reliance on a single study with few patients and/or few events).

It is important to note that Goldman et al. only presents initial results from the first 400 patients in a trial that includes nearly 5000 patients (NCT04292899) [45]. The trial completed recruitment in July 2020 and we await the results from the full cohort of patients.

Additional information
The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [46].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Up to 10 days' treatment</th>
<th>Intervention 5 days' treatment</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 0.73 (CI 95% 0.4 — 1.33) Based on data from 781 participants in 2 studies. ³ (Randomized controlled)</td>
<td>59 per 1000</td>
<td>43 per 1000</td>
<td>Moderate Due to serious imprecision ³</td>
<td>Remdesivir 5-day treatment probably has little or no impact on death (40 deaths).</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Low Due to very serious imprecision ³</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases death at 28 days (5 deaths).</td>
</tr>
<tr>
<td>Acute respiratory failure or ARDS</td>
<td>Within 30 days of commencing treatment</td>
<td>Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 participants in 1 studies. ³ (Randomized controlled)</td>
<td>117 per 1000</td>
<td>55 per 1000</td>
<td>Low Due to very serious imprecision ³</td>
<td>Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (34 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very low Due to very serious imprecision ³</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 30 days of commencing treatment</td>
<td>Relative risk 0.39 (CI 95% 0.08 — 2.01) Based on data from 397 participants in 1 ³</td>
<td>397 per 1000</td>
<td>7 per 1000</td>
<td>Very low Due to very serious imprecision ³</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention 5 days’ treatment</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td>--------------------------</td>
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<tr>
<td>Clinical recovery</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.2 (CI 95% 1.02 – 1.41) Based on data from 397 participants in 1 study. ^7 (Randomized controlled)</td>
<td>Relative risk 1.2 per 1000</td>
<td>538 per 1000</td>
<td>Low</td>
<td>Remdesivir 5-day treatment may improve clinical recovery slightly (235 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 108 more per 1000 (CI 95% 11 more – 221 more)</td>
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</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow up</td>
<td>Relative risk 0.64 (CI 95% 0.47 – 0.87) Based on data from 781 participants in 2 studies. ^11 (Randomized controlled)</td>
<td>Relative risk 0.64 per 1000</td>
<td>200 per 1000</td>
<td>Moderate</td>
<td>Remdesivir 5-day treatment probably decreases serious adverse events slightly (129 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 72 fewer per 1000 (CI 95% 90 fewer – 26 fewer)</td>
<td></td>
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</tr>
<tr>
<td>Adverse events</td>
<td>End of follow up</td>
<td>Relative risk 0.93 (CI 95% 0.84 – 1.03) Based on data from 781 participants in 2 studies. ^13 (Randomized controlled)</td>
<td>Relative risk 0.93 per 1000</td>
<td>662 per 1000</td>
<td>Moderate</td>
<td>Remdesivir 5-day treatment probably makes little or no difference to adverse events (503 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 46 fewer per 1000 (CI 95% 106 fewer – 20 more)</td>
<td></td>
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</tr>
<tr>
<td>Discontinuation due to</td>
<td>During treatment</td>
<td>Relative risk 0.59 (CI 95% 0.3 – 1.15) Based on data from 781 participants in 2 studies. ^15 (Randomized controlled)</td>
<td>Relative risk 0.59 per 1000</td>
<td>56 per 1000</td>
<td>Low</td>
<td>Remdesivir 5-day treatment may make little or no difference to discontinuation due to adverse events (35 events).</td>
</tr>
<tr>
<td>adverse events</td>
<td></td>
<td></td>
<td>Difference: 23 fewer per 1000 (CI 95% 39 fewer – 8 more)</td>
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</tr>
<tr>
<td>Discharged from hospital</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.06 (CI 95% 0.93 – 1.2) Based on data from 781 participants in 2 studies. ^17 (Randomized controlled)</td>
<td>Relative risk 1.06 per 1000</td>
<td>638 per 1000</td>
<td>Moderate</td>
<td>Remdesivir 5-day treatment probably makes little or no difference to number of patients discharged from hospital at day 14 (515 events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 38 more per 1000 (CI 95% 45 fewer – 128 more)</td>
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<tr>
<td>Discharged from hospital</td>
<td>Within 28 days of commencing</td>
<td>Relative risk 0.99 (CI 95% 0.92 – 1.06) Based on data from 384 participants in 1 study. ^18 (Randomized controlled)</td>
<td>Relative risk 0.99 per 1000</td>
<td>902 per 1000</td>
<td>Low</td>
<td>Remdesivir 5-day treatment may make little or no difference to number of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 9 fewer per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Up to 10 days’ treatment</td>
<td>Intervention 5 days’ treatment</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>treatment</td>
<td>studies. 19 (Randomized controlled)</td>
<td></td>
<td>1000 (CI 95% 72 fewer – 54 more)</td>
<td></td>
<td>discharged from hospital at day 28 (344 events).</td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision:** serious. due to few events.
4. **Imprecision:** very serious. Low number of patients, Only data from one study, due to few events.
6. **Imprecision:** very serious. Low number of patients, Only data from one study.
8. **Imprecision:** very serious. Low number of patients, Only data from one study.
10. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Only data from one study.
12. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.
14. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
16. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. due to few events.
18. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
20. **Imprecision:** very serious. Low number of patients, Only data from one study.

**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** Remdesivir
- **Comparator:** Standard care
Summary

Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?

Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 [43][44][47][50][61][574]. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 [50].

Study characteristics

For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Number of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>666</td>
<td>[47][61]</td>
</tr>
<tr>
<td>Moderate-Critical</td>
<td>6513</td>
<td>[43][50][574]</td>
</tr>
<tr>
<td>Severe-Critical</td>
<td>236</td>
<td>[44]</td>
</tr>
</tbody>
</table>

What are the main results?

Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale [43] or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale [47]. Clinical improvement was defined as an improvement of 2 or more points on a 7-point [47] or 6-point ordinal scale [44].

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design [62]. The study included 86 pregnant and postpartum women with severe COVID-19 in the USA who received compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline. Two-thirds of pregnant women and all postpartum women were in ICU.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in children and adolescents. The preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population [499]. Trials are currently recruiting in this population.
Our confidence in the results
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or ARDS (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [46].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [hospital no ventilation]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. 1 (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious imprecision 2</td>
<td>Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.</td>
</tr>
<tr>
<td>All-cause mortality [ventilation]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies. 3 (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious imprecision 4</td>
<td>Remdesivir probably increases death in hospitalised patients requiring ventilation.</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from 2,120 participants in 3 studies. 3 (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious imprecision and serious inconsistency 6</td>
<td>We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 participants in 1 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low</td>
<td>Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).</td>
</tr>
<tr>
<td>Patients requiring ventilation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 participants in 2 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate</td>
<td>Remdesivir probably has no impact on number of patients requiring ventilation.</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 participants in 3 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low</td>
<td>We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low</td>
<td>We are uncertain whether remdesivir increases or decreases septic shock (13 events).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.82 (CI 95% 0.65 — 1.04) Based on data from 2,689 participants in 4 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate</td>
<td>Remdesivir probably decreases serious adverse events slightly.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 2,704 participants in 4 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate</td>
<td>Remdesivir probably has no impact on adverse events.</td>
</tr>
</tbody>
</table>
### Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce

**Table 1:** Outcomes and Study Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to adverse events</td>
<td>During treatment</td>
<td>Relative risk 1.73 (CI 95% 0.57 – 5.28) Based on data from 1,880 participants in 3 studies. 19 (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious risk of bias and serious imprecision 20</td>
<td>We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 95% 0.94 – 1.13) Based on data from 6,365 participants in 3 studies. 21 (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious imprecision 22</td>
<td>Remdesivir probably makes little or no difference to discharge from hospital.</td>
</tr>
<tr>
<td>Time to recovery</td>
<td>Days</td>
<td>Hazard Ratio 1.24 (CI 95% 1.08 – 1.42) Based on data from 1,643 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious risk of bias 23</td>
<td>Remdesivir may decrease time to recovery by a few days.</td>
</tr>
<tr>
<td>Time to improvement</td>
<td>Days</td>
<td>Hazard Ratio 1.17 (CI 95% 1 – 1.38) Based on data from 810 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious risk of bias 24</td>
<td>Remdesivir may decrease time to improvement slightly.</td>
</tr>
</tbody>
</table>

2. **Imprecision: serious.** Wide confidence intervals.
4. **Imprecision: serious.** Wide confidence intervals.
6. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Imprecision: serious.** Wide confidence intervals.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Low number of patients, Only data from one study.
10. **Imprecision: serious.** Wide confidence intervals.


12. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies, The direction of the effect is not consistent between the included studies.


14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies.


16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


20. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Wide confidence intervals.


22. **Imprecision: serious.** Wide confidence intervals.

23. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

24. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

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**Not recommended**

Do not start remdesivir in adults hospitalised with COVID-19 who require non-invasive or invasive ventilation.

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**Remdesivir should be continued with the appropriate dose and duration, if it was started prior to requiring ventilation.**

**Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).**

It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

**Use of remdesivir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include remdesivir.**

This is a **high priority** recommendation and will be updated as soon as new evidence becomes available.

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Evidence To Decision

Benefits and harms
In patients who are hospitalised with COVID-19 and who require ventilation, risk of death may be higher in patients using remdesivir compared with standard care.

Older people living with frailty or cognitive impairment
People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

People requiring palliative care
In addition to the concerns in the general adult population, there is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

Certainty of the Evidence
Certainty of the evidence is moderate for death at day 28 in hospitalised adults who require ventilation. Certainty is also moderate for patients requiring ventilation, discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is low for all other outcomes.

Preference and values
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is clear evidence demonstrating harms of remdesivir in patients requiring ventilation, informed patients would not choose this treatment.

Resources and other considerations
There are no identified resource issues as the recommendation reflects usual care.

Equity
There are no identified equity issues as the recommendation reflects usual care.

Acceptability
There are no identified acceptability issues as the recommendation reflects usual care.

Feasibility
There are no identified feasibility issues as the recommendation reflects usual care.

Rationale
Remdesivir in adults hospitalised with COVID-19 who require ventilation probably increases the risk of death—its use should be avoided in this population.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Remdesivir
Comparator: Standard care

Summary
Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?
Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 [43][44][47][50][61][574]. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 [50].

Study characteristics
For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Number of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>666</td>
<td>[47][61]</td>
</tr>
<tr>
<td>Moderate-Critical</td>
<td>6513</td>
<td>[43][50][574]</td>
</tr>
<tr>
<td>Severe-Critical</td>
<td>236</td>
<td>[44]</td>
</tr>
</tbody>
</table>

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale [43] or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale [47]. Clinical improvement was defined as an improvement of 2 or more points on a 7-point [47] or 6-point ordinal scale [44].

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design [62]. The study included 86 pregnant and postpartum women with severe COVID-19 in the USA who received compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline. Two-thirds of pregnant women and all postpartum women were in ICU.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in children and adolescents. The
Preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population [499]. Trials are currently recruiting in this population.

**Our confidence in the results**
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or ARDS (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [46].

---

**Outcome** | **Study results and measurements** | **Comparator** | **Intervention** | **Certainty of the Evidence** | **Plain language summary**
--- | --- | --- | --- | --- | ---
All-cause mortality [hospital no ventilation] | Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. (Randomized controlled) | | | | Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] | Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies. (Randomized controlled) | | | | Remdesivir probably increases death in hospitalised patients requiring ventilation.
Respiratory failure or ARDS | Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from 2,120 participants in 3 studies. (Randomized controlled) | | | | We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.34 – 3.01) Based on data from 1,296 participants in 2 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious risk of bias and serious inconsistency</td>
<td>We are uncertain whether remdesivir increases or decreases septic shock (13 events).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.82 (CI 95% 0.65 – 1.04) Based on data from 2,689 participants in 4 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious risk of bias and serious inconsistency</td>
<td>Remdesivir probably decreases serious adverse events slightly.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.03 (CI 95% 0.92 – 1.16) Based on data from</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious risk of bias</td>
<td>Remdesivir probably has no impact on adverse events.</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.86 – 1.14) Based on data from 1,876 participants in 3 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious risk of bias and serious inconsistency</td>
<td>We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.</td>
</tr>
<tr>
<td>Patients requiring ventilation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.04 (CI 95% 0.89 – 1.21) Based on data from 5,034 participants in 2 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious risk of bias</td>
<td>Remdesivir probably has no impact on number of patients requiring ventilation.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.57 (CI 95% 0.42 – 0.79) Based on data from 766 participants in 1 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<tr>
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<td>Comparator</td>
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</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
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<tr>
<td>Time to recovery Days</td>
<td>Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious risk of bias</td>
<td>Remdesivir may decrease time to recovery by a few days.</td>
<td></td>
</tr>
<tr>
<td>Time to improvement Days</td>
<td>Hazard Ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious risk of bias</td>
<td>Remdesivir may decrease time to improvement slightly.</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse events During treatment</td>
<td>Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.</td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital Within 28 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 95% 0.94 — 1.13) Based on data from 6,365 participants in 3 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious imprecision</td>
<td>Remdesivir probably makes little or no difference to discharge from hospital.</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse events During treatment</td>
<td>2,704 participants in 4 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>17 more per 1000 (CI 95% 44 fewer — 88 more)</td>
<td>We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.</td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision: serious.** Wide confidence intervals.
4. **Imprecision: serious.** Wide confidence intervals.
6. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Imprecision: serious.** Wide confidence intervals.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for
6.1.7.2 Remdesivir for pregnant or breastfeeding women
Consider using remdesivir in pregnant or breastfeeding women hospitalised with moderate to severe COVID-19 who do not require ventilation.

In patients hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [51]. For a full description of the rationale underpinning this decision please see here.

The recommended regimen is daily intravenous infusion (200 mg initial dose, 100 mg maintenance), optimal duration of remdesivir treatment is unclear, however current evidence does not suggest a clear benefit of 10 days over 5 days.

On 31 July 2020, the Australian Government provided specific criteria that needed to be met in order to access remdesivir for clinical treatment. These included age ≥ 18 years (or 12–17 years weighing ≥ 40 kg), an oxygen saturation of SpO2 ≤ 92% on room air and requiring supplemental oxygen, and alanine aminotransferase (ALT) < 5 x upper limit of normal (ULN) and/or ALT < 3 x ULN and bilirubin < 2 ULN. Patients with evidence of multiorgan failure, renal failure or those receiving mechanical ventilation for > 48 hours at time of application or extracorporeal membrane oxygenation (ECMO) are unable to receive remdesivir.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [46].

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

### Evidence To Decision

#### Benefits and harms

There remains uncertainty around the benefits and harms of remdesivir for pregnant or breastfeeding women with COVID-19. Evidence from trials of non-pregnant adults comparing 10-day to 5-day courses of remdesivir is too uncertain to inform decisions regarding length of treatment at this point.

In non-pregnant patients who are hospitalised with moderate COVID-19 and who do not require ventilation (non-invasive ventilation, mechanical ventilation or ECMO), remdesivir probably reduces the risk of death.

Evidence from randomised trials versus standard care demonstrates that remdesivir has an acceptable safety profile in non-pregnant adults and may reduce the incidence of serious adverse events. Based on the results of two studies that compared 10-day to 5-day courses of remdesivir, it is unclear which of these regimens provide the optimal duration of treatment—current evidence does not suggest a clear benefit for 10 days over 5 days.

While the safety profile of remdesivir has not been described for pregnant and breastfeeding women, some observational data on the use of remdesivir in pregnant women with severe COVID-19 suggests that it is well tolerated, with a low incidence of serious adverse events [62].

#### Certainty of the Evidence

Certainty of the evidence is low for death at day 28 as the estimates are imprecise and indirect since pregnant women were excluded from the trials. Certainty is also low for patients requiring ventilation, discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is very low for all other outcomes.
### Preference and values
Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point.

The Consumer Panel believes that as there is uncertainty regarding the benefits and possible harms of this treatment to mother or unborn child, some informed pregnant or breastfeeding women may prefer to wait until the available evidence is clearer, while other informed pregnant or breastfeeding women may want this treatment.

### Resources and other considerations
Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Criteria for accessing remdesivir from the National Medical Stockpile, released by the Australian Government on 31 July 2020, limits the treatment course to 5 days for eligible patients.

### Equity
Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however, as remdesivir is only accessible through special arrangements with the Australian Government, this may affect equity based on geographic area and access to remdesivir.

### Acceptability
No important issues with the recommended alternative

We have no systematically collected evidence regarding acceptability by pregnant or breastfeeding women.

### Feasibility
Important issues, or potential issues not investigated

Intravenous remdesivir (Veklury; Gilead Sciences Pty Ltd) was granted provisional approval for the treatment of COVID-19 by the Therapeutic Goods Administration on 10 July 2020 under the Black Triangle Scheme (ARTG numbers: 338419, 338420; AusPAR).

Treatment with remdesivir is not feasible in patients who do not meet eligibility for clinical treatment specified by the Australian Government Department of Health. Implementability may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and more general criteria (such as geographic area).

### Rationale

Remdesivir in patients hospitalised with COVID-19 who do not require ventilation probably reduces the risk of death.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [51]. For a full description of the rationale underpinning this decision please see here.

Observational data on use of remdesivir in pregnant women with severe COVID-19 suggests it is well tolerated, though further studies are needed in this population. Considering the decreased risk of death, its use should be considered in this population. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.
**Clinical Question/ PICO**

**Population:** Remdesivir dosage for COVID-19  
**Intervention:** 5 days’ treatment  
**Comparator:** Up to 10 days’ treatment

**Summary**
There remains uncertainty whether a 5-day course of remdesivir is more effective and safer than a 10-day course.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials that compared 5-day to 10-day treatment with remdesivir in 781 hospitalised patients with severe COVID-19 [45][47].

**Study characteristics**
For a comprehensive description, see the study characteristics table.

**What are the main results?**
There is a lower risk of death within 14 days of treatment with a 5-day versus a 10-day course of remdesivir (16 fewer per 1000; RR 0.73, CI 95% 0.40 to 1.33; 781 patients in 2 studies). The evidence is more uncertain for death within 28 days of treatment (5 fewer per 1000; RR 0.67, CI 95% 0.11 to 3.99; 384 patients in 1 study).

There is probably little difference between a 5-day and 10-day course of remdesivir regarding adverse events, discontinuation of treatment due to adverse events and discharge from hospital.

**Our confidence in the results**
Certainty of the evidence is moderate for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is low for death within 28 days, acute respiratory failure or ARDS, clinical recovery within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation [45], lack of blinding), serious imprecision (too few events) and very serious imprecision (reliance on a single study with few patients and/or few events).

It is important to note that Goldman et al. only presents initial results from the first 400 patients in a trial that includes nearly 5000 patients (NCT04292899) [45]. The trial completed recruitment in July 2020 and we await the results from the full cohort of patients.

**Additional information**
The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [46].

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**Outcome**  
**Timeframe**  
**Study results and measurements**  
**Comparator** Up to 10 days’ treatment  
**Intervention** 5 days’ treatment  
**Certainty of the Evidence** (Quality of evidence)  
**Plain language summary**

| All-cause mortality | Relative risk 0.73  
| (CI 95% 0.4 – 1.33) | 59 per 1000  
| Based on data from 781 participants in 2 studies. 1 (Randomized controlled) | Difference: 16 fewer per 1000  
| (CI 95% 35 fewer – 19 more) | Moderate  
| Due to serious imprecision 2 | Remdesivir 5-day treatment probably has little or no impact on death (40 deaths). |

| All-cause | Relative risk 0.67  
| 16 11 | Low | We are uncertain |

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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Comparator Up to 10 days’ treatment</th>
<th>Intervention 5 days’ treatment</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mortality</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>(CI 95% 0.11 — 3.99)</td>
<td>per 1000</td>
<td>Due to very serious imprecision 4</td>
<td>whether remdesivir 5-day treatment increases or decreases death at 28 days (5 deaths).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on data from 384 participants in 1 studies.</td>
<td>5 fewer per 1000 (CI 95% 14 fewer — 48 more)</td>
<td></td>
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</tr>
<tr>
<td><strong>Acute respiratory failure or ARDS</strong></td>
<td>Within 30 days of commencing treatment</td>
<td>Relative risk 0.47 (CI 95% 0.24 — 0.94)</td>
<td>117 per 1000</td>
<td>Low</td>
<td>Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (34 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on data from 397 participants in 1 studies.</td>
<td>62 fewer per 1000 (CI 95% 89 fewer — 7 fewer)</td>
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</tr>
<tr>
<td><strong>Septic shock</strong></td>
<td>Within 30 days of commencing treatment</td>
<td>Relative risk 0.39 (CI 95% 0.08 — 2.01)</td>
<td>538 per 1000</td>
<td>Very low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (7 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on data from 397 participants in 1 studies.</td>
<td>108 more per 1000 (CI 95% 11 more — 221 more)</td>
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</tr>
<tr>
<td><strong>Clinical recovery</strong></td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.2 (CI 95% 1.02 — 1.41)</td>
<td>200 per 1000</td>
<td>Low</td>
<td>Remdesivir 5-day treatment may improve clinical recovery slightly (235 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on data from 397 participants in 1 studies.</td>
<td>72 fewer per 1000 (CI 95% 106 fewer — 26 fewer)</td>
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</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>End of follow up</td>
<td>Relative risk 0.64 (CI 95% 0.47 — 0.87)</td>
<td>662 per 1000</td>
<td>Moderate</td>
<td>Remdesivir 5-day treatment probably decreases serious adverse events slightly (129 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on data from 781 participants in 2 studies.</td>
<td>46 fewer per 1000 (CI 95% 106 fewer — 20 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>End of follow up</td>
<td>Relative risk 0.93 (CI 95% 0.84 — 1.03)</td>
<td>616 per 1000</td>
<td>Moderate</td>
<td>Remdesivir 5-day treatment probably makes little or no difference to adverse events (503 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on data from 781 participants in 2 studies.</td>
<td>46 fewer per 1000 (CI 95% 106 fewer — 20 more)</td>
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</tr>
</tbody>
</table>
### Outcome Timeframe

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to adverse events During treatment</td>
<td>Relative risk 0.59 (CI 95% 0.3 — 1.15) Based on data from 781 participants in 2 studies.</td>
<td>56 per 1000</td>
<td>Due to serious risk of bias and imprecision 16 Remdesivir 5-day treatment may make little or no difference to discontinuation due to adverse events (35 events).</td>
</tr>
<tr>
<td>Discharged from hospital Within 14 days of commencing treatment</td>
<td>Relative risk 1.06 (CI 95% 0.93 — 1.2) Based on data from 781 participants in 2 studies.</td>
<td>638 per 1000</td>
<td>Due to serious risk of bias 18 Remdesivir 5-day treatment probably makes little or no difference to number of patients discharged from hospital at day 14 (515 events)</td>
</tr>
<tr>
<td>Discharged from hospital Within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.92 — 1.06) Based on data from 384 participants in 1 studies.</td>
<td>902 per 1000</td>
<td>Due to very serious imprecision 20 Remdesivir 5-day treatment may make little or no difference to number of patients discharged from hospital at day 28 (344 events).</td>
</tr>
</tbody>
</table>

2. Imprecision: serious, due to few events.
4. Imprecision: very serious. Low number of patients, Only data from one study, due to few events.
6. Imprecision: very serious. Low number of patients, Only data from one study.
8. Imprecision: very serious. Low number of patients, Only data from one study.
10. Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Only data from one study.
12. Risk of Bias: serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.
of reference used for intervention.

16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Due to few events.


18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


20. **Imprecision: very serious.** Low number of patients, Only data from one study.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Remdesivir</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Summary

Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

**What is the evidence informing this recommendation?**

Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 [43][44][47][50][61][574]. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 [50].

**Study characteristics**

For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

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<th>Disease severity</th>
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<th>References</th>
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</thead>
<tbody>
<tr>
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<td>666</td>
<td>[47][61]</td>
</tr>
<tr>
<td>Moderate-Critical</td>
<td>6513</td>
<td>[43][50][574]</td>
</tr>
<tr>
<td>Severe-Critical</td>
<td>236</td>
<td>[44]</td>
</tr>
</tbody>
</table>

**What are the main results?**

Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale [43] or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale [47]. Clinical improvement was defined as an improvement of 2 or more points on a 7-point [47] or 6-point ordinal scale [44].

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design [62]. The study included 86 pregnant and postpartum women with severe COVID-19 in the USA who received
compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline. Two-thirds of pregnant women and all postpartum women were in ICU.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in children and adolescents. The preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population [499]. Trials are currently recruiting in this population.

Our confidence in the results
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or ARDS (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [46].
<table>
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<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
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</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [ventilation]</td>
<td>Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies.</td>
<td></td>
<td>219 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Remdesivir probably increases death in hospitalised patients requiring ventilation.</td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from 2,120 participants in 3 studies.</td>
<td></td>
<td>121 per 1000</td>
<td>Low Due to serious imprecision and serious inconsistency</td>
<td>We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).</td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 participants in 1 studies.</td>
<td></td>
<td>225 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).</td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients requiring ventilation</td>
<td>Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 participants in 2 studies.</td>
<td></td>
<td>114 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Remdesivir probably has no impact on number of patients requiring ventilation.</td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 participants in 3 studies.</td>
<td></td>
<td>711 per 1000</td>
<td>Low Due to serious risk of bias and serious inconsistency</td>
<td>We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.</td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
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</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Difference: 10 per 1000</td>
<td>10 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 fewer per 1000 (CI 95% 7 fewer — 20 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.82 (CI 95% 0.65 — 1.04) Based on data from 2,689 participants in 4 studies.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 273 per 1000</td>
<td>224 per 1000</td>
<td>Moderate</td>
<td>Due to serious risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49 fewer per 1000 (CI 95% 96 fewer — 11 more)</td>
<td></td>
<td></td>
<td>Remdesivir probably decreases serious adverse events slightly.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 2,704 participants in 4 studies.</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 553 per 1000</td>
<td>570 per 1000</td>
<td></td>
<td>Remdesivir probably has no impact on adverse events.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 more per 1000 (CI 95% 44 fewer — 88 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>During treatment</td>
<td>Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3 studies.</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 93 per 1000</td>
<td>161 per 1000</td>
<td></td>
<td>We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68 more per 1000 (CI 95% 40 fewer — 398 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 95% 0.94 — 1.13) Based on data from 6,365 participants in 3 studies.</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 693 per 1000</td>
<td>714 per 1000</td>
<td></td>
<td>Remdesivir probably makes little or no difference to discharge from hospital.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 more per 1000 (CI 95% 42 fewer — 90 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to recovery</td>
<td>Days</td>
<td>Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
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<td>-------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Improvement Days</td>
<td>Based on data from 810 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>risk of bias</td>
<td>Improvement slightly.</td>
</tr>
</tbody>
</table>


2. **Imprecision:** serious. Wide confidence intervals.


4. **Imprecision:** serious. Wide confidence intervals.


6. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Imprecision:** serious. Wide confidence intervals.


8. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Low number of patients, Only data from one study.


10. **Imprecision:** serious. Wide confidence intervals.


12. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** serious. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., The direction of the effect is not consistent between the included studies.


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22. **Imprecision:** serious. Wide confidence intervals.
23. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

24. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

---

**Not recommended**

Do not start remdesivir in pregnant or breastfeeding women hospitalised with COVID-19 who require ventilation.

*Remdesivir should be continued with the appropriate dose and duration, if it was started prior to requiring ventilation.*

*Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).*

*Use of remdesivir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include remdesivir.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

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**Evidence To Decision**

**Benefits and harms**

In pregnant or breastfeeding women who are hospitalised with COVID-19 and who require ventilation, risk of death may be higher in patients using remdesivir compared with standard care.

**Certainty of the Evidence**

Certainty of the evidence is low for death at day 28 in hospitalised adults who require ventilation. Certainty is also low for patients requiring ventilation, discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is very low for all other outcomes.

**Preference and values**

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point.

The Consumer Panel believes that as there is clear evidence demonstrating harms of remdesivir in patients requiring ventilation, informed pregnant or breastfeeding women would not choose this treatment.

**Resources and other considerations**

There are no identified resource issues as the recommendation reflects usual care.

**Equity**

There are no identified equity issues as the recommendation reflects usual care.
Rationale
Remdesivir in adults hospitalised with COVID-19 who require ventilation probably increases the risk of death—its use should be avoided in pregnant and breastfeeding women.

Clinical Question/ PICO
Population: Patients with COVID-19
Intervention: Remdesivir
Comparator: Standard care

Summary
Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?
Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 [43][44][47][50][61][574]. The majority of evidence is from the WHO Solidarity trial which randomised 5451patients with moderate to critical COVID-19 [50].

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What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

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</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [hospital no ventilation] Within 28 days of commencing treatment</td>
<td>Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. ¹ (Randomized controlled)</td>
<td></td>
<td>88 per 1000</td>
<td>71 per 1000</td>
<td>Moderate Due to serious imprecision ² Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
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<tr>
<td>--------------------------------</td>
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<td>---------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>All-cause mortality [ventilation]</strong> within 28 days of commencing treatment</td>
<td>Relative risk 1.16 (CI 95% 0.96 – 1.41) Based on data from 1,332 participants in 5 studies. ⁷ (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious imprecision ⁴</td>
<td>Remdesivir probably increases death in hospitalised patients requiring ventilation.</td>
</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong> within 28 days of commencing treatment</td>
<td>Relative risk 0.82 (CI 95% 0.5 – 1.33) Based on data from 2,120 participants in 3 studies. ⁵ (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious imprecision and serious inconsistency ⁶</td>
<td>We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).</td>
</tr>
<tr>
<td><strong>Invasive mechanical ventilation or ECMO</strong> within 28 days of commencing treatment</td>
<td>Relative risk 0.57 (CI 95% 0.42 – 0.79) Based on data from 766 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious risk of bias and serious imprecision ⁸</td>
<td>Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).</td>
</tr>
<tr>
<td><strong>Patients requiring ventilation</strong> within 28 days of commencing treatment</td>
<td>Relative risk 1.04 (CI 95% 0.89 – 1.21) Based on data from 5,034 participants in 2 studies. ⁷ (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious imprecision ¹⁰</td>
<td>Remdesivir probably has no impact on number of patients requiring ventilation.</td>
</tr>
<tr>
<td><strong>Clinical recovery</strong> within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.86 – 1.14) Based on data from 1,876 participants in 3 studies. ¹¹ (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious risk of bias and serious inconsistency ¹²</td>
<td>We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Remdesivir</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies.</td>
<td>10 per 1000</td>
<td>10 per 1000</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Important</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.82 (CI 95% 0.65 — 1.04) Based on data from 2,689 participants in 4 studies.</td>
<td>273 per 1000</td>
<td>224 per 1000</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Important</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 2,704 participants in 4 studies.</td>
<td>553 per 1000</td>
<td>570 per 1000</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Important</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>Due to adverse events</td>
<td>Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3 studies.</td>
<td>93 per 1000</td>
<td>161 per 1000</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Important</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 95% 0.94 — 1.13) Based on data from 6,365 participants in 3 studies.</td>
<td>693 per 1000</td>
<td>714 per 1000</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Important</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to recovery</td>
<td>Days</td>
<td>Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 participants in 2 studies.</td>
<td>240 per 1000</td>
<td>261 per 1000</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Important</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to</td>
<td></td>
<td>Hazard Ratio 1.17 (CI 95% 1 — 1.38)</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table - Remdesivir

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>6 important</td>
<td>Based on data from 810 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>risk of bias²⁴</td>
<td>improvement slightly.</td>
</tr>
</tbody>
</table>


2. **Imprecision**: serious. Wide confidence intervals.


4. **Imprecision**: serious. Wide confidence intervals.


6. **Inconsistency**: serious. The direction of the effect is not consistent between the included studies. **Imprecision**: serious. Wide confidence intervals.


8. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision**: serious. Low number of patients, Only data from one study.


10. **Imprecision**: serious. Wide confidence intervals.


12. **Risk of Bias**: serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency**: serious. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.. The direction of the effect is not consistent between the included studies.


14. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency**: serious. The direction of the effect is not consistent between the included studies.


16. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


18. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


20. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision**: serious. Wide confidence intervals.


22. **Imprecision**: serious. Wide confidence intervals.
6.1.7.3 Remdesivir for children and adolescents

Use of remdesivir in children or adolescents with COVID-19 should be considered in consultation with an appropriate clinical reference group. The Australasian Society for Infectious Diseases (ASID) paediatric special interest group (ANZPID) has formed a clinical reference group to advise paediatric infection specialists on therapy for children with COVID-19. The ANZPID COVID-19 Clinical Reference Group can be urgently convened to discuss individual patient management and provide a recommendation to the treating team on the use of a disease-modifying treatment when needed. Informed consent from parents/caregivers should also be obtained.

Remdesivir is available in two presentations:

- Veklury® (remdesivir) 100 mg / 20 mL concentrate for injection: patients aged 18 years of over, or aged 12-17 AND weighing ≥ 40 kg.
- Veklury® (remdesivir) 100 mg lyophilised powder for injection: patients under 12 years of age and/or < 40 kg

Evidence To Decision

**Benefits and harms**

In adults who are hospitalised with moderate COVID-19 and who do not require ventilation (non-invasive ventilation, mechanical ventilation or ECMO), remdesivir probably reduces the incidence of death.

Evidence from randomised trials versus standard care demonstrates that remdesivir has an acceptable safety profile and may reduce the incidence of serious adverse events. Based on the results of two studies that compared 10-day to 5-day courses of remdesivir, it is unclear which of these regimens provide the optimal duration of treatment—current evidence does not suggest a clear benefit for 10 days over 5 days.

It is unclear how this benefit extrapolates to paediatric population given the much lower case fatality rate and the different form of presentation in children.

The trials are all based on adult patients. There remains uncertainty around the benefits and harms of remdesivir for children and adolescents with COVID-19.
Certainty of the Evidence

Certainty of the evidence is low for death at day 28 in patients who do not require oxygen and in patients who require oxygen but not ventilation and for patients who require ventilation. Certainty is also low for patients requiring ventilation, discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is very low for all other outcomes.

Preference and values

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Equity

There is a risk of creating inequity as some populations, including most children, are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Inequity may be further exacerbated in individuals who are eligible for treatment based on compassionate grounds due to factors that may limit access (such as geographic area).

Acceptability

We have no systematically collected evidence regarding acceptability. However, obtaining and maintaining intravenous access in children may be more difficult than in adults and may therefore affect acceptability.

Feasibility

On 10 July, the Therapeutic Goods Administration granted provisional approval to use remdesivir in hospitalised adolescents (aged 12 years and older weighing at least 40 kg) with severe COVID-19 symptoms (requiring oxygen or high level support to breathe).

Implementability may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and more general criteria (such as geographic area).

Rationale

Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Given the absence of children in the included studies, it remains uncertain, that the potential benefits and harms observed in the adult population can be extrapolated to children and adolescents. Because of this, the Taskforce gives a conditional recommendation against the use of remdesivir outside the context of a randomised trial for children and adolescents [43][45][47].

Clinical Question/ PICO

- Population: Remdesivir dosage for COVID-19
- Intervention: 5 days' treatment
### Summary

There remains uncertainty whether a 5-day course of remdesivir is more effective and safer than a 10-day course.

### What is the evidence informing this recommendation?

Evidence comes from two randomised trials that compared 5-day to 10-day treatment with remdesivir in 781 hospitalised patients with severe COVID-19 [45][47].

### Study characteristics

For a comprehensive description, see the study characteristics table.

### What are the main results?

- There is a lower risk of death within 14 days of treatment with a 5-day versus a 10-day course of remdesivir (16 fewer per 1000; RR 0.73, CI 95% 0.40 to 1.33; 781 patients in 2 studies). The evidence is more uncertain for death within 28 days of treatment (5 fewer per 1000; RR 0.67, CI 95% 0.11 to 3.99; 384 patients in 1 study).

- There is probably little difference between a 5-day and 10-day course of remdesivir regarding adverse events, discontinuation of treatment due to adverse events and discharge from hospital.

### Our confidence in the results

Certainty of the evidence is moderate for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is low for death within 28 days, acute respiratory failure or ARDS, clinical recovery within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation [45], lack of blinding), serious imprecision (too few events) and very serious imprecision (reliance on a single study with few patients and/or few events).

It is important to note that Goldman et al. only presents initial results from the first 400 patients in a trial that includes nearly 5000 patients (NCT04292899) [45]. The trial completed recruitment in July 2020 and we await the results from the full cohort of patients.

### Additional information

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [46].

### Outcome Table

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Up to 10 days’ treatment</th>
<th>Intervention 5 days’ treatment</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 0.73 (CI 95% 0.4 – 1.33) Based on data from 781 participants in 2 studies. 2 (Randomized controlled)</td>
<td>59 per 1000</td>
<td>Moderate</td>
<td>Due to serious imprecision 2 Remdesivir 5-day treatment probably has little or no impact on death (40 deaths).</td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.67 (CI 95% 0.11 – 3.99) Based on data from 384 participants in 1 studies. 3 (Randomized controlled)</td>
<td>16 per 1000</td>
<td>Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases death at 28 days (5 deaths).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 16 fewer per 1000 (CI 95% 35 fewer – 19 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator Up to 10 days’ treatment</td>
<td>Intervention 5 days’ treatment</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
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<td>-------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Acute respiratory failure or ARDS</td>
<td>Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 participants in 1 studies.</td>
<td>117 per 1000</td>
<td>55 per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (34 events).</td>
</tr>
<tr>
<td>Within 30 days of commencing treatment</td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>Relative risk 0.39 (CI 95% 0.08 — 0.01) Based on data from 397 participants in 1 studies.</td>
<td>538 per 1000</td>
<td>646 per 1000</td>
<td>Very low Due to very serious imprecision</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (7 events).</td>
</tr>
<tr>
<td>Within 30 days of commencing treatment</td>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Relative risk 1.2 (CI 95% 1.02 — 1.41) Based on data from 397 participants in 1 studies.</td>
<td>200 per 1000</td>
<td>128 per 1000</td>
<td>Low Due to serious risk of bias and imprecision</td>
<td>Remdesivir 5-day treatment may improve clinical recovery slightly (235 events).</td>
</tr>
<tr>
<td>Within 14 days of commencing treatment</td>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 participants in 2 studies.</td>
<td>662 per 1000</td>
<td>616 per 1000</td>
<td>Moderate Due to serious adverse events</td>
<td>Remdesivir 5-day treatment probably decreases serious adverse events slightly (129 events).</td>
</tr>
<tr>
<td>End of follow up</td>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 0.93 (CI 95% 0.84 — 1.03) Based on data from 781 participants in 2 studies.</td>
<td>56 per 1000</td>
<td>33 per 1000</td>
<td>Low Due to serious risk of bias and imprecision</td>
<td>Remdesivir 5-day treatment may make little or no difference to discontinuation due</td>
</tr>
<tr>
<td>End of follow up</td>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>Relative risk 0.59 (CI 95% 0.3 — 1.15) Based on data from 781 participants in 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>--------------------------------</td>
<td>------------</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>treatment</td>
<td>Up to 10 days’ treatment</td>
<td>Difference: 23 fewer per 1000 (CI 95% 39 fewer — 8 more)</td>
<td>Remdesivir 5-day treatment probably makes little or no difference to number of patients discharged from hospital at day 14 (515 events).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.06 (CI 95% 0.93 — 1.2) Based on data from 781 participants in 2 studies.</td>
<td>638 per 1000</td>
<td>Moderate</td>
<td>Due to serious risk of bias</td>
</tr>
<tr>
<td>Discharged from hospital</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.92 — 1.06) Based on data from 384 participants in 1 study.</td>
<td>902 per 1000</td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
</tbody>
</table>

2. **Imprecision:** serious. due to few events.
4. **Imprecision:** very serious. Low number of patients, Only data from one study, due to few events.
6. **Imprecision:** very serious. Low number of patients, Only data from one study.
8. **Imprecision:** very serious. Low number of patients, Only data from one study.
10. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Only data from one study.
12. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.
14. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
16. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
Imprecision: serious, due to few events.


18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


20. **Imprecision: very serious.** Low number of patients, Only data from one study.

### Clinical Question/ PICO

**Population:** Patients with COVID-19  
**Intervention:** Remdesivir  
**Comparator:** Standard care

**Summary**

Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

**What is the evidence informing this recommendation?**

Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 [43][44][47][50][61][574]. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 [50].

**Study characteristics**

For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Number of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>666</td>
<td>[47][61]</td>
</tr>
<tr>
<td>Moderate-Critical</td>
<td>6513</td>
<td>[43][50][574]</td>
</tr>
<tr>
<td>Severe-Critical</td>
<td>236</td>
<td>[44]</td>
</tr>
</tbody>
</table>

**What are the main results?**

Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale [43] or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale [47]. Clinical improvement was defined as an improvement of 2 or more points on a 7-point [47] or 6-point ordinal scale [44].

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design [62]. The study included 86 pregnant and postpartum women with severe COVID-19 in the USA who received compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline.
Two-thirds of pregnant women and all postpartum women were in ICU.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in children and adolescents. The preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population [499]. Trials are currently recruiting in this population.

**Our confidence in the results**
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or ARDS (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [46].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
</table>
| All-cause mortality [hospital no ventilation] Within 28 days of commencing treatment | Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. 1 (Randomized controlled) | 88 per 1000 | 71 per 1000 | Moderate | Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.

1 Critical
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [ventilation]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate</td>
<td>Remdesivir probably increases death in hospitalised patients requiring ventilation.</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from 2,120 participants in 3 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low</td>
<td>We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 participants in 1 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low</td>
<td>Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).</td>
</tr>
<tr>
<td>Patients requiring ventilation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 participants in 2 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Moderate</td>
<td>Remdesivir probably has no impact on number of patients requiring ventilation.</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 participants in 3 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low</td>
<td>We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.94 — 3.01) Based on data from 1,296 participants in 2 studies.</td>
<td>Standard care</td>
<td>Remdesivir</td>
<td>Low</td>
<td>We are uncertain whether remdesivir increases or decreases septic shock (13 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
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<td>Standard care</td>
<td>Remdesivir</td>
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<td>Outcome</td>
<td>Timeframe</td>
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2. **Imprecision: serious.** Wide confidence intervals.


4. **Imprecision: serious.** Wide confidence intervals.


6. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Imprecision: serious.** Wide confidence intervals.


8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Low number of patients, Only data from one study.


10. **Imprecision: serious.** Wide confidence intervals.


12. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies/ The direction of the effect is not consistent between the included studies.


14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies.


16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


20. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Wide confidence intervals.


22. **Imprecision: serious.** Wide confidence intervals.

23. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

24. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
### 6.1.8 Sotrovimab

#### 6.1.8.1 Sotrovimab for adults

**Conditional recommendation**

Consider using sotrovimab within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which sotrovimab is conditionally recommended for use (see Remark), decisions about the appropriateness of treatment with sotrovimab should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

* Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of sotrovimab is unclear in partially or fully vaccinated individuals. See consensus recommendation for guidance on use of sotrovimab in vaccinated patients or in immunocompromised patients regardless of vaccination status.

In patients with confirmed COVID-19 who do not require oxygen, sotrovimab probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on the COMET-ICE trial [617], in which unvaccinated adults were treated with a single one-hour intravenous infusion of 500 mg of sotrovimab. Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- Diabetes (requiring medication)
- Obesity (BMI ≥ 30 kg/m²)
- Chronic kidney disease (i.e. eGFR < 60 by MDRD)
- Congestive heart failure (NYHA class II or greater)
- Chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion)
- Moderate-to-severe asthma (requiring an inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months)
- Age ≥ 55 years

Pregnant & breastfeeding women and children & adolescents were not included in the trial. However trials are underway in which children over 12 years of age are eligible for inclusion (OPTIMISE-C19, NCT04913675).

The efficacy of sotrovimab in vaccinated or immunocompromised patients is unknown.

As of 28 January 2022, the Taskforce has made conditional recommendations supporting the use of nirmatrelvir plus ritonavir, sotrovimab, and casirivimab plus imdevimab in adult outpatients with mild COVID-19. The relative effectiveness of these agents, or the effectiveness of these agents when used in combination, is unclear.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

### Evidence To Decision

**Benefits and harms**

In non-hospitalised adults with mild COVID-19 who receive treatment within five days of symptom onset, sotrovimab probably decreases hospitalisation and serious adverse events. Based on the results of the COMET-ICE trial, sotrovimab has an acceptable safety profile.

**Older people living with frailty or cognitive impairment**

People aged over 65 years were included in the trial but no details were reported for frailty or cognitive impairment.

**People requiring palliative care**

There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trial for this population. In particular, the benefits for symptom management are uncertain.
Pregnant and breastfeeding women
There is uncertainty around the benefits and harms of sotrovimab for pregnant or breastfeeding women as they were excluded from the trial.

Children and adolescents
There is uncertainty around the benefits and harms of sotrovimab for children or adolescents as they were excluded from the trial. There are presently two randomised trials underway in which children aged 12 years and over are eligible for inclusion (OPTIMISE-C19, NCT04913675).

Certainty of the Evidence
Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, the requirement of non-invasive ventilation or HFNO and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement of invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and low number of events).

For children & adolescents and pregnant & breastfeeding women, certainty has been downgraded further due to serious indirectness (absence of inclusion of these populations in the study).

Preference and values
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that some patients would opt for treatment while others might want to wait for more evidence.

Pregnant and breastfeeding women
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. At this point, sotrovimab remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Equity
We have no systematically collected evidence regarding impact on equity.

Acceptability
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.
**Feasibility**

Intravenous sotrovimab (Xevudy; GlaxoSmithKline Australia Pty Ltd) was granted provisional approval for the treatment of COVID-19 by the Therapeutic Goods Administration on 20 August 2021 under the Black Triangle Scheme (ARTG number: 364110; AusPAR).

There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

**Rationale**

**General adult population**

In non-hospitalised adults with mild COVID-19 and one or more risk factors for disease progression, sotrovimab probably reduces incidence of hospitalisation when used within five days of symptom onset. Because of this, the Taskforce gives a conditional recommendation for sotrovimab both within and outside a randomised trial.

**Clinical Question/ PICO**

- **Population:** Patients with mild or moderate COVID-19
- **Intervention:** Sotrovimab
- **Comparator:** Placebo

**Summary**

Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of symptom onset.

**What is the evidence informing this recommendation?**

Evidence comes from one randomised trial (COMET-ICE) that compared sotrovimab with placebo in 583 adult outpatients with mild-to-moderate COVID-19 [617].

**Publication status**

Final results of the COMET-ICE trial, which includes efficacy and safety analyses in all 1057 patients, are currently only available in the form of a clinical study report (CSR), which has yet to be published.

**Study characteristics**

Median age of participants was 52 years and 54% were women. All eligible patients required one or more risk factors for disease progression, including diabetes (requiring medication), obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or adults over 55 years of age. Pregnant women were ineligible, and only six patients were aged under 19 years.

**What are the main results?**

Sotrovimab probably decreases the incidence of hospitalisation (42 fewer per 1000; RR 0.24, CI 95% 0.11 to 0.55; 1057 patients in 1 study), the composite outcome of hospitalisation (for longer than 24 hours) or death (46 fewer per 1000; RR 0.20, CI 95% 0.08 to 0.48; 1057 patients in 1 study) and serious adverse events (40 fewer per 1000; RR 0.35, CI 95% 0.18 to 0.68; 1049 patients from 1 study). We are unsure if sotrovimab impacts death or the requirement for invasive mechanical ventilation.

Sotrovimab probably has little impact on ICU admission, the requirement of non-invasive ventilation or HFNO, or adverse events.

**Our confidence in the results**

Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).
### Additional information

There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation (≥ 24 hours) or death [composite] Within 29 days of treatment</td>
<td>Relative risk 0.2 (CI 95% 0.08 — 0.48) Based on data from 1,057 participants in 1 studies.</td>
<td>Placebo</td>
<td>Sotrovimab</td>
<td>Moderate Due to serious imprecision</td>
<td>Sotrovimab probably decreases hospitalisation (≥ 24 hours) or death (36 events).</td>
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<tr>
<td>All-cause mortality Within 29 days of treatment</td>
<td>Relative risk 0.2 (CI 95% 0.01 — 4.16) Based on data from 1,057 participants in 1 studies.</td>
<td>Placebo</td>
<td>Sotrovimab</td>
<td>Low Due to very serious imprecision</td>
<td>We are uncertain whether sotrovimab impacts death (2 events).</td>
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<tr>
<td>Hospitalisation [any cause any duration] Within 29 days of treatment</td>
<td>Relative risk 0.21 (CI 95% 0.09 — 0.5) Based on data from 1,057 participants in 1 studies.</td>
<td>Placebo</td>
<td>Sotrovimab</td>
<td>Moderate Due to serious imprecision</td>
<td>Sotrovimab probably decreases hospitalisation [any cause or duration] (35 events).</td>
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<tr>
<td>ICU admission Within 29 days of treatment</td>
<td>Relative risk 0.05 (CI 95% 0.01 — 0.81) Based on data from 1,057 participants in 1 studies.</td>
<td>Placebo</td>
<td>Sotrovimab</td>
<td>Moderate Due to serious imprecision</td>
<td>Sotrovimab probably has little impact on ICU admission (10 events).</td>
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<tr>
<td>Invasive mechanical ventilation Within 29 days of treatment</td>
<td>Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 1,057 participants in 1 studies.</td>
<td>Placebo</td>
<td>Sotrovimab</td>
<td>Low Due to very serious imprecision</td>
<td>We are uncertain whether sotrovimab impacts invasive mechanical ventilation (4 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<tr>
<td>Non-invasive ventilation / HFNO</td>
<td>Relative risk 0.05 (CI 95% 0.0 - 0.81) Based on data from 1,057 participants in 1 studies.</td>
<td>19 per 1000</td>
<td>1 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably has little impact on non-invasive ventilation / HFNO (10 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 0.93 (CI 95% 0.74 - 1.17) Based on data from 1,049 participants in 1 studies.</td>
<td>234 per 1000</td>
<td>218 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably has little impact on adverse events (237 events).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.35 (CI 95% 0.18 - 0.68) Based on data from 1,049 participants in 1 studies.</td>
<td>61 per 1000</td>
<td>21 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably decreases serious adverse events (43 events).</td>
</tr>
</tbody>
</table>

2. Imprecision: serious. Only data from one study.
4. Imprecision: very serious. Only data from one study, due to few events.
8. Imprecision: serious. Only data from one study.
10. Imprecision: very serious. Only data from one study, due to few events.
In addition to at-risk unvaccinated adults, also consider using sotrovimab within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunosuppressed or not immunocompetent regardless of vaccination status; or
- have received one or two doses of vaccine and who are at high risk of disease on the basis of age and multiple risk factors

Available research does not currently provide enough evidence to determine the benefits of sotrovimab in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from sotrovimab.

There is no evidence evaluating the effectiveness of sotrovimab in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this, and the lower risk of deterioration in these patients, it is unlikely that sotrovimab will have a significant treatment benefit in patients who have received three doses of vaccine, unless the patient is immunosuppressed.

There is no evidence on the effectiveness of sotrovimab in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that sotrovimab will be beneficial for immunosuppressed patients.

Immunocompromising conditions include:

- Primary or acquired immunodeficiency
  - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
  - Other significantly immunocompromising conditions

- Immunosuppressive therapy (current or recent)
  - Chemotherapy, whole body radiotherapy or total lymphoid irradiation
  - High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - All biological disease-modifying anti-rheumatic drugs (DMARDs) and most other (e.g. conventional synthetic) DMARDs [550]

6.1.8.2 Sotrovimab for pregnant women
Conditional recommendation

Consider using sotrovimab for the treatment of COVID-19 within 5 days of symptom onset in pregnant women in the second or third trimester who do not require oxygen and who have one or more additional risk factors for disease progression.

Please note: The Taskforce has made additional recommendations on the use of sotrovimab in immunosuppressed and fully vaccinated patients. These are available below.

In adult, non-pregnant patients with confirmed COVID-19 who do not require oxygen, sotrovimab probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on the COMET-ICE trial [617], in which non-vaccinated adults were treated with a single one-hour intravenous infusion of 500 mg sotrovimab. Pregnant and breastfeeding women were not included in this trial, and there are currently no data on the effects of sotrovimab on a pregnant woman or baby.

Sotrovimab is a human immunoglobulin G (IgG) and may cross the placenta from mother to baby. The potential impact of this is not known. However, it is known that pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby [567]. Sotrovimab can therefore be considered if the benefit justifies the potential risk.

Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- Pre-gestational diabetes (requiring medication)
- Obesity (BMI > 30 kg/m2)
- Chronic kidney disease (i.e. eGFR < 60 by MDRD)
- Congestive heart failure (NYHA class II or greater)
- Chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion)
- Moderate-to-severe asthma (requiring an inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months)

The efficacy of sotrovimab in vaccinated or immunocompromised patients is unknown.

There are no available data on the excretion of sotrovimab in human milk, and the potential benefits and risks to a breastfed baby are not known. The median elimination half-life of sotrovimab is 49 days [565], and human IgGs are known to be excreted in breast milk. A decision whether to discontinue breastfeeding or to abstain from sotrovimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

There is uncertainty around the benefits and harms of sotrovimab for pregnant or breastfeeding women with COVID-19.

In non-hospitalised adults with mild COVID-19 who receive treatment within five days of symptom onset, sotrovimab probably decreases hospitalisation and serious adverse events. Based on the results of the COMET-ICE trial, sotrovimab has an acceptable safety profile in non-pregnant adults.

There are currently no data on the effects of sotrovimab on a pregnant woman or baby. As sotrovimab is a human immunoglobulin G (IgG), it may cross the placenta from mother to baby. The potential impact of this is not known. However, it is known that pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby [567].
There are no available data on the excretion of sotrovimab in human milk, and the potential benefits and risks to a breastfed baby are not known. The median elimination half-life of sotrovimab is 49 days [565], and human IgGs are known to be excreted in breast milk. A decision whether to discontinue breastfeeding or to abstain from sotrovimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

Certainty of the Evidence

In non-pregnant adults, certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, the requirement of non-invasive ventilation or HFNO and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement of invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence of inclusion of these populations in the study).

Preference and values

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. At this point, sotrovimab remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Equity

We have no systematically collected evidence regarding impact on equity.

Acceptability

We have no systematically collected evidence regarding acceptability by pregnant or breastfeeding women.

Feasibility

Intravenous sotrovimab (Xevudy; GlaxoSmithKline Australia Pty Ltd.) was granted provisional approval for the treatment of COVID-19 by the Therapeutic Goods Administration on 20 August 2021 under the Black Triangle Scheme (ARTG number: 364110; AusPAR).

There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

Rationale

In non-hospitalised, non-pregnant adults with mild COVID-19 and one or more risk factors for disease progression, sotrovimab probably reduces the incidence of hospitalisation when used within five days of symptom onset. The available trial did not include pregnant or breastfeeding women.

There are currently no data on the effects of sotrovimab on pregnant women or their babies. As sotrovimab is a human immunoglobulin G (IgG), it may cross the placenta, though the potential impact of this is not known.
However, pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby [567].

There are no available data on the excretion of sotrovimab in human milk, and the potential benefits and risks to a breastfed baby are not known. The median elimination half-life of sotrovimab is 49 days [565], and human IgGs are known to be excreted in breast milk. A decision whether to discontinue breastfeeding or to abstain from sotrovimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

Clinical Question/ PICO

| Population: | Patients with mild or moderate COVID-19 |
| Intervention: | Sotrovimab |
| Comparator: | Placebo |

Summary
Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of symptom onset.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (COMET-ICE) that compared sotrovimab with placebo in 583 adult outpatients with mild-to-moderate COVID-19 [617].

Publication status
Final results of the COMET-ICE trial, which includes efficacy and safety analyses in all 1057 patients, are currently only available in the form of a clinical study report (CSR), which has yet to be published.

Study characteristics
Median age of participants was 52 years and 54% were women. All eligible patients required one or more risk factors for disease progression, including diabetes (requiring medication), obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or adults over 55 years of age. Pregnant women were ineligible, and only six patients were aged under 19 years.

What are the main results?
Sotrovimab probably decreases the incidence of hospitalisation (42 fewer per 1000; RR 0.24, CI 95% 0.11 to 0.55; 1057 patients in 1 study), the composite outcome of hospitalisation (for longer than 24 hours) or death (46 fewer per 1000; RR 0.20, CI 95% 0.08 to 0.48; 1057 patients in 1 study) and serious adverse events (40 fewer per 1000; RR 0.35, CI 95% 0.18 to 0.68; 1049 patients from 1 study). We are unsure if sotrovimab impacts death or the requirement for invasive mechanical ventilation.

Sotrovimab probably has little impact on ICU admission, the requirement of non-invasive ventilation or HFNO, or adverse events.

Our confidence in the results
Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).

Additional information
There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.
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<tr>
<th>Outcome</th>
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<th>Certainty of the Evidence (Quality of evidence)</th>
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<tr>
<td>Hospitalisation (≥ 24 hours)</td>
<td>Within 29 days of treatment</td>
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<td>57 per 1000</td>
<td>11 per 1000</td>
<td>Moderate Due to serious imprecision ²</td>
<td>Sotrovimab probably decreases hospitalisation (≥ 24 hours) or death (36 events).</td>
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<td>All-cause mortality</td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.2 (CI 95% 0.01 — 4.16) Based on data from 1,057 participants in 1 studies.</td>
<td>4 per 1000</td>
<td>1 per 1000</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>We are uncertain whether sotrovimab impacts death (2 events).</td>
</tr>
<tr>
<td>Hospitalisation (any cause)</td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.21 (CI 95% 0.09 — 0.5) Based on data from 1,057 participants in 1 studies.</td>
<td>55 per 1000</td>
<td>12 per 1000</td>
<td>Moderate Due to serious imprecision ⁶</td>
<td>Sotrovimab probably decreases hospitalisation [any cause or duration] (35 events).</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies.</td>
<td>19 per 1000</td>
<td>1 per 1000</td>
<td>Moderate Due to serious imprecision ⁸</td>
<td>Sotrovimab probably has little impact on ICU admission (10 events).</td>
</tr>
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<td>Invasive mechanical ventilation</td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 1,057 participants in 1 studies.</td>
<td>8 per 1000</td>
<td>1 per 1000</td>
<td>Low Due to very serious imprecision ¹⁰</td>
<td>We are uncertain whether sotrovimab impacts invasive mechanical ventilation (4 events).</td>
</tr>
<tr>
<td>Non-invasive ventilation / HFNO</td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies.</td>
<td>19 per 1000</td>
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<td><strong>Adverse events</strong></td>
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<td><strong>Sotrovimab</strong></td>
<td><strong>Moderate</strong> Due to serious imprecision</td>
<td>Sotrovimab probably has little impact on adverse events (237 events).</td>
<td></td>
</tr>
<tr>
<td>Within 29 days of treatment</td>
<td>Difference: 234 per 1000</td>
<td>218 per 1000</td>
<td>16 fewer per 1000 ( CI 95% 61 fewer — 40 more )</td>
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<td></td>
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<td><strong>Sotrovimab</strong></td>
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<td>Sotrovimab probably decreases serious adverse events (43 events).</td>
<td></td>
</tr>
<tr>
<td>Within 29 days of treatment</td>
<td>Difference: 61 per 1000</td>
<td>21 per 1000</td>
<td>40 fewer per 1000 ( CI 95% 50 fewer — 20 fewer )</td>
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2. **Imprecision: serious.** Only data from one study.
4. **Imprecision: very serious.** Only data from one study, due to few events.
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15. Systematic review [541] with included studies: COMET-ICE final. **Baseline/comparator:** Control arm of reference used for intervention.
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Consensus recommendation

Within the population of pregnant women for whom sotrovimab is conditionally recommended for use (as listed above), decisions about the appropriateness of treatment with sotrovimab should be based on the patient’s individual risk of severe disease, on the basis of multiple risk factors, and COVID-19 vaccination status.

Consider using sotrovimab in unvaccinated or partially vaccinated patients and patients who are immunosuppressed regardless of vaccination status.

Do not routinely use sotrovimab in fully vaccinated patients unless immunosuppressed.

The available research does not currently provide enough evidence to determine the benefits of sotrovimab in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from sotrovimab.

There is no evidence evaluating the effectiveness of sotrovimab in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this and the lower risk of deterioration in these patients, it is unlikely that sotrovimab will be particularly valuable in fully vaccinated patients, unless the patient is immunosuppressed.

There are no evidence on the effectiveness of sotrovimab in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that sotrovimab will be beneficial for immunosuppressed patients.

Immunocompromising conditions include:

- Primary or acquired immunodeficiency
  - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
  - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)
  - Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
  - Other significantly immunocompromising conditions
- Immunosuppressive therapy (current or recent)
  - Chemotherapy or radiotherapy
  - High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days
  - All biologics and most disease-modifying anti-rheumatic drugs (DMARDs) [550]

Clinical Question/ PICO

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Summary

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Sotrovimab probably has little impact on ICU admission, the requirement of non-invasive ventilation or HFNO, or adverse events.

**Our confidence in the results**

Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).

**Additional information**

There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

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2. Imprecision: serious. Only data from one study.
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6.3.8.3 Sotrovimab for children and adolescents

**Evidence To Decision**

**Benefits and harms**

In non-hospitalised adults with mild COVID-19 who receive treatment within five days of symptom onset, sotrovimab probably decreases hospitalisation and serious adverse events. Based on the results of the COMET-ICE trial, sotrovimab has an acceptable safety profile.

**Older people living with frailty or cognitive impairment**

People aged over 65 years were included in the trial but no details were reported for frailty or cognitive impairment.

**People requiring palliative care**

There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trial for this population. In particular, the benefits for symptom management are uncertain.

**Pregnant and breastfeeding women**

There is uncertainty around the benefits and harms of sotrovimab for pregnant or breastfeeding women as they were excluded from the trial.
Children and adolescents
There is uncertainty around the benefits and harms of sotrovimab for children or adolescents as they were excluded from the trial. There are presently two randomised trials underway in which children aged 12 years and over are eligible for inclusion (OPTIMISE-C19, NCT04913675).

Certainty of the Evidence

Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, the requirement of non-invasive ventilation or HFNO and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement of invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and low number of events).

For children & adolescents, certainty has been downgraded further due to serious indirectness (absence of inclusion of these populations in the study).

Preference and values
We have no systematically collected information regarding patients' preferences and values.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. At this point, sotrovimab remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Equity
We have no systematically collected evidence regarding impact on equity.

Acceptability
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

Feasibility
The Therapeutic Goods Administration is currently considering an application by the Sponsor regarding conditional approval of sotrovimab within Australia to treat patients with mild COVID-19 who have one or more risk factors. There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.
Clinical Question/ PICO

**Population:** Special populations with mild or moderate COVID-19

**Intervention:** Sotrovimab

**Comparator:** Placebo

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**Summary**

Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of symptom onset.

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<td>Plain language summary</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------</td>
<td>------------</td>
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<td>---------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Timeframe</td>
<td>Relative risk 0.35 (CI 95% 0.18 — 0.68) Based on data from 1,049 participants in 1 studies.</td>
<td>Placebo</td>
<td>Sotrovimab</td>
<td>Only data from one study. Due to serious indirectness.</td>
<td>Sotrovimab may decrease serious adverse events (43 events).</td>
</tr>
<tr>
<td>6 important</td>
<td>(Randomized controlled)</td>
<td>( CI 95% 61 fewer — 40 more )</td>
<td></td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Within 29 days of treatment</td>
<td>61 per 1000</td>
<td>21 per 1000</td>
<td>Difference: 40 fewer per 1000 ( CI 95% 50 fewer — 20 fewer )</td>
<td></td>
</tr>
</tbody>
</table>

2. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
4. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study.
6. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
7. Systematic review [540] with included studies: COMET-ICE final. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
10. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, due to few events.
12. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
14. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.
15. Systematic review [541] with included studies: COMET-ICE final. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study.

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**Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce**

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Consensus recommendation

Consider using, in exceptional circumstances, sotrovimab for the treatment of COVID-19 within 5 days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40 kg who do not require oxygen and who are at high risk of deterioration.

Consider using sotrovimab only in unvaccinated or partially vaccinated children and adolescents, or those who are immunosuppressed regardless of vaccination status. Do not routinely use sotrovimab in fully vaccinated patients unless immunosuppressed.

Decisions about the appropriateness of treatment with sotrovimab should be based on the patient’s individual risk of severe disease, on the basis of age or multiple risk factors, and COVID-19 vaccination status.

Decisions to provide sotrovimab to a child or adolescent should be based on the individual’s combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Available research does not currently provide enough evidence to determine the benefits of sotrovimab in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from sotrovimab. Based on international cohorts [580] potential factors to consider in patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

There is no evidence evaluating the effectiveness of sotrovimab in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this and the lower risk of deterioration in these patients, it is unlikely that sotrovimab will be particularly valuable in fully vaccinated patients, unless the patient is immunosuppressed.

There is no evidence on the effectiveness of sotrovimab in immunosuppressed children and adolescents. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that sotrovimab will be beneficial for immunosuppressed patients.

Clinical Question/ PICO

Population: Patients with mild or moderate COVID-19

Intervention: Sotrovimab

Comparator: Placebo

Summary

Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of symptom onset.

What is the evidence informing this recommendation?

Evidence comes from one randomised trial (COMET-ICE) that compared sotrovimab with placebo in 583 adult outpatients with mild-to-moderate COVID-19 [617].

Publication status

Final results of the COMET-ICE trial, which includes efficacy and safety analyses in all 1057 patients, are currently only available in the form of a clinical study report (CSR), which has yet to be published.

Study characteristics

Median age of participants was 52 years and 54% were women. All eligible patients required one or more risk factors for disease progression, including diabetes (requiring medication), obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or adults over 55
years of age. Pregnant women were ineligible, and only six patients were aged under 19 years.

What are the main results?
Sotrovimab probably decreases the incidence of hospitalisation (42 fewer per 1000; RR 0.24, CI 95% 0.11 to 0.55; 1057 patients in 1 study), the composite outcome of hospitalisation (for longer than 24 hours) or death (46 fewer per 1000; RR 0.20, CI 95% 0.08 to 0.48; 1057 patients in 1 study) and serious adverse events (40 fewer per 1000; RR 0.35, CI 95% 0.18 to 0.68; 1049 patients from 1 study). We are unsure if sotrovimab impacts death or the requirement for invasive mechanical ventilation.

Sotrovimab probably has little impact on ICU admission, the requirement of non-invasive ventilation or HFNO, or adverse events.

Our confidence in the results
Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).

Additional information
There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation (≥ 24 hours) or death [composite]</td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.2 (CI 95% 0.08 — 0.48) Based on data from 1,057 participants in 1 studies (Randomized controlled)</td>
<td>57 per 1000</td>
<td>11 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably decreases hospitalisation (≥ 24 hours) or death (36 events).</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.2 (CI 95% 0.01 — 4.16) Based on data from 1,057 participants in 1 studies (Randomized controlled)</td>
<td>4 per 1000</td>
<td>1 per 1000</td>
<td>Low</td>
<td>We are uncertain whether sotrovimab impacts death (2 events).</td>
</tr>
<tr>
<td>Hospitalisation [any cause any duration]</td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.21 (CI 95% 0.09 — 0.5) Based on data from 1,057 participants in 1 studies (Randomized controlled)</td>
<td>55 per 1000</td>
<td>12 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably decreases hospitalisation [any cause any duration] (35 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td><strong>ICU admission</strong></td>
<td>Within 29 days of treatment</td>
<td>Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. (Randomized controlled)</td>
<td>19 per 1000</td>
<td>1 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably has little impact on ICU admission (10 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference:</td>
<td>18 fewer per</td>
<td>Due to serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1000</td>
<td>1000</td>
<td>imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference:</td>
<td>1000</td>
<td>Low</td>
<td>We are uncertain whether sotrovimab impacts invasive mechanical ventilation (4 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 1,057 participants in 1 studies. (Randomized controlled)</td>
<td>8 per 1000</td>
<td>1 per 1000</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference:</td>
<td>7 fewer per</td>
<td>Due to very serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1000</td>
<td>1000</td>
<td>imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. (Randomized controlled)</td>
<td>19 per 1000</td>
<td>1 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably has little impact on non-invasive ventilation / HFNO (10 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference:</td>
<td>18 fewer per</td>
<td>Due to serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1000</td>
<td>1000</td>
<td>imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative risk 0.93 (CI 95% 0.74 — 1.17) Based on data from 1,049 participants in 1 studies. (Randomized controlled)</td>
<td>234 per 1000</td>
<td>218 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably has little impact on adverse events (237 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference:</td>
<td>16 fewer per</td>
<td>Due to serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1000</td>
<td>1000</td>
<td>imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative risk 0.35 (CI 95% 0.18 — 0.68) Based on data from 1,049 participants in 1 studies. (Randomized controlled)</td>
<td>61 per 1000</td>
<td>21 per 1000</td>
<td>Moderate</td>
<td>Sotrovimab probably decreases serious adverse events (43 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference:</td>
<td>40 fewer per</td>
<td>Due to serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1000</td>
<td>1000</td>
<td>imprecision</td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision:** serious. Only data from one study.
4. **Imprecision:** very serious. Only data from one study, due to few events.
5. Systematic review [624] with included studies: COMET-ICE final. **Baseline/comparator:** Control arm of reference used for intervention.
6.2 Disease-modifying treatments that are not recommended

6.2.1 Aspirin

Not recommended

Do not use aspirin for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of aspirin for treatment of COVID-19 may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include aspirin.

Aspirin may still be considered for other evidence-based indications in people who have COVID-19.

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

General adult population

Evidence indicates no difference between aspirin and standard care in incidence of death, requirement of mechanical ventilation or duration of hospital stay. Uncertainty remains regarding the incidence of adverse or serious adverse events.

Certainty of the Evidence

Certainty of the evidence is moderate for all outcomes due to serious imprecision (reliance on a single study).
Rationale

Based on the available evidence, aspirin is no more effective than standard care in treating patients with COVID-19. We therefore recommend that aspirin should not be used.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with COVID-19</td>
<td>Aspirin</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary

Evidence indicates that aspirin is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?

Evidence comes from a single randomised trial (RECOVERY) that compared aspirin with standard care in 14,892 adults hospitalised with moderate to critical COVID-19 [629].

Study characteristics

Median age of participants was 59 years and the proportion of women was 38%. Two-thirds of patients required either no oxygen or simple (low-flow) oxygen, 28% required non-invasive ventilation and 5% required invasive mechanical ventilation. Most patients (94%) received concomitant corticosteroids.

What are the main results?

Aspirin probably has no impact on mortality (5 fewer deaths per 1000; RR 0.97, CI 95% 0.90 to 1.04; 14,892
patients in 1 study) or invasive mechanical ventilation (6 fewer per 1000; RR 0.95, CI 95% 0.87 to 1.05; 14,162 patients in 1 study). There is probably little difference between aspirin and standard care for the composite outcome of death or invasive mechanical ventilation, or discharge from hospital at 28 days.

**Our confidence in the results**

Certainty of the evidence is moderate for all outcomes due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator standard care</th>
<th>Intervention Aspirin</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality Within 28 days of commencing treatment 9 Critical</td>
<td>Relative risk 0.97 (CI 95% 0.9 — 1.04) Based on data from 14,892 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>172 per 1000</td>
<td>167 per 1000</td>
<td>Moderate Due to serious imprecision ²</td>
<td>Aspirin probably has little or no impact on death.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death End of follow-up 9 Critical</td>
<td>Relative risk 0.96 (CI 95% 0.9 — 1.03) Based on data from 14,162 participants in 1 studies. ³ (Randomized controlled)</td>
<td>219 per 1000</td>
<td>210 per 1000</td>
<td>Moderate Due to serious imprecision ⁴</td>
<td>Aspirin probably has little impact on invasive mechanical ventilation or death.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation End of follow-up 9 Critical</td>
<td>Relative risk 0.95 (CI 95% 0.87 — 1.05) Based on data from 14,162 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td>116 per 1000</td>
<td>110 per 1000</td>
<td>Moderate Due to serious imprecision ⁶</td>
<td>Aspirin probably has little impact on invasive mechanical ventilation.</td>
</tr>
<tr>
<td>Discharge from hospital End of follow-up 6 Important</td>
<td>Relative risk 1.02 (CI 95% 1.0 — 1.04) Based on data from 14,892 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td>736 per 1000</td>
<td>751 per 1000</td>
<td>Moderate Due to serious imprecision ⁸</td>
<td>Aspirin probably has little impact on discharge from hospital.</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** no serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Only data from one study.
4. **Risk of Bias: no serious**. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious**. Only data from one study.


8. **Risk of Bias: no serious**. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious**. Only data from one study.

### 6.2.2 Azithromycin

**Not recommended**

Do not use azithromycin for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of azithromycin may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include azithromycin.

This is a **moderate priority** recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

## Evidence To Decision

### Benefits and harms

#### General adult population

Evidence indicates no difference between azithromycin and standard care in incidence of death, requirement of mechanical ventilation or ECMO, or duration of hospital stay. Uncertainty remains regarding the incidence of adverse or serious adverse events.

According to the Therapeutic Goods Administration, reported adverse events are generally mild or moderate and include rash, heart palpitations, urinary tract infection, headache, fatigue and gastrointestinal symptoms such as dyspepsia and vomiting [103].

#### Pregnant and breastfeeding women

As azithromycin has only been taken by a limited number of pregnant women and women of childbearing age, its safety profile is therefore uncertain.

#### Children and adolescents

The safety and effectiveness of azithromycin in children has not been established.

## Certainty of the Evidence

### General adult population

Certainty of the evidence is high for the critical outcome of mortality (day 28). Certainty is moderate for patients...
Based on the available evidence, azithromycin is no more effective than standard care in treating patients with COVID-19. We therefore recommend that azithromycin should not be used.

**Rationale**

Based on the available evidence, azithromycin is no more effective than standard care in treating patients with COVID-19. We therefore recommend that azithromycin should not be used.

**Clinical Question/ PICO**

- **Population**: Patients with COVID-19
- **Intervention**: Azithromycin
- **Comparator**: Standard care

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

As azithromycin is not recommended there are no resource considerations.

**Equity**

As azithromycin is not recommended there are no equity considerations.

**Acceptability**

As azithromycin is not recommended there are no acceptability considerations.

**Feasibility**

As azithromycin is not recommended there are no feasibility considerations.

**Substantial variability is expected or uncertain**

requiring mechanical ventilation or ECMO, serious adverse events, discharge from hospital, and time to discharge from hospital—all based on serious imprecision due to wide confidence intervals or reliance on a single study (duration of hospital stay). Certainty is low for adverse events, clinical progression and discharge from hospital based on very serious imprecision due to wide confidence intervals and reliance on a single study.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is downgraded further because of indirectness due to limited inclusion (or absence) of these populations in the trials.
Summary
Evidence indicates that azithromycin is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from five randomised trials that compared azithromycin with standard care in almost 10,000 adults hospitalised with COVID-19 [101][102][106][109][142]. The vast majority of data are from the RECOVERY trial, which included 7763 adults hospitalised with moderate-to-critical COVID-19 [106]. One trial compared azithromycin with standard care in 1388 adult outpatients with mild COVID-19 [109], two trials compared azithromycin plus hydroxychloroquine with hydroxychloroquine alone in 397 adults hospitalised with severe or critical COVID-19 [101] and 331 with moderate COVID-19 [142], and one trial compared azithromycin plus hydroxychloroquine and lopinavir-ritonavir with hydroxychloroquine and lopinavir-ritonavir alone in 111 adults hospitalised with severe COVID-19 [102].

Study characteristics
For a comprehensive description, see the study characteristics table.

What are the main results?
Azithromycin has no impact on death compared with standard care (2 more deaths per 1000 patients with azithromycin; RR 1.01, CI 95% 0.92 to 1.10; 9595 patients in 4 studies) and has little impact on the number of patients requiring mechanical ventilation or ECMO (4 fewer per 1000 patients; RR 0.94, CI 95% 0.79 to 1.14; 8433 patients in 2 studies).

Azithromycin probably increases the incidence of serious adverse events (RR 1.13, CI 95% 0.90 to 1.42; 877 patients in 2 studies), probably decreases the number of patients discharged from hospital at 28 days (RR 0.92, CI 95% 0.71 to 1.19; 8161 patients in 2 studies), and probably has no impact on median duration of hospital stay.

We are uncertain if azithromycin increases or decreases adverse events or clinical progression (as measured by admission to ICU).

Our confidence in the results
Certainty of the evidence is high for the critical outcomes of mortality and number of patients requiring mechanical ventilation or ECMO.

Certainty is moderate for serious adverse events, discharge from hospital, and time to discharge from hospital (duration of hospital stay)—all based on serious imprecision due to wide confidence intervals or reliance on a single study.

Certainty is low for adverse events and clinical progression (defined as admission to ICU) based on very serious imprecision due to wide confidence intervals and reliance on a single study.

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, reported adverse events are generally mild or moderate and include rash, heart palpitations, urinary tract infection, dizziness, headache, fatigue and gastrointestinal symptoms such as dyspepsia and vomiting [103].

Additional published studies
The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

<table>
<thead>
<tr>
<th>Trial and Source</th>
<th>Date</th>
<th>Number</th>
<th>Comparison &amp; Population</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hinks 2021 Lancet Respir Med</td>
<td>9 Jul</td>
<td>292</td>
<td>Azithromycin vs standard care in mild-to-moderate COVID-19</td>
<td>Death or ho 28 days</td>
</tr>
<tr>
<td>Oldenburg 2021 JAMA</td>
<td>16 Jul</td>
<td>263</td>
<td>Azithromycin vs placebo in outpatients with COVID-19</td>
<td>Absence of at day 14</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Azithromycin</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>All-cause mortality Within 28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.92 — 1.1) Based on data from 9,595 participants in 4 studies. ³ (Randomized controlled)</td>
<td>172 per 1000</td>
<td>174 per 1000</td>
<td>High</td>
</tr>
<tr>
<td>Mechanical ventilation or ECMO Within 28 days of commencing treatment</td>
<td>Relative risk 0.94 (CI 95% 0.79 — 1.14) Based on data from 8,433 participants in 2 studies. ² (Randomized controlled)</td>
<td>60 per 1000</td>
<td>56 per 1000</td>
<td>High</td>
</tr>
<tr>
<td>Supplemental oxygen ³ Within 28 days of commencing treatment</td>
<td>Relative risk 0.84 (CI 95% 0.38 — 1.85) Based on data from 1,122 participants in 1 studies. ³ (Randomized controlled)</td>
<td>24 per 1000</td>
<td>20 per 1000</td>
<td>Low</td>
</tr>
<tr>
<td>Serious adverse events End of treatment</td>
<td>Relative risk 1.13 (CI 95% 0.9 — 1.42) Based on data from 877 participants in 2 studies. ⁶ (Randomized controlled)</td>
<td>194 per 1000</td>
<td>219 per 1000</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adverse events End of treatment</td>
<td>Relative risk 1.17 (CI 95% 0.91 — 1.5) Based on data from 438 participants in 1 studies. ⁸ (Randomized controlled)</td>
<td>337 per 1000</td>
<td>394 per 1000</td>
<td>Low</td>
</tr>
<tr>
<td>ICU admission End of follow-up</td>
<td>Relative risk 0.48 (CI 95% 0.17 — 1.35) Based on data from 1,231 participants in 2 studies. ¹⁰ (Randomized controlled)</td>
<td>18 per 1000</td>
<td>9 per 1000</td>
<td>Low</td>
</tr>
</tbody>
</table>

Relative risk values are calculated per 1000 participants. Differences are calculated per 1000 participants. Certainty of the Evidence is graded as High, Moderate, or Low based on the quality of evidence.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Azithromycin</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical recovery</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.96 (CI 95% 0.88 – 1.05) Based on data from 1,129 participants in 1 studies. (Randomized controlled)</td>
<td>658 per 1000</td>
<td>632 per 1000</td>
<td>Low Due to very serious imprecision 13</td>
<td>We are uncertain whether azithromycin increases or decreases clinical recovery (731 events).</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Discharge from hospital</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.92 (CI 95% 0.71 – 1.19) Based on data from 8,161 participants in 2 studies. (Randomized controlled)</td>
<td>586 per 1000</td>
<td>539 per 1000</td>
<td>Moderate Due to serious imprecision 15</td>
<td>Azithromycin probably decreases discharge from hospital slightly (4765 events).</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Duration of hospital stay</strong></td>
<td>Mean</td>
<td>Based on data from: 442 participants in 2 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious inconsistency and imprecision 17</td>
<td>Azithromycin may have little impact on duration of hospital stay.</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>Median</td>
<td>Lower better Based on data from: 7,764 participants in 1 studies. (Randomized controlled)</td>
<td>13 (Median)</td>
<td>12 (Median)</td>
<td>Moderate Due to serious imprecision 19</td>
<td>Azithromycin probably makes little difference to duration of hospital stay.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. The number of people who required supplemental oxygen who were not already receiving supplemental oxygen at baseline
5. **Imprecision: very serious.** Only data from one study, due to few events.
7. **Imprecision: serious.** Wide confidence intervals.
9. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.
11. **Imprecision: very serious.** due to few events.
13. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
6.2.3 Colchicine

**Not recommended**

Do not use colchicine for the treatment of COVID-19.

*This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.*

*Use of colchicine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include colchicine.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

**Evidence To Decision**

**Benefits and harms**

**General adult population**

Evidence indicates no difference between colchicine and standard care in incidence of death, requirement of mechanical ventilation or ECMO, or duration of hospital stay. Uncertainty remains regarding the incidence of adverse or serious adverse events.

**Certainty of the Evidence**

Certainty of the evidence is high for mortality, mechanical ventilation and discharge from hospital, and moderate for adverse and serious adverse events due to serious imprecision (wide confidence intervals).

Certainty is low for discontinuation due to adverse events, clinical progression, admission to ICU and discharge from hospital due to very serious imprecision (either reliance on a single study and wide confidence intervals, or few events).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel

Substantial variability is expected or uncertain
believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

As colchicine is not recommended there are no resource considerations.

**Equity**

As colchicine is not recommended there are no equity considerations.

**Acceptability**

As colchicine is not recommended there are no acceptability considerations.

**Feasibility**

As colchicine is not recommended there are no feasibility considerations.

**Rationale**

Based on the available evidence, colchicine is no more effective than standard care in treating patients with COVID-19. We therefore recommend that colchicine should not be used.

**Clinical Question/ PICO**

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

**Summary**

Evidence indicates that colchicine is no more effective than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

The majority of evidence comes from the RECOVERY trial, which included 11,340 patients hospitalised with moderate-to-critical COVID-19 [612]. An additional three randomised trials were included—two that compared colchicine with standard care in 140 adults hospitalised with COVID-19 [215][217] and one (COLCORONA trial) that compared colchicine with placebo in 4488 non-hospitalised adults with confirmed COVID-19 [483].

**Publication status**

One study is only available as a preprint and has therefore not been peer reviewed (Lopes et al. posted to medRxiv on 11 August 2020 [217]).

The final results of Lopes et al. [217] were published in RMD Open on 7 February 2021 (doi: 10.1136/rmdopen-2020-001455) and will be included in a future version of the guideline.
Version 44: Due to inconsistencies which have been identified in the data reported in the study by Salehdazeh et al. (preprint posted to Research Square on 21 Sep 2020) [219], this study has been removed from our analyses. The study contributed data to one outcome (duration of hospital stay) and the removal of these data did not change the strength or direction of the recommendation.

**Study characteristics**
In RECOVERY the mean age of participants was ~63 years and 30% were women. In COLCORONA mean age was ~55 years and 54% were women.

What are the main results?
Colchicine has no impact on death (0 fewer per 1000; RR 1.00, CI 95% 0.93 to 1.07; 15,968 patients in 4 studies), mechanical ventilation (1 more per 1000; RR 1.01, CI 95% 0.91 to 1.13; 15,404 patients in 3 studies) or discharge from hospital. We are uncertain whether colchicine increases or decreases the likelihood of experiencing a serious adverse event. However, colchicine probably increases adverse events (147 more per 1000; RR 1.93, CI 95% 1.18 to 3.16; 4517 patients in 2 studies).

For the outcomes of discontinuation due to adverse events, clinical progression (defined as an increase of 2 grades on a 7-grade scale) and ICU admission, there were too few events to determine whether colchicine makes a difference.

Our confidence in the results
Certainty of the evidence is high for mortality, mechanical ventilation and discharge from hospital, and moderate for adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for discontinuation due to adverse events, clinical progression, admission to ICU and discharge from hospital due to very serious imprecision (either reliance on a single study and wide confidence intervals, or few events).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known acute harms for colchicine include diarrhoea and stomach cramps. Colchicine overdose can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock [214]. There are several known and potential interactions with other drugs [214]. Paediatricians have limited experience with colchicine in children and adolescents for other indications. To date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population. Colchicine should be avoided in pregnancy and during breastfeeding, and in children under 2 years of age.

Caution should be taken when prescribing colchicine to older people living with frailty or cognitive impairment who may be more susceptible to cumulative toxicity.

Additional published studies
The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

<table>
<thead>
<tr>
<th>Trial and Source</th>
<th>Date</th>
<th>Number</th>
<th>Comparison &amp; Population</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mareev 2021 Cardiology</td>
<td>9 Jul</td>
<td>43</td>
<td>Colchicine vs standard care in hospitalised patients</td>
<td>Change in clinical outcomes (SHOCs-CC)</td>
</tr>
<tr>
<td>Pascual-Figal 2021 Int J Gen Med</td>
<td>11 Sep</td>
<td>103</td>
<td>Colchicine vs standard care in non-mechanically ventilated patients</td>
<td>Clinical status (SHOCs-CC)</td>
</tr>
<tr>
<td>PRINCIPLE trial 2021 medRxiv</td>
<td>23 Sep</td>
<td>1301</td>
<td>Colchicine vs standard care in adults in the community</td>
<td>Self-reported incidence of death</td>
</tr>
<tr>
<td>Absalón-Aguilar 2021 J Gen Intern Med</td>
<td>9 Nov</td>
<td>116</td>
<td>Colchicine vs placebo in severe patients</td>
<td>Progression to severe disease or death</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>--------------------------------</td>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Within 21–28 days of commencing treatment</td>
<td>Relative risk 1 (CI 95% 0.93 – 1.07) Based on data from 15,968 participants in 4 studies.</td>
<td>Standard care</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Within 21–28 days of commencing treatment</td>
<td>Relative risk 1.01 (CI 95% 0.91 – 1.13) Based on data from 15,404 participants in 3 studies.</td>
<td>Standard care</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.78 (CI 95% 0.61 – 1) Based on data from 4,517 participants in 2 studies.</td>
<td>Standard care</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.93 (CI 95% 1.18 – 3.16) Based on data from 4,517 participants in 2 studies.</td>
<td>Standard care</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>During treatment</td>
<td>Based on data from 140 participants in 2 studies.</td>
<td>Standard care</td>
<td>Colchicine</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Within 21 days of commencing treatment</td>
<td>Based on data from 35 participants in 1 studies.</td>
<td>Standard care</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Clinical progression</td>
<td></td>
<td>Relative risk 0.13 (CI 95% 0.02 – 1.02)</td>
<td>Standard care</td>
<td>Colchicine</td>
</tr>
</tbody>
</table>
### 6.2.4 Convalescent plasma

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Colchicine</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of 2 grades on 7-grade scale; 21 days after commencing treatment</td>
<td>Based on data from 105 participants in 1 studies. 11 (Randomized controlled)</td>
<td>per 1000</td>
<td>per 1000</td>
<td><strong>Difference:</strong> 122 fewer per 1000 (CI 95% 137 fewer — 3 more)</td>
<td><strong>seriously imprecise</strong> 12 clinical deterioration to determine whether colchicine makes a difference (8 events).</td>
</tr>
<tr>
<td>Discharge from hospital End of treatment</td>
<td>Relative risk 0.99 (CI 95% 0.97 — 1.01) Based on data from 11,375 participants in 2 studies. 13 (Randomized controlled)</td>
<td>704 per 1000</td>
<td>697 per 1000</td>
<td><strong>Difference:</strong> 7 fewer per 1000 (CI 95% 21 fewer — 7 more)</td>
<td><strong>High</strong> Colchicine has little or no impact on discharge from hospital.</td>
</tr>
</tbody>
</table>

4. **Imprecision:** serious. SAEs only occurred in one study.
6. **Imprecision:** serious. Wide confidence intervals.
8. **Imprecision:** very serious. Low number of patients, due to few events.
10. **Imprecision:** very serious. Low number of patients, Only data from one study, Wide confidence intervals.
12. **Imprecision:** very serious. Low number of patients, Only data from one study.
Not recommended


This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of convalescent plasma may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include convalescent plasma.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

General adult population
Evidence indicates no difference between convalescent plasma and standard care in incidence of death, requirement of mechanical ventilation or non-invasive ventilation, or discharge from hospital.

Although convalescent plasma may result in more adverse events and serious adverse events compared with standard care, it remains unclear if convalescent plasma is safe for the treatment of COVID-19.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There are additional concerns regarding harms as convalescent plasma has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. There is insufficient evidence pertaining to the safety of convalescent plasma for pregnant or breastfeeding women (for any indication) [111].

Certainty of the Evidence

General adult population
Certainty of the evidence is moderate due to serious imprecision for mortality (wide confidence intervals) and non-invasive ventilation (reliance on a single study). Certainty is high for invasive mechanical ventilation and number of patients discharged from hospital.

Certainty of the evidence for the majority of remaining outcomes is low due to serious risk of bias (often as a result of poor reporting of baseline neutralising antibodies in included patients) and serious imprecision (wide confidence intervals). The exceptions are respiratory failure or ARDS, clinical recovery and negative PCR, for which certainty is very low (due to the above factors and also reliance on a single study).

For some outcomes, certainty has been downgraded due to the high prevalence of baseline neutralising antibodies (NAb) in trial participants. One study excluded patients with a NAb titer of 1:640 or lower [112]. Three studies did not report specific NAb titers of included patients [117][121][123]. The remaining studies detected NAb in 76% [118], 49% [115], 80% [481] and 54% [120] of patients at baseline. The RECOVERY trial measured neutralising antibodies in 81% of included patients at baseline, in which 62% were found to be SARS-CoV-2 seropositive [124].

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.
General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

Resources and other considerations
As convalescent plasma is not recommended there are no resource considerations.

Equity
As convalescent plasma is not recommended there are no equity considerations.

Acceptability
As convalescent plasma is not recommended there are no acceptability considerations.

Feasibility
As convalescent plasma is not recommended there are no feasibility considerations.

Clinical Question/ PICO
Population: Patients with COVID-19
Intervention: Convalescent plasma
Comparator: Standard care

Summary
Evidence indicates that convalescent plasma is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from 15 randomised trials that compared convalescent plasma with standard care in over 16,000 patients with COVID-19. The vast majority of data are from the RECOVERY trial, which included 11,558 adults hospitalised with mild-to-severe COVID-19 [124], and REMAP-CAP, which included 2000 critically ill adults with COVID-19 [578].

Publication status
One study is only available as a preprint and has therefore not been peer reviewed [115].

Study characteristics
For a comprehensive description, see the study characteristics table.

What are the main results?
In the RECOVERY trial there was no significant difference in the primary endpoint of 28-day mortality in patients receiving convalescent plasma compared with usual care: 1399 (24%) of 5795 patients allocated to convalescent
plasma and 1408 (24%) of 5763 patients allocated to usual care died within 28 days (RR 1.00, 95% CI 0.93 to 1.07). The 28-day mortality risk ratio was similar in all prespecified subgroups of patients.

When combined with mortality data from the other included trials, results show that compared with standard care, convalescent plasma probably has little impact on death (5 fewer per 1000 patients; RR 0.98, CI 95% 0.93 to 1.04; 16,121 patients in 15 studies). In addition, convalescent plasma probably has little impact on the requirement of non-invasive ventilation and has no impact on the requirement of invasive mechanical ventilation or hospital discharge.

Convalescent plasma may increase the incidence of serious adverse events and adverse events, and also increase the rate of resolution of dyspnoea. We remain uncertain whether convalescent plasma has an impact on respiratory failure or ARDS, admission to ICU, clinical deterioration, clinical improvement, clinical recovery, negative PCR, time to improvement and time to discharge from hospital.

**Our confidence in the results**

Certainty of the evidence is high for invasive mechanical ventilation and number of patients discharged from hospital. Certainty is moderate due to serious imprecision for death (wide confidence intervals) and non-invasive ventilation (reliance on a single study).

Certainty for the majority of remaining outcomes is low due to serious risk of bias (often as a result of poor reporting of baseline neutralising antibodies in included patients) and serious imprecision (wide confidence intervals). The exceptions are respiratory failure or ARDS, clinical recovery and negative PCR, for which certainty is very low (due to the above factors and also reliance on a single study).

For some outcomes, certainty has been downgraded due to the high prevalence of baseline neutralising antibodies (NAb) in trial participants. One study excluded patients with a NAb titer of 1:640 or lower [112]. Eight studies did not report specific NAb titers of included patients [117][121][123][531][532][533][563][578]. Other studies detected NAb in 76% [118], 49% [115], 80% [481] and 54% [120] of patients at baseline. The RECOVERY trial measured neutralising antibodies in 81% of included patients at baseline, in which 62% were found to be SARS-CoV-2 seropositive [124].

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence of these populations in the included studies).

**Additional published studies**

The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

<table>
<thead>
<tr>
<th>Trial and Source</th>
<th>Date</th>
<th>Number</th>
<th>Comparison &amp; Population</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Respir Res</td>
<td></td>
<td></td>
<td>Convalescent plasma vs placebo in high-risk outpatients with COVID-19</td>
<td>Disease progression</td>
</tr>
<tr>
<td>Korley 2021 NEJM</td>
<td>18 Aug</td>
<td>511</td>
<td>Convalescent plasma vs standard care in adults hospitalised with COVID-19</td>
<td>Death or mechanical ventilation</td>
</tr>
<tr>
<td>Devos 2021 Eur</td>
<td>26 Aug</td>
<td>483</td>
<td>Convalescent plasma vs standard care in adults hospitalised with COVID-19</td>
<td>Disease progression</td>
</tr>
<tr>
<td>Respir J</td>
<td></td>
<td></td>
<td>Convalescent plasma vs placebo in adults hospitalised with COVID-19</td>
<td>Clinical severity score</td>
</tr>
<tr>
<td>Avendaño-Solá 2021</td>
<td>2 Sep</td>
<td>350</td>
<td>Convalescent plasma vs standard care in adults hospitalised with COVID-19</td>
<td>Death or mechanical ventilation</td>
</tr>
<tr>
<td>J Clin Invest</td>
<td></td>
<td></td>
<td>Convalescent plasma vs standard care in adults hospitalised with COVID-19</td>
<td>Clinical severity score</td>
</tr>
<tr>
<td>Bar 2021 J Clin</td>
<td>17 Nov</td>
<td>80</td>
<td>Convalescent plasma vs standard care in adults hospitalised with COVID-19</td>
<td>Death or mechanical ventilation</td>
</tr>
<tr>
<td>Invest</td>
<td></td>
<td></td>
<td>Convalescent plasma vs standard care in adults hospitalised with COVID-19</td>
<td>Clinical severity score</td>
</tr>
<tr>
<td>Menichetti 2021</td>
<td>29 Nov</td>
<td>487</td>
<td>Convalescent plasma vs standard care in adults hospitalised with COVID-19</td>
<td>Death or mechanical ventilation</td>
</tr>
<tr>
<td>JAMA Netw Open</td>
<td></td>
<td></td>
<td>Convalescent plasma vs standard care in adults hospitalised with COVID-19</td>
<td>Clinical severity score</td>
</tr>
<tr>
<td>Ortigoza 2021 JAMA13 Dec Intern Med</td>
<td></td>
<td>941</td>
<td>Convalescent plasma vs placebo in adults hospitalised with COVID-19</td>
<td>Death or mechanical ventilation</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>-------------------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>Standard care</td>
<td>Convalescent plasma</td>
<td>High</td>
<td>Convalescent plasma probably has little impact on death.</td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk 0.98 (CI 95% 0.93 — 1.04) Based on data from 16,121 participants in 15 studies.</td>
<td>256 per 1000</td>
<td>251 per 1000</td>
<td>5 fewer per 1000 (CI 95% 18 fewer — 10 more)</td>
<td></td>
</tr>
<tr>
<td><em>(Randomized controlled)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Invasive mechanical ventilation** |                  |                               | High                      | Convalescent plasma makes little or no difference to invasive mechanical ventilation. |
| Within 28 days of commencing treatment |                  |                               |                           |                        |
| 9 Critical                      |                  |                               |                           |                        |
| Relative risk 0.98 (CI 95% 0.89 — 1.08) Based on data from 11,898 participants in 4 studies. | 124 per 1000 | 122 per 1000 | 2 fewer per 1000 (CI 95% 14 fewer — 10 more) |
| *(Randomized controlled)*       |                  |                               |                           |                        |

| **Respiratory failure or ARDS** |                  |                               | Very low                  | We are uncertain whether convalescent plasma increases or decreases respiratory failure or ARDS. |
| Within 28 days of commencing treatment |                  |                               |                           |                        |
| 9 Critical                      |                  |                               |                           |                        |
| Relative risk 0.4 (CI 95% 0.08 — 2) Based on data from 160 participants in 1 studies. | 239 per 1000 | 232 per 1000 | 7 fewer per 1000 (CI 95% 26 fewer — 12 more) |
| *(Randomized controlled)*       |                  |                               |                           |                        |

| **Non-invasive ventilation**    |                  |                               | Moderate                   | Convalescent plasma probably has little or no impact on non-invasive ventilation. |
| Within 28 days of commencing treatment |                  |                               |                           |                        |
| 6 Important                     |                  |                               |                           |                        |
| Relative risk 0.97 (CI 95% 0.89 — 1.05) Based on data from 7,005 participants in 1 studies. | 395 per 1000 | 581 per 1000 | 186 more per 1000 (CI 95% 245 fewer — 1,872 more) |
| *(Randomized controlled)*       |                  |                               |                           |                        |

| **Serious adverse events**      |                  |                               | Moderate                   | Convalescent plasma probably has little impact on serious adverse events. |
| Within 28 days of commencing treatment |                  |                               |                           |                        |
| 6 Important                     |                  |                               |                           |                        |
| Relative risk 1.23 (CI 95% 0.95 — 1.6) Based on data from 3,420 participants in 5 studies. | 102 per 1000 | 125 per 1000 | 23 more per 1000 (CI 95% 5 fewer — 61 more) |
| *(Randomized controlled)*       |                  |                               |                           |                        |

<p>| <strong>Adverse events</strong>              |                  |                               | Low                       | Convalescent plasma may increase adverse events (222 events). |
| Within 28 days of commencing treatment |                  |                               |                           |                        |
| 6 Important                     |                  |                               |                           |                        |
| Relative risk 1.47 (CI 95% 0.38 — 5.74) Based on data from 457 participants in 3 studies. | 395 per 1000 | 581 per 1000 | 186 more per 1000 (CI 95% 245 fewer — 1,872 more) |
| <em>(Randomized controlled)</em>       |                  |                               |                           |                        |</p>
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.97 (CI 95% 0.86 — 1.1) Based on data from 595 participants in 3 studies. 11 (Randomized controlled)</td>
<td>Standard care</td>
<td>668 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision 12</td>
<td>Convalescent plasma may make little or no difference to clinical improvement at day 28 (388 events).</td>
</tr>
<tr>
<td><strong>ICU admission</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.75 (CI 95% 0.36 — 1.59) Based on data from 493 participants in 2 studies. 13 (Randomized controlled)</td>
<td>Standard care</td>
<td>373 per 1000</td>
<td>Low Due to serious risk of bias and imprecision 14</td>
<td>Convalescent plasma may decrease ICU admission slightly (194 events).</td>
</tr>
<tr>
<td><strong>Clinical deterioration</strong></td>
<td>(progression to severe/critical)</td>
<td>Relative risk 0.71 (CI 95% 0.18 — 2.78) Based on data from 545 participants in 2 studies. 16 (Randomized controlled)</td>
<td>Standard care</td>
<td>74 per 1000</td>
<td>Low Due to serious risk of bias and imprecision 17</td>
<td>Convalescent plasma may have little impact on clinical deterioration (progression to severe/critical) at day 28 (37 events).</td>
</tr>
<tr>
<td><strong>Clinical recovery</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.9 (CI 95% 0.76 — 1.06) Based on data from 333 participants in 1 studies. 18 (Randomized controlled)</td>
<td>Standard care</td>
<td>371 per 1000</td>
<td>Very low Due to serious risk of bias and very serious imprecision 19</td>
<td>We are uncertain whether convalescent plasma worsens clinical recovery (223 events).</td>
</tr>
<tr>
<td><strong>Resolution of dyspnoea</strong></td>
<td>End of treatment</td>
<td>Relative risk 1.21 (CI 95% 0.87 — 1.68) Based on data from 797 participants in 2 studies. 20 (Randomized controlled)</td>
<td>Standard care</td>
<td>449 per 1000</td>
<td>Low Due to serious risk of bias and imprecision 21</td>
<td>Convalescent plasma may increase resolution of dyspnoea slightly (285 events).</td>
</tr>
<tr>
<td><strong>Viral nucleic acid negative</strong></td>
<td>72 hours after commencing treatment</td>
<td>Relative risk 2.33 (CI 95% 1.54 — 3.52) Based on data from 87 participants in 1 studies. 22 (Randomized controlled)</td>
<td>Standard care</td>
<td>331 of 734</td>
<td>Very low Due to serious risk of bias and very serious imprecision 23</td>
<td>Convalescent plasma may increase number of patients who are viral nucleic acid negative at 72 hours.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
</tr>
<tr>
<td>---------</td>
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<td>-----------------------------------------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative risk 1</td>
<td>Standard care</td>
<td>Convalescent plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>(CI 95% 0.97 – 1.02)</td>
<td>Baseline/comparator</td>
<td>666 per 1000</td>
<td>High</td>
<td>Convalescent plasma has little or no impact on hospital discharge.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Based on data from 12,233 participants in 5 studies.</td>
<td>Rasheed 2020 (n=49) and Simonovich 2020 (n=333) both reported time to improvement, defined as a reduction of two or more points on an 8-point ordinal scale. Results in Rasheed favoured convalescent plasma (mean 4.5 days vs 8.5 days). Results in Simonovich showed no difference (12 days for both groups).</td>
<td>666 per 1000</td>
<td>Low</td>
<td>We are uncertain whether convalescent plasma increases or decreases time to improvement.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td>Based on data from studies. (Randomized controlled)</td>
<td>Based on data from: 382 participants in 2 studies. (Randomized controlled)</td>
<td>Low</td>
<td>Convalescent plasma probably has little impact on time to discharge from hospital.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agarwal 2020 (n=464) and Simonovich 2020 (n=333) both reported time to discharge from hospital. Both studies demonstrated slightly lower time to discharge in the control vs convalescent plasma group (median 13 days vs 14 days, and median 12 days vs 13 days, respectively).</td>
<td>Due to serious risk of bias and imprecision 26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to discharge from hospital</td>
<td>Days</td>
<td>Days</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. **Risk of Bias:** serious. Due to either high or unknown levels of neutralising antibodies at baseline in the majority of studies for both treatment and control groups. **Imprecision:** very serious. Due to few events, Low number of patients, Wide confidence intervals.
6. **Imprecision:** serious. Only data from one study.
8. **Imprecision:** serious. Wide confidence intervals.
10. **Risk of Bias:** serious. Due to either high or unknown levels of neutralising antibodies at baseline in the majority of studies for both treatment and control groups. **Imprecision:** serious. Wide confidence intervals.
6.2.5 Hydroxychloroquine

Not recommended

Do not use hydroxychloroquine for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of hydroxychloroquine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include hydroxychloroquine.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
Evidence To Decision

Benefits and harms
In addition to uncertainty around benefits for patients with COVID-19, there are well-known harms with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

Certainty of the Evidence

General adult population
Certainty of the evidence is high for death, number of patients requiring mechanical ventilation and number of patients discharged from hospital at day 28. Certainty is moderate for number of patients requiring ventilation (due to reliance on a single study), adverse events and serious adverse events (due to lack of blinding of patients and personnel). Certainty is low for hospitalisation (due to lack of blinding and low number of events) and for virological clearance and duration of hospital stay (due to low number of patients and reliance on a single/two small studies).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
Certainty of the evidence is low for death, requirement for mechanical ventilation/ECMO, discharge from hospital and adverse events (due to serious imprecision or risk of bias and indirectness). Certainty is very low for serious adverse events, virological clearance and hospitalisation (due to serious inconsistency, indirectness and imprecision).

Preference and values
The Consumer Panel believes that as there is substantial evidence demonstrating well-known harms of hydroxychloroquine, informed patients would not choose this treatment.

Resources and other considerations
As hydroxychloroquine is not recommended there are no resource considerations.

Equity
As hydroxychloroquine is not recommended there are no equity considerations.

Acceptability
As hydroxychloroquine is not recommended there are no acceptability considerations.

Feasibility
As hydroxychloroquine is not recommended there are no feasibility considerations.

Rationale
Based on the available evidence, hydroxychloroquine is potentially harmful and no more effective than standard care in treating patients with COVID-19. We therefore recommend that hydroxychloroquine should not be used.
Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary
Evidence indicates that hydroxychloroquine is potentially harmful and no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from 22 randomised trials that compared hydroxychloroquine with standard care in over 10,600 patients (see table for references). The majority of evidence comes from the RECOVERY and SOLIDARITY trials, which randomised 4716 and 1853 patients hospitalised with COVID-19, respectively [148][50].

Publication status
Four studies, which contribute fewer than 200 patients to the results, are only available as preprints and have therefore not been peer reviewed [129][135][277][477].

See table at the end of this summary for details of additional studies of hydroxychloroquine not yet included in the guideline.

Removal of studies
Version 44: Due to inconsistencies which have been identified in the data reported in the study by Abd-Elsalam et al. (Am J Med Hyg, 14 Aug 2020) [144], this study has been removed from our analyses. The study contributed data to two outcomes (mortality and invasive mechanical ventilation) and the removal of these data did not change the strength or direction of the recommendation.

Study characteristics
Mean or median age across the trials ranged from 37 to 66 years, with the exception of one study in which the median age was 77 years [154]. The proportion of women ranged from 20 to 72% with the exception of one study in which only 1.5% of participants were female [159]. In the two largest trials women comprised approximately 40% of included patients. There was significant variability in disease severity among patients included in the trials (see table).

Disease severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Number of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>1405</td>
<td>[136][137][158][184][477]</td>
</tr>
<tr>
<td>Mild-Moderate</td>
<td>916</td>
<td>[142][153][154][159]</td>
</tr>
<tr>
<td>Moderate</td>
<td>192</td>
<td>[128][129][135][277]</td>
</tr>
<tr>
<td>Mild-Moderate-Severe</td>
<td>2676</td>
<td>[145][147][152][159]</td>
</tr>
<tr>
<td>Moderate-Severe</td>
<td>4881</td>
<td>[145][147][148]</td>
</tr>
<tr>
<td>Severe</td>
<td>612</td>
<td>[478][480][575]</td>
</tr>
</tbody>
</table>

What are the main results?
Hydroxychloroquine has little or no impact on the two critical outcomes of death and the need for mechanical ventilation. For every 1000 patients given hydroxychloroquine, 10 more are likely to die compared with those receiving standard care (RR 1.06, CI 95% 0.97 to 1.16; 10,382 patients in 19 studies) and seven more are likely to require mechanical ventilation (RR 1.08, CI 95% 0.91 to 1.28; 5701 patients in 8 studies). Hydroxychloroquine also has little or no impact on the number of patients requiring any form of ventilation (i.e. non-invasive ventilation, invasive mechanical ventilation and ECMO) or the number of patients discharged from hospital at day 28.

Hydroxychloroquine probably increases the risk of adverse events (216 more per 1000 patients (RR 1.67, CI 95% 1.21 to 2.30; 2077 patients in 11 studies)) but probably has little impact on serious adverse events (6 more per 1000 patients (RR 1.09, CI 95% 0.86 to 1.37; 2721 patients in 11 studies)).

For all other outcomes—virological clearance, hospitalisation and discharge from hospital—we are uncertain if
hydroxychloroquine makes a difference compared with standard care.

Our confidence in the results
Certainty of the evidence is high for death, number of patients requiring mechanical ventilation and number of patients discharged from hospital at day 28. Certainty is moderate for number of patients requiring any form of ventilation (due to reliance on a single study), adverse or serious adverse events (due to lack of blinding of patients and personnel). Certainty is low for hospitalisation (due to lack of blinding and low number of events) and for virological clearance and duration of hospital stay (due to low number of patients and reliance on a single/two small studies).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiomyopathy [133]. There are several known and potential interactions with other drugs [133]. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms [133].

Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications. To date, no specific information on the benefits or harms of hydroxychloroquine use has been collected in this population.

Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, with no increase in fetal malformations [138][139]. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine [138][139][140]. While this evidence is reassuring, further research is needed.

Additional published studies
The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

<table>
<thead>
<tr>
<th>Trial and Source</th>
<th>Date</th>
<th>Number</th>
<th>Comparison &amp; Population</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz 2021 CMAJ Open</td>
<td>18 Jun</td>
<td>148</td>
<td>HCQ vs placebo in community-dwelling individuals with confirmed COVID-19</td>
<td>Composite outcome of hospitalisation, IMV or death at 28 days</td>
</tr>
<tr>
<td>REMAP-CAP 2021 Intensive Care Med</td>
<td>12 Jul</td>
<td>412</td>
<td>HCQ vs standard care in critically ill patients</td>
<td>Organ support-free days</td>
</tr>
<tr>
<td>Gupta 2021 Med J Armed Forces India</td>
<td>26 Jul</td>
<td>110</td>
<td>HCQ vs standard care in moderate to severely ill patients</td>
<td>Days of hospitalisation until discharge or death</td>
</tr>
<tr>
<td>Byakika-Kibwika 2021 BMC Infect Dis</td>
<td>6 Dec</td>
<td>105</td>
<td>HCQ vs standard care in adults with non-severe COVID-19</td>
<td>Viral clearance; symptom resolution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Hydroxychloroquine</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 1.06 (CI 95% 0.97 — 1.16) Based on data from 10,188 participants in 18 studies. (^1) (Randomized controlled)</td>
<td></td>
<td>169 per 1000</td>
<td>High</td>
<td>Hydroxychloroquine does not decrease death.</td>
</tr>
<tr>
<td>End of follow-up 9 Critical</td>
<td></td>
<td></td>
<td>179 per 1000</td>
<td>10 more per 1000 ( CI 95% 5 fewer — 27 more )</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Hydroxychloroquine</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td><strong>Invasive mechanical ventilation or ECMO</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.09 (CI 95% 0.9 – 1.32) Based on data from 5,507 participants in 7 studies.</td>
<td>86 per 1000</td>
<td>94 per 1000</td>
<td><strong>High</strong></td>
</tr>
<tr>
<td><strong>Patients requiring ventilation</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.09 (CI 95% 0.79 – 1.49) Based on data from 1,686 participants in 1 studies.</td>
<td>80 per 1000</td>
<td>87 per 1000</td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.09 (CI 95% 0.86 – 1.37) Based on data from 2,721 participants in 11 studies.</td>
<td>68 per 1000</td>
<td>74 per 1000</td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.67 (CI 95% 1.21 – 2.3) Based on data from 2,077 participants in 11 studies.</td>
<td>322 per 1000</td>
<td>538 per 1000</td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td><strong>Discharge from hospital</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.96 – 1.01) Based on data from 7,365 participants in 5 studies.</td>
<td>694 per 1000</td>
<td>680 per 1000</td>
<td><strong>High</strong></td>
</tr>
<tr>
<td><strong>Discontinuation due to adverse events</strong></td>
<td>During treatment</td>
<td>Relative risk 2.13 (CI 95% 0.65 – 6.95) Based on data from 398 participants in 2 studies.</td>
<td>20 per 1000</td>
<td>43 per 1000</td>
<td><strong>Low</strong></td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td></td>
<td>Relative risk 1.05 (CI 95% 0.91 – 1.2)</td>
<td>756 per 1000</td>
<td>794 per 1000</td>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Hydroxychloroquine</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Within 28 days after commencing treatment</td>
<td>Based on data from 247 participants in 1 studies.</td>
<td>per 1000</td>
<td>per 1000</td>
<td>serious imprecision 11</td>
<td>hydroxychloroquine improves or worsens clinical improvement (191 events).</td>
</tr>
<tr>
<td>Clinical deterioration</td>
<td>Relative risk 0.81 (CI 95% 0.35 — 1.89)</td>
<td>89 per 1000</td>
<td>72 per 1000</td>
<td>Low</td>
<td>We are uncertain whether hydroxychloroquine improves or worsens clinical deterioration (20 events).</td>
</tr>
<tr>
<td>Virological clearance (negative PCR)</td>
<td>Relative risk 1.02 (CI 95% 0.93 — 1.11)</td>
<td>410 per 1000</td>
<td>418 per 1000</td>
<td>Low</td>
<td>Hydroxychloroquine may have little impact on virological clearance (negative PCR).</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>Relative risk 0.68 (CI 95% 0.41 — 1.13)</td>
<td>55 per 1000</td>
<td>37 per 1000</td>
<td>Low</td>
<td>We are uncertain whether hydroxychloroquine decreases or increases hospitalisation (62 events).</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>Based on data from: 128 participants in 1 studies.</td>
<td>6.8 (Mean)</td>
<td>9.75 (Mean)</td>
<td>Low</td>
<td>We are uncertain whether hydroxychloroquine increases or decreases duration of hospital stay.</td>
</tr>
</tbody>
</table>

3. Includes non-invasive ventilation, invasive ventilation, mechanical ventilation, ECMO
5. Imprecision: **serious**. Only data from one study.
6.2.6 Hydroxychloroquine plus azithromycin

Do not use hydroxychloroquine plus azithromycin for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Although certainty of the evidence is low, this recommendation is supported by the observation that neither hydroxychloroquine nor azithromycin as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

There are concerns regarding the safety of hydroxychloroquine plus azithromycin. Hydroxychloroquine has several known and potential interactions with other drugs. See the Summary for details of the adverse events of hydroxychloroquine and azithromycin when administered individually.

Certainty of the Evidence

General adult population

Certainty of the evidence is low for the critical outcomes of mortality at day 15 and the need for invasive mechanical
Rationale

General adult population
There is currently limited evidence about the effect of hydroxychloroquine plus azithromycin on patient-relevant outcomes in the treatment of COVID-19. However, when used individually, neither of these treatments has demonstrated improvements in clinical outcomes. We therefore recommend that hydroxychloroquine plus azithromycin should not be used to treat COVID-19.

<table>
<thead>
<tr>
<th>Preference and values</th>
<th>Substantial variability is expected or uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>General adult population</td>
<td>We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.</td>
</tr>
<tr>
<td>Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment</td>
<td>In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resources and other considerations</th>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>As hydroxychloroquine plus azithromycin is not recommended there are no resource considerations.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equity</th>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>As hydroxychloroquine plus azithromycin is not recommended there are no equity considerations.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acceptability</th>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>As hydroxychloroquine plus azithromycin is not recommended there are no acceptability considerations.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>As hydroxychloroquine plus azithromycin is not recommended there are no feasibility considerations.</td>
<td></td>
</tr>
</tbody>
</table>

Ventilation due to very serious imprecision (wide confidence intervals and reliance on a single study), and very low for mortality at the end of treatment due to serious risk of bias and very serious imprecision (wide confidence intervals and no events).

Certainty of the evidence is low for the important outcomes of adverse events, hospitalisation and virological clearance (negative PCR) due to serious risk of bias (lack of patient and personnel blinding) and serious imprecision (wide confidence intervals, few events or reliance on a single study). Certainty is very low for all remaining outcomes (serious adverse events, discharge from hospital and duration of hospital stay).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low for all outcomes because of indirectness due to limited inclusion (or absence) of these populations in the trials.
**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** Hydroxychloroquine plus azithromycin
- **Comparator:** Standard care

**Summary**

There remains significant uncertainty whether hydroxychloroquine plus azithromycin is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from three randomised trials that compared hydroxychloroquine plus azithromycin with standard care. One trial included 444 adults hospitalised with moderate illness (345 with laboratory-confirmed COVID-19) [142] and two included 464 adult outpatients with mild COVID-19 [158][159].

**Study characteristics**

Mean age of participants ranged from 37 to 50 years across the three studies. There were significant differences in the proportion of women enrolled: 43% in Cavalcanti et al., 57% in Johnston et al. and only 1% in Omrani et al. Pregnant women were ineligible in all studies.

**What are the main results?**

For death and serious adverse events, there were too few events (eight deaths and seven who experienced serious adverse events) to determine whether hydroxychloroquine plus azithromycin makes a difference. We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases the likelihood of invasive mechanical ventilation, discharge from hospital and incidence of hospitalisation, but it may increase slightly the duration of hospital stay and virological clearance (negative PCR), and result in more adverse events.

**Our confidence in the results**

Certainty of the evidence is low or very low for all outcomes. This judgement is based on serious or very serious imprecision (wide confidence intervals, reliance on a single study and/or few observed events) and/or serious risk of bias (lack of blinding).

**Additional information**

According to the Therapeutic Goods Administration, known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiomyopathy. There are several known and potential interactions with other drugs. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms [133].

For azithromycin, reported adverse events are generally mild or moderate and include rash, heart palpitations, urinary tract infection, dizziness, headache, fatigue and gastrointestinal symptoms such as dyspepsia and vomiting [103].

In addition to the known harms associated with hydroxychloroquine and azithromycin, there are concerns regarding the safety of combination treatment using these two therapeutics.

Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications. To date, no specific information on the benefits or harms of hydroxychloroquine use has been collected in this population. The safety and effectiveness of azithromycin powder for solution for infusion for the treatment of infections in children has not been established. Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in neonates (treatment up to 42 days of life) [103].

Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, with no increase in fetal malformations [138][139]. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine [138][139][140]. While this evidence is reassuring, further research is needed. Azithromycin is classified as a Category B1 drug (drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed).

**Additional published studies**

The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current
recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

<table>
<thead>
<tr>
<th>Trial and Source</th>
<th>Date</th>
<th>Number</th>
<th>Comparison &amp; Population</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivapalan 2021 Eur Respir J</td>
<td>3 Jun</td>
<td>117</td>
<td>Azithromycin plus hydroxychloroquine vs placebo in hospitalised adults</td>
<td>Alive hospital</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>Within 15 days of commencing treatment</td>
<td>Relative risk 0.6 (CI 95% 0.15 — 2.49) Based on data from 345 participants in 1 studies. 1 (Randomized controlled)</td>
<td>Standard care</td>
<td>HCQ+AZM</td>
<td>Low</td>
<td>There were too few who died to determine whether hydroxychloroquine plus azithromycin makes a difference (8 events).</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>End of follow-up</td>
<td>Based on data from 459 participants in 2 studies. 3 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases all-cause mortality (0 events).</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive mechanical ventilation</strong></td>
<td>Within 15 days of commencing treatment</td>
<td>Relative risk 1.59 (CI 95% 0.8 — 3.18) Based on data from 345 participants in 1 studies. 5 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low</td>
<td>We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases the need for invasive mechanical ventilation (31 events).</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 2.38 (CI 95% 1.05 — 5.37) Based on data from 576 participants in 2 studies. 7 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low</td>
<td>Hydroxychloroquine plus azithromycin may increase adverse events (158 events).</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.85 (CI 95% 0.36 — 9.43) Based on data from 715 participants in 2 studies. 9 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low</td>
<td>There were too few who experienced a serious adverse event to determine whether hydroxychloroquine plus azithromycin makes a difference (7 events).</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention HCQ+AZM</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
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<td>--------------------------</td>
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<td>-----------------------------------------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital Within 15 days of commencing treatment</td>
<td>Relative risk 0.96 (CI 95% 0.86 — 1.08) Based on data from 345 participants in 1 studies.</td>
<td>13 per 1000</td>
<td>10 per 1000</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>Hydroxychloroquine plus azithromycin may have little impact on discharge from hospital (266 events).</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation End of follow-up</td>
<td>Relative risk 0.77 (CI 95% 0.09 — 6.83) Based on data from 459 participants in 2 studies.</td>
<td>315 per 1000</td>
<td>202 per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>Hydroxychloroquine plus azithromycin may have little or no difference on hospitalisation (5 events)</td>
<td></td>
</tr>
<tr>
<td>Virological clearance (negative PCR) End of follow-up</td>
<td>Relative risk 0.64 (CI 95% 0.43 — 0.96) Based on data from 292 participants in 1 studies.</td>
<td>9.5 (Mean)</td>
<td>10.3 (Mean)</td>
<td>Low Due to very serious imprecision</td>
<td>Hydroxychloroquine plus azithromycin may decrease virological clearance slightly (75 events)</td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay Days</td>
<td>Based on data from: 345 participants in 1 studies.</td>
<td>9.5 (Mean)</td>
<td>10.3 (Mean)</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain if hydroxychloroquine plus azithromycin increases duration of hospital stay.</td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision:** very serious. due to few events, Only data from one study.
4. **Risk of Bias:** serious. due to missing outcome data. **Imprecision:** very serious. Only data from one study, Low number of patients, due to no events.
6. **Imprecision:** very serious. due to few events, Only data from one study.
8. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Wide confidence intervals.
10. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
6.2.7 Interferon β-1a

**Imprecision: very serious.** due to few events.


12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.


14. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, due to few events.


16. **Imprecision: very serious.** Wide confidence intervals, Low number of patients. Only data from one study.


18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.

**Not recommended**

Do not use subcutaneous or intravenous interferon β-1a for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of subcutaneous or intravenous interferon β-1a may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include interferon β-1a.

Information regarding the use of inhaled interferon β-1a for the treatment of COVID-19 can be found [here](#).

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

### Evidence To Decision

**Benefits and harms**

**General adult population**

Subcutaneous and intravenous interferon β-1a does not impact on the incidence of death or number of patients requiring ventilation. Although included trials did not report on adverse or serious adverse events, there are well-known side effects and harms associated with interferon β-1a including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

**Children and adolescents, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as interferon β-1a has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Pregnant and breastfeeding women**

Evidence suggests that interferon β-1a in pregnant women is not associated with an increase in early pregnancy loss,
stillbirths or congenital anomalies.

Certainty of the Evidence

General adult population
Certainty of the evidence is high for mortality, patients requiring ventilation and discharge from hospital. For the remaining outcomes (septic shock and duration of hospital stay), certainty is very low due to non-blinding of patients and personnel, reliance on a single study, low patient and event numbers and wide confidence intervals.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

Resources and other considerations

As interferon β-1a is not recommended there are no resource considerations.

Equity

As interferon β-1a is not recommended there are no equity considerations.

Acceptability

As interferon β-1a is not recommended there are no acceptability considerations.

Feasibility

As interferon β-1a is not recommended there are no feasibility considerations.

Rationale

Based on the available evidence, interferon β-1a administered subcutaneously or intravenously is no more effective than standard care in treating patients with COVID-19. We therefore recommend that Interferon β-1a should not be used.

Clinical Question/ PICO

Population: Patients with COVID-19
Evidence indicates that interferon β-1a given subcutaneously or intravenously is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials that compared subcutaneous or intravenous interferon β-1a with standard care. The vast majority of data come from the WHO SOLIDARITY trial, which included 4100 adults hospitalised with moderate to critical COVID-19 [50]. The second, smaller trial randomised 81 adults hospitalised with severe COVID-19 [163].

Study characteristics
In the SOLIDARITY trial, 35% of patients were under 50 years of age, 46% were aged 50–69 years, and 19% were 70 years or older; 37% were women. In the smaller study, mean age was 56–60 years across the two arms and 46% were women. In both studies pregnant women were ineligible.

In the SOLIDARITY trial, patients received three doses of interferon β-1a (44 µg subcutaneously) over six days, while patients on high-flow oxygen, ventilators or ECMO were given 10 µg intravenously once daily for six days.

What are the main results?
There were no differences in incidence of death, requirement of ventilation and discharge from hospital between interferon β-1a and standard care at day 28. We are uncertain whether treatment with interferon β-1a has an impact on the number of people experiencing septic shock and duration of hospital stay.

Our confidence in the results
Certainty of the evidence is high for mortality, patients requiring ventilation and discharge from hospital. For incidence of septic shock and duration of hospital stay, certainty is very low due to non-blinding of patients and personnel, reliance on a single study, low patient and event numbers and wide confidence intervals.

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration highlights several potential side effects associated with the use of interferon β-1a, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation. Interferon β-1a is also associated with immune reactions that can produce flu-like symptoms [160][161].

Paediatricians have limited experience with interferon β-1a in children and adolescents for other indications. To date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population.

Interferon β-1a is used in pregnancy for the treatment of multiple sclerosis. Evidence has shown no correlation between the use of Interferon β-1a and increases in early pregnancy loss, stillbirths or congenital anomalies [162].

Additional published studies
The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

<table>
<thead>
<tr>
<th>Trial and Source</th>
<th>Date</th>
<th>Number</th>
<th>Comparison &amp; Population</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darazam 2021 Sci Rep</td>
<td>13 Apr</td>
<td>40</td>
<td>Interferon β-1a vs standard care in hospitalised adults</td>
<td>Time to clinical impr</td>
</tr>
<tr>
<td>REMAP-CAP 2021 medRxiv</td>
<td>25 Jun</td>
<td>19 IFN 406 SC</td>
<td>Interferon β-1a vs standard care in adults with severe infection</td>
<td>Mortality support</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
</tr>
<tr>
<td>---------</td>
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<td>--------------------------------</td>
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<td>--------------</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong>&lt;br&gt;Within 28 days of commencing treatment</td>
<td>Relative risk 1.07 (CI 95% 0.91 – 1.27) Based on data from 4,181 participants in 2 studies. 1 (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1a</td>
<td>112 per 1000</td>
</tr>
<tr>
<td><strong>Patients requiring ventilation</strong>&lt;br&gt;Within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.83 – 1.17) Based on data from 3,912 participants in 2 studies. 2 (Randomized controlled)</td>
<td>Control arm of reference used for intervention</td>
<td>Interferon β-1a</td>
<td>116 per 1000</td>
</tr>
<tr>
<td><strong>Septic shock</strong>&lt;br&gt;Within 28 days of commencing treatment</td>
<td>Relative risk 1.67 (CI 95% 0.7 – 3.99) Based on data from 91 participants in 1 studies. 3 (Randomized controlled)</td>
<td>Control arm of reference used for intervention</td>
<td>Interferon β-1a</td>
<td>778 per 1000</td>
</tr>
<tr>
<td><strong>Discharge from hospital</strong>&lt;br&gt;Within 28 days of commencing treatment</td>
<td>Relative risk 0.95 (CI 95% 0.92 – 0.99) Based on data from 4,181 participants in 2 studies. 5 (Randomized controlled)</td>
<td>Control arm of reference used for intervention</td>
<td>Interferon β-1a</td>
<td>12.3 (Mean)</td>
</tr>
<tr>
<td><strong>Duration of hospital stay</strong>&lt;br&gt;Mean days to discharge</td>
<td>Based on data from: 81 participants in 1 studies. 6 (Randomized controlled)</td>
<td>Control arm of reference used for intervention</td>
<td>Interferon β-1a</td>
<td>12.3 (Mean)</td>
</tr>
</tbody>
</table>

4. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** very serious. Low number of patients, Only data from one study.
6.2.8 Interferon β-1a plus lopinavir-ritonavir

Control arm of reference used for intervention.
7. **Risk of Bias**: serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision**: very serious. Low number of patients, Only data from one study.

---

**Not recommended**


This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Although certainty of the evidence is low, this recommendation is supported by the observation that neither intravenous interferon β-1a nor lopinavir-ritonavir as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

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**Evidence To Decision**

**Benefits and harms**

We are unclear whether interferon β-1a plus lopinavir-ritonavir increases or decreases incidence of death, adverse events or serious adverse events.

Subcutaneous and intravenous interferon β-1a does not impact on the incidence of death or number of patients requiring ventilation. Although included trials did not report on adverse or serious adverse events, there are well-known side effects and harms associated with interferon β-1a including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

With regards to lopinavir-ritonavir, evidence indicates no difference in incidence of death, requirement of mechanical ventilation or duration of hospital stay between lopinavir-ritonavir and standard care. Uncertainty remains regarding the incidence of serious adverse events and adverse events, however there are well-known side effects and harms associated with lopinavir-ritonavir, including gastrointestinal symptoms, hyperglycaemia, pancreatitis, QT and PR interval prolongation and hepatic impairment.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence is low for mortality due to very serious imprecision (wide confidence intervals and reliance on a single study), and very low for adverse and serious adverse events due to serious risk of bias (patients, personnel and outcome assessors unblinded) and very serious imprecision (wide confidence intervals and reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low for all
Rationale

General adult population
There is currently limited evidence about the effect of interferon β-1a plus lopinavir-ritonavir on patient-relevant outcomes in the treatment of COVID-19. However, when used individually, neither of these treatments has demonstrated improvements in clinical outcomes when administered to patients with COVID-19. We therefore recommend that interferon β-1a plus lopinavir-ritonavir should not be used to treat COVID-19.

Preference and values

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

Resources and other considerations

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no resource considerations.

Equity

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no equity considerations.

Acceptability

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no acceptability considerations.

Feasibility

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no feasibility considerations.

Rationale

General adult population
There is currently limited evidence about the effect of interferon β-1a plus lopinavir-ritonavir on patient-relevant outcomes in the treatment of COVID-19. However, when used individually, neither of these treatments has demonstrated improvements in clinical outcomes when administered to patients with COVID-19. We therefore recommend that interferon β-1a plus lopinavir-ritonavir should not be used to treat COVID-19.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Interferon β-1a plus lopinavir-ritonavir
Comparator: Standard care

Summary

There remains significant uncertainty whether inhaled interferon β-1a plus lopinavir-ritonavir is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared inhaled interferon β-1a plus lopinavir-ritonavir with placebo in 293 adults hospitalised with moderate or severe COVID-19 [480].

**Study characteristics**
Median age of participants was ~63 years and 29% were women. Patients in the intervention group received 44 µg of subcutaneous IFN-ß1a on days 1, 3 and 6, and 400 mg lopinavir and 100 mg ritonavir every 12 hours for 14 days. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
We are uncertain whether inhaled interferon β-1a plus lopinavir-ritonavir increases or decreases mortality at day 28. Patients treated with interferon β-1a plus lopinavir-ritonavir had more adverse and serious adverse events.

**Our confidence in the results**
Certainty of the evidence is low for mortality at day 28 due to very serious imprecision (low patient numbers and reliance on a single study). Certainty is very low for adverse and serious adverse events due to very serious imprecision (reliance on a single study, wide confidence intervals and few patients) and serious risk of bias (lack of blinding of participants and assessors).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included study).

**Additional information**
The Therapeutic Goods Administration highlights several potential side effects associated with the use of interferon β-1a, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation. Interferon β-1a is also associated with immune reactions that can produce flu-like symptoms.

According to the Therapeutic Goods Administration, there are well-known side effects and harms associated with lopinavir-ritonavir. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation and PR interval prolongation. Chronic harms include increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir-ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs.

Paediatricians have limited experience with interferon β-1a in children and adolescents for other indications. To date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population. Paediatricians have considerable experience with lopinavir-ritonavir in children and adolescents for other indications. To date, no specific information on its benefits or harms for children and adolescents has been collected for treating COVID-19 in this population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong>&lt;br&gt;Within 28 days of commencing treatment</td>
<td>Relative risk 1.19&lt;br&gt;(CI 95% 0.57 – 2.49)&lt;br&gt;Based on data from 293 participants in 1 studies.&lt;br&gt;1 (Randomized controlled)</td>
<td><strong>81</strong>&lt;br&gt;per 1000</td>
<td><strong>96</strong>&lt;br&gt;per 1000</td>
<td>Low&lt;br&gt;Due to very serious imprecision 2</td>
<td>We are uncertain whether interferon β-1a plus lopinavir-ritonavir increases or decreases all-cause mortality (26 events)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong>&lt;br&gt;End of follow-up</td>
<td>Relative risk 1.41&lt;br&gt;(CI 95% 1.09 – 1.81)&lt;br&gt;Based on data from 292 participants in 1 studies.&lt;br&gt;3 (Randomized controlled)</td>
<td><strong>385</strong>&lt;br&gt;per 1000</td>
<td><strong>543</strong>&lt;br&gt;per 1000</td>
<td>Very low&lt;br&gt;Due to serious risk of bias and very serious imprecision 4</td>
<td>We are uncertain whether interferon β-1a plus lopinavir-ritonavir increases serious adverse events (135 events)</td>
</tr>
</tbody>
</table>
### 6.2.9 Lopinavir-ritonavir

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Interferon β-1a plus lopinavir-ritonavir</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
</table>
| Adverse events    | Relative risk 1.15 (CI 95% 1.01 – 1.3) Based on data from 292 participants in 1 studies. 
  5 (Randomized controlled) | 709 per 1000 | 815 per 1000 | Very low
  Due to serious risk of bias and very serious imprecision 6 | We are uncertain whether interferon β-1a plus lopinavir-ritonavir increases adverse events (222 events). |
| End of follow-up | Important | Difference: 106 more per 1000 (CI 95% 7 more – 213 more) |


2. **Risk of Bias:** no serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.


4. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.


6. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** very serious. Low number of patients, Only data from one study, Wide confidence intervals. **Publication bias:** no serious.

---

**6.2.9 Lopinavir-ritonavir**

**Not recommended**


*This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.*

*Use of lopinavir-ritonavir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include lopinavir-ritonavir.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*
Evidence To Decision

**Benefits and harms**

**General adult population**
Evidence indicates no difference in incidence of death, requirement of mechanical ventilation or duration of hospital stay between lopinavir-ritonavir and standard care. Uncertainty remains regarding the incidence of serious adverse events and adverse events, however there are well-known side effects and harms associated with lopinavir-ritonavir.

Although most information on side effects is derived from long-term use, potential acute harms include: gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation and PR interval prolongation. Chronic harms include: increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir-ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs.

Harms associated with short-term use have been reported in three trials [130][131][173]. These include transient elevation of alanine aminotransferase and gastrointestinal symptoms, such as diarrhoea.

**Children and adolescents**
Paediatricians have considerable experience with the use of lopinavir-ritonavir in children and adolescents for other indications.

**Pregnant and breastfeeding women**
Lopinavir-ritonavir is recommended for pregnant and breastfeeding women living with HIV as part of highly active antiretroviral therapy. Studies of women receiving lopinavir-ritonavir for this indication have shown a favourable safety profile.

**People requiring palliative care and older people living with frailty or cognitive impairment**
The benefits of lopinavir-ritonavir for symptom management for this population are uncertain.

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence is high for mortality, mechanical ventilation or ECMO and discharge from hospital at day 28. Certainty is moderate for patients requiring ventilation (reliance on a single study) and low for respiratory failure (inconsistency in direction of effect and wide confidence intervals), clinical improvement at day 14 (lack of blinding of patients/personnel and wide confidence intervals) and time to discharge from hospital (lack of blinding of patients/personnel and reliance on a single study). Certainty is very low for adverse and serious adverse events.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is further downgraded because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of lopinavir-ritonavir during pregnancy and breastfeeding are unknown in the context of COVID-19.
Rationale
Based on the available evidence, lopinavir-ritonavir is no more effective than standard care in treating patients with COVID-19. We therefore recommend that lopinavir-ritonavir should not be used.

Clinical Question/ PICO
Population: Patients with COVID-19
Intervention: Lopinavir-ritonavir
Comparator: Standard care

Summary
Evidence indicates that lopinavir-ritonavir is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from seven randomised trials that compared lopinavir-ritonavir with standard care in 9389 patients with COVID-19 [50][130][131][173][180][184][480]. The vast majority of data come from the RECOVERY and WHO SOLIDARITY trials, which included 5040 [180] and 2771 patients [50] with moderate to critical COVID-19. The SOLIDARITY trial was stopped early for reasons of futility.

Study characteristics
In the RECOVERY trial, mean age was 66 years and 40% were women. In the SOLIDARITY trial, 37% of patients were under 50 years of age, 43% were aged 50–69 years, and 20% were 70 years or older; 40% were women. For the five smaller trials, mean or median age ranged from 41 to 63 years and the proportion of women ranged from 28 to 59%. In the RECOVERY trial, six women were pregnant at randomisation—of the remaining studies, four excluded pregnant and breastfeeding women, and for two their eligibility was unclear [173][184].

In the RECOVERY and SOLIDARITY trials, patients received lopinavir 400 mg plus ritonavir 100 mg orally twice daily for either 10 days or 14 days, respectively.

What are the main results?
There were no differences in incidence of death, requirement of mechanical ventilation or ECMO, discharge from hospital or time to discharge from hospital between lopinavir-ritonavir and standard care. Lopinavir-ritonavir may decrease the incidence of respiratory failure or ARDS. For all other outcomes, we are uncertain if lopinavir-ritonavir makes a difference.

Our confidence in the results
Certainty of the evidence is high for mortality, invasive mechanical ventilation or ECMO and discharge from hospital.
at day 28. Certainty is moderate for patients requiring ventilation (reliance on a single study) and low for respiratory failure (inconsistency in direction of effect and wide confidence intervals), clinical improvement at day 14 (lack of blinding of patients/personnel and wide confidence intervals) and time to discharge from hospital (lack of blinding of patients/personnel and reliance on a single study). Certainty is very low for adverse and serious adverse events.

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

### Additional information
According to the Therapeutic Goods Administration, there are well-known side effects and harms associated with lopinavir-ritonavir. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation and PR interval prolongation. Chronic harms include increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir-ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs [172].

Paediatricians have considerable experience with lopinavir-ritonavir in children and adolescents for other indications. To date, no specific information on its benefits or harms for children and adolescents has been collected for treating COVID-19 in this population.

Lopinavir-ritonavir is recommended for treating pregnant or breastfeeding women living with HIV, as part of highly active antiretroviral therapy. Studies of women receiving lopinavir-ritonavir for this indication have shown a favourable safety profile, with no increase in stillbirth, preterm birth, low birth weight or birth defects [174][175][176][178][179].

### Additional published studies
The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

<table>
<thead>
<tr>
<th>Trial and Source</th>
<th>Date</th>
<th>Number</th>
<th>Comparison &amp; Population</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMAP-CAP 2021</td>
<td>12 Jul</td>
<td>617</td>
<td>Lopinavir-ritonavir vs standard care in critically ill patients</td>
<td>Organ support-free days</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Lopinavir-ritonavir</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality End of treatment</td>
<td>Relative risk 1.02 (CI 95% 0.93 – 1.12) Based on data from 8,825 participants in 6 studies.</td>
<td>180 per 1000</td>
<td>184 per 1000</td>
<td>4 more per 1000 (CI 95% 13 fewer – 22 more)</td>
<td>High Lopinavir/ritonavir has no impact on mortality.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO End of treatment</td>
<td>Relative risk 1.15 (CI 95% 0.95 – 1.38) Based on data from 5,074 participants in 3 studies. (Randomized controlled)</td>
<td>84 per 1000</td>
<td>97 per 1000</td>
<td>13 more per 1000 (CI 95% 4 fewer – 32 more)</td>
<td>High Lopinavir-ritonavir has no impact on patients requiring invasive mechanical ventilation or ECMO.</td>
</tr>
<tr>
<td>Non-invasive or invasive ventilation</td>
<td>Relative risk 1.02 (CI 95% 0.8 – 1.29) Based on data from 95 per 1000</td>
<td>97 per 1000</td>
<td>Moderate Only one study</td>
<td>Lopinavir/ritonavir probably has no impact on patients requiring</td>
<td></td>
</tr>
</tbody>
</table>
### Table: Outcomes and Comparisons

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Timeframe</strong></td>
<td><strong>Study results and measurements</strong></td>
<td><strong>Comparator</strong></td>
<td><strong>Intervention</strong></td>
<td><strong>Certainty of the Evidence</strong></td>
<td><strong>Plain language summary</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standard care</td>
<td>Lopinavir-ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>End of treatment</td>
<td>Relative risk 1.1 (CI 95% 0.66 – 1.82) Based on data from 1,031 participants in 5 studies. 6 (Randomized controlled)</td>
<td>213 per 1000</td>
<td>234 per 1000</td>
<td>Low</td>
<td>Low Due to serious risk of bias and serious imprecision 7</td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>Day 14 after treatment</td>
<td>Relative risk 1.15 (CI 95% 0.92 – 1.42) Based on data from 534 participants in 3 studies. 10 (Randomized controlled)</td>
<td>324 per 1000</td>
<td>373 per 1000</td>
<td>Low</td>
<td>Low Due to serious risk of bias and serious imprecision 11</td>
</tr>
<tr>
<td><strong>Discharge from hospital</strong></td>
<td>28 Days after commencing treatment</td>
<td>Relative risk 1 (CI 95% 0.98 – 1.03) Based on data from 8,104 participants in 3 studies. 12</td>
<td>742 per 1000</td>
<td>742 per 1000</td>
<td>High</td>
<td>High Lopinavir/ritonavir has no impact on discharge from hospital at 28 days.</td>
</tr>
<tr>
<td><strong>Hospitalisation</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.24 (CI 95% 0.6 – 2.56)</td>
<td>53</td>
<td>66</td>
<td>Low</td>
<td>Low We are uncertain whether lopinavir-</td>
</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong></td>
<td>End of treatment</td>
<td>Relative risk 0.7 (CI 95% 0.49 – 1) Based on data from 540 participants in 3 studies. 5 (Randomized controlled)</td>
<td>231 per 1000</td>
<td>162 per 1000</td>
<td>Low</td>
<td>Low Due to serious inconsistency and serious imprecision</td>
</tr>
<tr>
<td><strong>Within 28 days after</strong></td>
<td><strong>commencing treatment</strong></td>
<td>2,545 participants in 1 studies. 3 (Randomized controlled)</td>
<td>Difference:</td>
<td>2 more per 1000 ( CI 95% 19 fewer – 28 more )</td>
<td></td>
<td>Non-invasive or invasive ventilation.</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Timeframe</strong></td>
<td><strong>Study results and measurements</strong></td>
<td><strong>Comparator</strong></td>
<td><strong>Intervention</strong></td>
<td><strong>Certainty of the Evidence</strong></td>
<td><strong>Plain language summary</strong></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>End of treatment</td>
<td>Relative risk 1.32 (CI 95% 0.93 – 1.86) Based on data from 1,031 participants in 5 studies. 8 (Randomized controlled)</td>
<td>396 per 1000</td>
<td>523 per 1000</td>
<td>Low</td>
<td>Low Due to serious risk of bias and serious imprecision 9</td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>Day 14 after treatment</td>
<td>Relative risk 1.15 (CI 95% 0.92 – 1.42) Based on data from 534 participants in 3 studies. 10 (Randomized controlled)</td>
<td>324 per 1000</td>
<td>373 per 1000</td>
<td>Low</td>
<td>Low Due to serious risk of bias and serious imprecision 11</td>
</tr>
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<td><strong>Discharge from hospital</strong></td>
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<td>742 per 1000</td>
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<td><strong>Hospitalisation</strong></td>
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<td>Low</td>
<td>Low We are uncertain whether lopinavir-</td>
</tr>
</tbody>
</table>

### Footnotes:
- 2 more per 1000 (CI 95% 19 fewer – 28 more)
- 231 per 1000
- 162 per 1000
- 69 fewer per 1000 (CI 95% 19 fewer – 28 more)
- 213 per 1000
- 234 per 1000
- 21 more per 1000 (CI 95% 19 fewer – 28 more)
- 396 per 1000
- 523 per 1000
- 127 more per 1000 (CI 95% 19 fewer – 28 more)
- 324 per 1000
- 373 per 1000
- 49 more per 1000 (CI 95% 19 fewer – 28 more)
- 742 per 1000
- 742 per 1000
- 0 fewer per 1000 (CI 95% 19 fewer – 28 more)
- 53
- 66
- Based on data from 540 participants in 3 studies.
- Based on data from 966 participants in 4 studies.
- Based on data from 1,031 participants in 5 studies.
- Based on data from 3 studies.
- Based on data from 4 studies.
- Based on data from 5 studies.
- Based on data from 3 studies.
- Based on data from 8,104 participants in 3 studies.
- Based on data from 3 studies.
- Based on data from 3 studies.
- Based on data from 3 studies.
- Based on data from 3 studies.


4. **Imprecision:** serious. Only data from one study.


7. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Wide confidence intervals.


9. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias. **Imprecision:** serious. Wide confidence intervals.


11. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias. **Imprecision:** serious. Wide confidence intervals.


14. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.

15. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** serious. Only data from one study.
6.3 Disease-modifying treatments not recommended outside of clinical trials

Many therapies are being evaluated to determine their effectiveness and safety in treating people with COVID-19. Since the start of the pandemic over 3000 randomised trials have been registered (see COVID-NMA Initiative). We continually monitor new research for randomised trials that evaluate any disease-modifying treatments for COVID-19. As each new trial is published, our panels assess and make recommendations on whether the treatment should be used in the clinical care of patients.

While there is sufficient evidence to make recommendations in support of using or not using a growing number of treatments, for many treatments the evidence is uncertain because there are too few trials or the overall patient numbers are low. In this section of the guideline we list all those treatments that are only recommended for use in research, i.e. in randomised trials with appropriate ethical approval.

As soon as sufficient evidence emerges that changes the recommendation from 'research only', the treatment is moved to one of the ‘Disease-modifying treatments’ sections above.

6.3.1 Antiandrogens

6.3.1.1 Dutasteride

**Evidence To Decision**

<table>
<thead>
<tr>
<th>Benefits and harms</th>
<th>Important harms</th>
</tr>
</thead>
</table>

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are common side effects and harms associated with dutasteride, including impotence, altered libido and breast disorders.

**Children and adolescents**

Dutasteride is contraindicated in children as its use not been studied in this population.

**Pregnant and breastfeeding women**

Dutasteride is contraindicated for use in women as it has not been studied in this population. In pregnant women, pre-clinical data suggest that the suppression of circulating levels of dihydrotestosterone may inhibit the development of a male fetus carried by a woman exposed to dutasteride.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence for each outcome is very low due to serious risk of bias and very serious imprecision (low number of patients and/or observed events and reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people**

Only in research settings

Do not use dutasteride for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

*Dutasteride should still be considered for other evidence-based indications in people who have COVID-19.*

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use dutasteride to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, the use of dutasteride is contraindicated for pregnant and breastfeeding women.

Resources and other considerations

Important issues, or potential issues not investigated

General adult population
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

Important issues, or potential issues not investigated

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

Important issues, or potential issues not investigated

General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.
Rationale

General adult population
There is currently limited evidence about the impact of dutasteride on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that dutasteride should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of dutasteride for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Dutasteride
Comparator: Standard Care

Summary
There remains significant uncertainty whether dutasteride is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared dutasteride with placebo in 130 adult males hospitalised with mild COVID-19 [234].

Note: the study authors have confirmed the randomisation process and use of a matching placebo tablet, and that no hospitalisations occurred.

Study characteristics
Mean age of participants was 42 years; no women were included in the study. Patients received dutasteride 0.5 mg or placebo once a day for 30 days or until full remission of COVID-19 symptoms. Both groups also received nitazoxanide 500 mg twice a day for six days and azithromycin 500 mg a day for five days.

What are the main results?
No patients in either arm required hospitalisation. It is unclear whether dutasteride increases or decreases time to clinical recovery.

Our confidence in the results
Certainty of the evidence is very low for all outcomes due to serious risk of bias and very serious imprecision (reliance on a single study with low patient numbers and few events).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness due to the absence of these populations in the included studies.

Additional information
Dutasteride is contraindicated in children as its use not been studied in this population [233].

Pregnant and breastfeeding women
Dutasteride has not been studied in women. As a result, the safety profile is unknown in this population and its use should be avoided. Furthermore, dutasteride is contraindicated in breastfeeding women because pre-clinical data suggest that the suppression of circulating levels of dihydrotestosterone may inhibit the development of a male fetus carried by a woman exposed to dutasteride [233].
### 6.3.2 Antineoplastics

#### 6.3.2.1 Angiotensin 2 receptor agonist (C21)

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard Care</th>
<th>Intervention Dutasteride</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation</td>
<td>Based on data from 87 participants in 1 studies.</td>
<td></td>
<td></td>
<td>2</td>
<td>No patients required hospitalisation.</td>
</tr>
<tr>
<td>End of Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to recovery Remission</td>
<td>Based on data from: 87 participants in 1 studies.</td>
<td></td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>of all symptoms</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
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</tbody>
</table>

2. **Risk of Bias:** serious. Selective outcome reporting. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Only data from one study, Low number of patients. **Publication bias:** no serious.
3. Systematic review [232]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias:** serious. Selective outcome reporting. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study, **Publication bias:** no serious.

**Hospitalisation**

- **End of Follow-up**
  - 9 Critical

**Time to recovery Remission of all symptoms**

- 6 Important

**Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard Care</th>
<th>Intervention Dutasteride</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>Time to recovery Remission</td>
<td>Based on data from: 87 participants in 1 studies.</td>
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<tr>
<td>of all symptoms</td>
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<tr>
<td>6 Important</td>
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</tr>
</tbody>
</table>

**General adult population**

**Benefits and harms**

C21 should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use C21 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**Evidence To Decision**

**Benefits and harms**

**General adult population**
As the safety profile for C21 is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There are additional concerns regarding harms as C21 has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

Certainty of the Evidence

Certainty of the evidence is very low for mortality due to very serious imprecision (wide confidence intervals, few events and reliance on a single study) and serious publication bias (the study was commercially funded). Certainty for the remaining outcomes is also very low due to the above factors with the addition of serious risk of bias (insufficient information regarding randomisation).

Preference and values

General adult population

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women

We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.
People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale
General adult population
There is currently limited evidence about the impact of C21 on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that C21 should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of C21 to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO
Population: Patients with COVID-19
Intervention: C21
Comparator: Placebo

Summary
There remains significant uncertainty whether angiotensin 2 receptor agonist (C21) is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared C21 with placebo in 106 adults hospitalised with COVID-19 [620].

Study characteristics
Mean age of participants was 53 years and 25% were women. Pregnant and breastfeeding women were ineligible.

What are the main results?
Insufficient patients received supplemental oxygen, invasive mechanical ventilation or died to determine whether C21 makes a difference to these outcomes.

Our confidence in the results
Certainty of the evidence is very low for all outcomes. This judgement is based on very serious imprecision (low patient numbers, wide confidence intervals and reliance on a single study with few events), serious risk of bias (randomisation process) and serious publication bias (commercially funded).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As of 28 May 2021, angiotensin II receptor agonist C21 is not listed in the Australian Register of Therapeutic
Goods and is not approved for use in Australia. The safety profile for C21 is incompletely characterised in humans.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality Day 14</td>
<td>Relative risk 0.36 (CI 95% 0.04 — 3.35) Based on data from 106 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>Placebo</td>
<td>C21</td>
<td>Very low Due to very serious imprecision and serious publication bias ²</td>
<td>We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases mortality (4 deaths).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation End of follow-up</td>
<td>Relative risk 0.27 (CI 95% 0.03 — 2.33) Based on data from 106 participants in 1 studies. ² (Randomized controlled)</td>
<td>Placebo</td>
<td>C21</td>
<td>Very low Due to very serious imprecision and serious publication bias ³</td>
<td>We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases invasive mechanical ventilation (5 events).</td>
</tr>
<tr>
<td>Supplemental oxygen End of follow-up</td>
<td>Relative risk 0.1 (CI 95% 0.01 — 0.73) Based on data from 106 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td>Placebo</td>
<td>C21</td>
<td>Very low Due to very serious imprecision and serious publication bias ⁶</td>
<td>We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases supplemental oxygen (12 events).</td>
</tr>
</tbody>
</table>

2. Risk of Bias: no serious. No information on concealment of allocation during randomization process, resulting in potential for selection bias. Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study. Publication bias: serious. Mostly commercially funded studies, due to preprint.
4. Imprecision: very serious. Low number of patients, Wide confidence intervals, Only data from one study. Publication bias: serious. Mostly commercially funded studies, due to [reason].
6. Risk of Bias: no serious. No information on concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study. Publication bias: serious. Mostly commercially funded studies, due to preprint.

6.3.2.2 Camostat mesilate
Do not use camostat mesilate for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval. Camostat mesilate should still be considered for other evidence-based indications in people who have COVID-19. Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use camostat mesilate to treat COVID-19 in these populations unless they are eligible to be enrolled in trials. This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

General adult population
As the safety profile for camostat mesilate is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There are additional concerns regarding harms as camostat mesilate has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

Certainty of the Evidence

Very low

Certainty of the evidence is low for mortality due to very serious imprecision (wide confidence intervals, few events and reliance on a single study). In addition to the above factors, certainty is very low for all remaining outcomes due to serious risk of bias (insufficient information regarding randomisation and allocation concealment).

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Resources and other considerations

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

Important issues, or potential issues not investigated

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.
**Rationale**

**General adult population**
There is currently limited evidence about the impact of camostat mesilate on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that camostat mesilate should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability**

**General adult population, children and adolescents, pregnant and breastfeeding women**
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

**General adult population**
There is currently limited evidence about the impact of camostat mesilate on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that camostat mesilate should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of camostat mesilate to treat COVID-19 in these populations should be avoided until evidence becomes available.

**Clinical Question/ PICO**

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Camostat mesilate</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Summary**
There remains significant uncertainty whether camostat mesilate is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared camostat mesilate with standard care in 208 adults.
hospitalised with COVID-19 [479].

**Study characteristics**
Median age of participants was 61 years and 40% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Insufficient patients required intensive care admission, invasive mechanical ventilation or died to determine whether camostat mesilate makes a difference to these outcomes. It is uncertain if camostat mesilate increases or decreases requirement for supplemental oxygen or increases adverse or serious adverse events.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes. This judgement is based on very serious imprecision (low patient numbers, wide confidence intervals and reliance on a single study with few events) and serious risk of bias (no information on concealment of allocation).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
As of 28 May 2021, camostat mesilate is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. The safety profile for camostat mesilate is incompletely characterised in humans.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>Day 28</td>
<td>Relative risk 0.99 (CI 95% 0.31 – 3.18) Based on data from 205 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>59 per 1000</td>
<td>58 per 1000</td>
<td>Low Due to very serious imprecision ²</td>
<td>We are uncertain whether camostat mesilate increases or decreases mortality (12 deaths).</td>
</tr>
<tr>
<td><strong>Invasive mechanical ventilation</strong></td>
<td>End of follow-up</td>
<td>Relative risk 2.15 (CI 95% 0.63 – 7.29) Based on data from 205 participants in 1 studies. ² (Randomized controlled)</td>
<td>44 per 1000</td>
<td>95 per 1000</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>We are uncertain whether camostat mesilate increases or decreases invasive mechanical ventilation (16 events).</td>
</tr>
<tr>
<td><strong>Supplemental oxygen</strong></td>
<td>End of follow-up</td>
<td>Relative risk 0.98 (CI 95% 0.84 — 1.16) Based on data from 205 participants in 1 studies. ³ (Randomized controlled)</td>
<td>765 per 1000</td>
<td>750 per 1000</td>
<td>Low Due to very serious imprecision ⁶</td>
<td>We are uncertain whether camostat mesilate increases or decreases supplemental oxygen (155 events).</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.68 (CI 95% 0.8 – 3.49) Based on data from 205 participants in 1</td>
<td>118 per 1000</td>
<td>198 per 1000</td>
<td>Low Due to very serious imprecision ⁸</td>
<td>We are uncertain whether camostat mesilate increases serious adverse events (38 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>6 important</td>
<td>studies. 7 (Randomized controlled)</td>
<td>Camostat mesilate</td>
<td>1000 24 fewer — 294 more</td>
<td>Low Due to very serious imprecision 10</td>
<td></td>
</tr>
<tr>
<td>End of follow-up</td>
<td>6 important</td>
<td>Relative risk 0.86 (CI 95% 0.55 — 1.33) Based on data from 205 participants in 1 studies. 7 (Randomized controlled)</td>
<td>324 per 1000</td>
<td>279 per 1000</td>
<td>We are uncertain whether camostat mesilate increases adverse events (60 events).</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>6 important</td>
<td>Relative risk 0.87 (CI 95% 0.38 — 1.97) Based on data from 205 participants in 1 studies. 11 (Randomized controlled)</td>
<td>118 per 1000</td>
<td>103 per 1000</td>
<td>Low Due to very serious imprecision 12</td>
<td></td>
</tr>
<tr>
<td>End of follow-up</td>
<td>6 important</td>
<td></td>
<td>Difference: 45 fewer per 1000 146 fewer — 107 more</td>
<td>15 fewer per 1000 73 fewer — 114 more</td>
<td>We are uncertain whether camostat mesilate increases or decreases ICU admission (22 events).</td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias: no serious**. No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious**. Wide confidence intervals, Low number of patients, Only data from one study.
4. **Risk of Bias: no serious**. No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious**. Wide confidence intervals, Low number of patients, Only data from one study.
6. **Risk of Bias: no serious**. No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious**. Wide confidence intervals, Low number of patients, Only data from one study.
8. **Risk of Bias: no serious**. No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious**. Low number of patients, Only data from one study, Wide confidence intervals.
10. **Risk of Bias: no serious**. No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious**. Wide confidence intervals, Low number of patients, Only data from one study.
12. **Risk of Bias: no serious**. No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious**. Low number of patients, Wide confidence intervals, Only data from one study.
6.3.3 Antiparasitic, antifungals and other anti-infective agents

6.3.3.1 Chloroquine

**Evidence To Decision**

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known harms with potentially severe adverse events. Although most of the information on side effects and harms associated with chloroquine is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as chloroquine has not been sufficiently tested in these populations. Chloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases in some countries. The available evidence is limited, though it is not associated with pregnancy loss, stillbirth or neonatal death [213]. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence for each outcome is very low. This is based on serious risk of bias due to non-blinding of participants and personnel and incomplete outcome data, and very serious imprecision due to the low number of patients and/or events for some outcomes and the reliance on a single study.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is additionally considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.
Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of chloroquine in pregnancy are unknown.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit.

Equity
General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

Special populations (people requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability
General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. In addition, although chloroquine is registered on the Australian Register of Therapeutic Goods, it is not marketed in Australia and is therefore not readily available.

Rationale
General adult population
There is currently limited evidence about the impact of chloroquine on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that chloroquine should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.
Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of chloroquine to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary
There remains significant uncertainty whether chloroquine is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared chloroquine with standard care in 30 adults hospitalised with moderate COVID-19 [135].

We have found one new study comparing chloroquine administered as nasal drops with standard care (Thakar et al. Indian J Med Res doi: 10.4103/ijmr.IJMR_3665_20). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

Publication status
The study is only available as a preprint (posted to medRxiv on 22 June 2020) and has therefore not been peer reviewed.

Study characteristics
Mean age was 45 years in the chloroquine group and 51 years in the control group; the proportion of women was 61% and 42% respectively. It is unclear if pregnant and breastfeeding women were eligible.

What are the main results?
No patients in either arm died, progressed to severe or critical disease, or experienced a serious adverse event. We are uncertain whether chloroquine increases or decreases time to clinical recovery, time to termination of oxygen therapy or the likelihood of experiencing adverse events. The study did not report results for respiratory failure or requirement for mechanical ventilation.

Our confidence in the results
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (patients, personnel and outcome assessors not blinded, and incomplete reporting of data) and very serious imprecision (low patient numbers, few observed events and reliance on a single study).

Additional information
Although listed on the Australian Register of Therapeutic Goods, chloroquine is not marketed in Australia and is not available for general use.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality within 28 days after</td>
<td>Based on data from 30 participants in 1</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>2</td>
<td>There were no deaths.</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
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<td>------------------------</td>
</tr>
<tr>
<td><strong>Progression to severe or critical disease</strong>&lt;br&gt;Within 28 days after commencing treatment</td>
<td>Based on data from 30 participants in 1 studies. &lt;sup&gt;3&lt;/sup&gt; (Randomized controlled)</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>Very low Due to serious risk of bias and very serious imprecision &lt;sup&gt;8&lt;/sup&gt;</td>
<td>No patients progressed to severe or critical disease.</td>
</tr>
<tr>
<td><strong>Adverse events</strong>&lt;br&gt;Within 28 days after commencing treatment</td>
<td>Relative risk 2.67 (CI 95% 0.68 – 10.46) Based on data from 30 participants in 1 studies. &lt;sup&gt;3&lt;/sup&gt; (Randomized controlled)</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>Very low Due to serious risk of bias and very serious imprecision &lt;sup&gt;8&lt;/sup&gt;</td>
<td>We are uncertain whether chloroquine increases or decreases adverse events (10 events).</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong>&lt;br&gt;Within 28 days after commencing treatment</td>
<td>Based on data from 30 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>Very low Due to serious risk of bias and very serious imprecision &lt;sup&gt;8&lt;/sup&gt;</td>
<td>There were no serious adverse events.</td>
</tr>
<tr>
<td><strong>Time to clinical recovery</strong>&lt;br&gt;Median time to clinical recovery (Days)</td>
<td>Measured by: Median time to clinical recovery; chloroquine: 5.5 days (IQR 3.25-7.5), control: 7.5 days (IQR 5.0-16.25) Lower better (Randomized controlled)</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>Very low Due to serious risk of bias and very serious imprecision &lt;sup&gt;8&lt;/sup&gt;</td>
<td>We are uncertain whether chloroquine increases or decreases time to clinical recovery.</td>
</tr>
<tr>
<td><strong>Time to termination of oxygen therapy</strong>&lt;br&gt;Median time from randomisation to termination of oxygen therapy (Days)</td>
<td>Measured by: Median time to termination of oxygen therapy; chloroquine: 8.5 days (IQR 0-9.25), control: 8 days (IQR 3.25-14) Lower better (Randomized controlled)</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>Very low Due to serious risk of bias and very serious imprecision &lt;sup&gt;8&lt;/sup&gt;</td>
<td>We are uncertain whether chloroquine increases or decreases time to termination of oxygen therapy.</td>
</tr>
</tbody>
</table>

2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Low number of patients, Only data from one study.


4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Low number of patients, Only data from one study.


6. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Low number of patients, Only data from one study.

7. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Only data from one study, Low number of patients.

8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Low number of patients, Only data from one study.

9. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Low number of patients, Only data from one study.

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**Clinical Question/ PICO**

**Population:** Special populations with COVID-19  
**Intervention:** Chloroquine  
**Comparator:** Standard care

**Summary**

There remains significant uncertainty whether chloroquine is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from a single randomised trial that compared chloroquine with standard care in 30 adults hospitalised with moderate COVID-19 [135].

We have found one new study comparing chloroquine administered as nasal drops with standard care (Thakar et al. Indian J Med Res doi: 10.4103/ijmr.IJMR_3665_20). This study is currently under review and an updated recommendation will be included in a future version of the guideline.
Publication status
The study is only available as a preprint paper (posted to medRxiv on 22 June 2020) and has therefore not been peer reviewed.

Study characteristics
Mean age was 45 years in the chloroquine group and 51 years in the control group; the proportion of women was 61% and 42% respectively. It is unclear if pregnant and breastfeeding women were eligible.

What are the main results?
No patients in either arm died, progressed to severe or critical disease, or experienced a serious adverse event. We are uncertain whether chloroquine increases or decreases time to clinical recovery, time to termination of oxygen therapy or the likelihood of experiencing adverse events. The study did not report results for respiratory failure or requirement for mechanical ventilation.

Our confidence in the results
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (patients, personnel and outcome assessors not blinded, and incomplete reporting of data), serious indirectness (limited inclusion of these populations) and very serious imprecision (low patient numbers, few observed events and reliance on a single study).

Additional information
Although listed on the Australian Register of Therapeutic Goods, chloroquine is not marketed in Australia and is not available for general use.

Children and adolescents
Paediatricians have considerable experience with using chloroquine in children and adolescents for other indications. To date, no specific information on benefits or harms for children and adolescents with COVID-19 has been collected.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days after commencing treatment</td>
<td>Based on data from 30 participants in 1 studies.</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>2</td>
</tr>
<tr>
<td>Progression to severe or critical disease</td>
<td>Within 28 days after commencing treatment</td>
<td>Based on data from 30 participants in 1 studies.</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>4</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Within 28 days after</td>
<td>Relative risk 2.67 (CI 95% 0.68 — 10.46)</td>
<td>Standard care</td>
<td>Chloroquine</td>
<td>Very low</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<td>------------------------</td>
</tr>
<tr>
<td>Timeframe</td>
<td></td>
<td>Standard care</td>
<td>Chloroquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>commencing treatment</td>
<td>studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>indirectness and very serious imprecision</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events Within 28 days after commencing treatment</td>
<td>Based on data from 30 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>?</td>
<td>There were no serious adverse events.</td>
</tr>
<tr>
<td>Time to clinical recovery Median time to clinical recovery (Days)</td>
<td>Measured by: Median time to clinical recovery; chloroquine: 5.5 days (IQR 3.25-7.5), control: 7.5 days (IQR 5.0-16.25) Lower better (Randomized controlled)</td>
<td>7.5 (Median)</td>
<td>5.5 (Median) CI 95%</td>
<td>Very low Due to serious risk of bias, serious indirectness and very serious imprecision</td>
<td>We are uncertain whether chloroquine increases or decreases time to clinical recovery.</td>
</tr>
<tr>
<td>Time to termination of oxygen therapy Median time from randomisation to termination of oxygen therapy (Days)</td>
<td>Measured by: Median time to termination of oxygen therapy; chloroquine: 8.5 days (IQR 0-9.25); control: 8 days (IQR 3.25-14) Lower better (Randomized controlled)</td>
<td>8 (Median)</td>
<td>8.5 (Median) CI 95%</td>
<td>Very low Due to serious risk of bias, serious indirectness and very serious imprecision</td>
<td>We are uncertain whether chloroquine increases or decreases time to termination of oxygen therapy.</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Indirectness:** serious. **Imprecision:** very serious. Low number of patients, Only data from one study.
4. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Indirectness:** serious. **Imprecision:** very serious. Low number of patients, Only data from one study.
6. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel,
resulting in potential for performance bias. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.

7. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: serious. Imprecision: very serious.** Only data from one study, Low number of patients.

8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.

9. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.

### 6.3.3.2 Doxycycline

We have found a new study comparing doxycycline with standard care in 1792 people aged 65 years or older (or 50 years or older with comorbidities) who had been unwell (for ≤ 14 days) with suspected COVID-19 or a positive PCR test for SARS-CoV-2 infection in the community (PRINCIPLE trial Lancet Respir Med doi: 10.1016/S2213-2600(21)00310-6). The study found that treatment with doxycycline was not associated with clinically meaningful reductions in time to recovery or hospital admissions or deaths related to COVID-19. As this evidence is insufficient to promote the use of doxycycline outside of clinical trials, we will await publication of additional studies before developing a recommendation.

---

**Only in research settings**

Do not use doxycycline for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Doxycycline should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in older people living with frailty and those receiving palliative care. Until further evidence is available, do not use doxycycline to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

Trials are not recommended in pregnant and breastfeeding patients, as doxycycline is contra-indicated in this group.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

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### Evidence To Decision

**Benefits and harms**

**General adult population**

Evidence indicates no difference between doxycycline and standard care for mortality, requirement for invasive mechanical ventilation, admission to hospital and mortality, intensive care admission, use of supplemental oxygen and serious adverse events. It is uncertain if doxycycline reduces recovery from COVID-19 compared with standard care.
### Certainty of the Evidence

#### General adult population
Certainty of the evidence is moderate for mortality due to serious imprecision (reliance on a single study, wide confidence intervals, and few events).

Certainty is low for invasive mechanical ventilation, hospitalisation and mortality, intensive care admission, supplemental oxygen, self-reported recovery and serious adverse events due to serious imprecision and serious risk of bias (reliance on a single study, wide confidence intervals, and lack of blinding of participants and outcome assessors).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Preference and values

#### General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

### Resources and other considerations

#### General adult population
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

#### General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

#### General adult population
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.
Rationale

There is currently limited evidence about the impact of doxycycline on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that doxycycline should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Doxycycline
Comparator: Standard care

Summary

Evidence indicates that doxycycline is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?

Evidence comes from a single randomised trial (PRINCIPLE) that compared doxycycline with standard care in 1792 adults with mild COVID-19 [577].

Study characteristics

Patients were 65 years and older (or 50 years and older with comorbidities) and not admitted to hospital at trial entry. Mean age of participants was 61 years and 56% were women. Comorbidities included COPD, asthma or lung disease (37%), diabetes (37%), hypertension (42%) and cardiovascular disease (14%).

What are the main results?

Doxycycline probably has no impact on mortality (4 more deaths per 1000; RR 3.11, CI 95% 0.61 to 16.01; 1792 patients in 1 study) or invasive mechanical ventilation (4 fewer per 1000; RR 0.49, CI 95% 0.12 to 2.05; 1378 patients in 1 study). There is probably little difference between doxycycline and standard care for the composite outcome of death or hospitalisation.

Although self-reported recovery was greater in the doxycycline group (31 more per 1000; RR 1.05, CI 95% 0.97 to 1.13), the open-label design makes this outcome at high risk of bias.

Our confidence in the results

Certainty of the evidence is moderate for mortality due to serious imprecision (reliance on a single study, wide confidence intervals and few events). Certainty is low for all other outcomes due to serious imprecision and risk of bias (reliance on single study, wide confidence intervals, lack of blinding of participants and outcome assessors).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 3.11 (CI 95%: 0.61 to 16.01)</td>
<td>Standard care</td>
<td>Doxycycline</td>
<td>Low Due to very serious imprecision</td>
<td>There were too few who died to determine whether doxycycline makes a difference (7 events).</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>Based on data from 1,792 participants in 1 study.</td>
<td>2 per 1000</td>
<td>6 per 1000</td>
<td>4 more per 1000</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Doxycycline</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.49 (CI 95% 0.12 – 2.05) Based on data from 1,378 participants in 1 studies.</td>
<td></td>
<td>( CI 95% 1 fewer – 30 more )</td>
<td>Low</td>
<td>There were too few who required invasive mechanical ventilation to determine whether doxycycline makes a difference (8 events).</td>
</tr>
<tr>
<td>Mortality or hospitalisation</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.19 (CI 95% 0.78 – 1.8) Based on data from 1,792 participants in 1 studies.</td>
<td></td>
<td>( CI 95% 7 fewer – 8 more )</td>
<td>Low</td>
<td>Doxycycline may have little or no difference on mortality or hospitalisation (84 events).</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.55 (CI 95% 0.16 – 1.93) Based on data from 1,375 participants in 1 studies.</td>
<td></td>
<td>( CI 95% 8 fewer – 9 more )</td>
<td>Low</td>
<td>There were too few who required ICU admission to determine whether doxycycline makes a difference (10 events).</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.55 – 1.76) Based on data from 1,378 participants in 1 studies.</td>
<td></td>
<td>( CI 95% 14 fewer – 24 more )</td>
<td>Moderate</td>
<td>Doxycycline probably has little impact on requirement for supplemental oxygen (44 events).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.11 (CI 95% 0.01 – 2.04) Based on data from 1,792 participants in 1 studies.</td>
<td></td>
<td>( CI 95% 5 fewer – 5 more )</td>
<td>Low</td>
<td>There were too few who experienced a serious adverse event to determine whether doxycycline makes a difference (5 events).</td>
</tr>
<tr>
<td>Recovery (self-reported)</td>
<td>End of follow-up</td>
<td>Relative risk 1.05 (CI 95% 0.97 – 1.13) Based on data from 1,424 participants in 1 studies.</td>
<td></td>
<td>( CI 95% 1 fewer – 30 more )</td>
<td>Low</td>
<td>Doxycycline may improve self-reported recovery slightly (898 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
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<td>-----------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>6 Important</td>
<td>(Randomized controlled)</td>
<td>Standard care</td>
<td>Doxycycline</td>
<td>(CI 95% 18 fewer — 80 more)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, due to few events. **Publication bias:** no serious.
4. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Only data from one study, Wide confidence intervals. **Publication bias:** no serious.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals, Only data from one study. **Publication bias:** no serious.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals, Only data from one study. **Publication bias:** no serious.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals, Only data from one study. **Publication bias:** no serious.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals, Only data from one study. **Publication bias:** no serious.
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals, Only data from one study. **Publication bias:** no serious.
6.3.3.3 Ivermectin

**Evidence To Decision**

**Only in research settings**

Do not use ivermectin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

*Ivermectin should still be considered for other evidence-based indications in people who have COVID-19.*

*Tries are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ivermectin to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are common side effects and harms associated with ivermectin, including diarrhoea, nausea and dizziness [269].

**Children and adolescents**

Ivermectin should not be used in children under five years of age as safety in this age group has not been established. The safety profile of ivermectin in children 5–12 years of age is similar to that observed in adults [269].

**Pregnant and breastfeeding women**

Limited information suggests that ivermectin is not associated with an increased risk of congenital abnormalities. Ivermectin may be used in women who are breastfeeding [270].

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence is low for mortality, invasive mechanical ventilation, adverse or serious events, discharge from hospital, admission to ICU and clinical improvement all due to very serious imprecision (reliance on a single study, limited number of patients, and/or wide confidence intervals). Certainty is very low for viral clearance, time to clinical recovery and duration of hospital stay due to very serious imprecision (reliance on a single study, limited number of patients, and/or wide confidence intervals) and serious risk of bias (inadequate randomisation).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is further considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of ivermectin during pregnancy and breastfeeding are unknown in the context of COVID-19.

**Resources and other considerations**

| Important issues, or potential issues not investigated |

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

| General adult population |

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

| Children and adolescents, pregnant and breastfeeding women |

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

| People requiring palliative care and older people living with frailty or cognitive impairment |

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability**

| General adult population, children and adolescents, pregnant and breastfeeding women |

We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

| People requiring palliative care and older people living with frailty or cognitive impairment |

Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**

| Important issues, or potential issues not investigated |

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

| General adult population |

There is currently limited evidence about the impact of ivermectin on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that ivermectin should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

| Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment |

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the
limited evidence in the general adult population, use of ivermectin for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

**Population:** Patients with COVID-19  
**Intervention:** Ivermectin  
**Comparator:** Standard care

**Summary**
There remains significant uncertainty whether ivermectin is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from 15 randomised trials that compared ivermectin with standard care in over 1800 adults with COVID-19 [267][273][274][275][277][278][280][282][283][514][518][521][530][564].

**Publication status**
Three studies are only available as preprints and have therefore not been peer reviewed (Shah Bukhari et al. posted to medRxiv on 5 February 2021 [278], Beltran-Gonzalez et al. posted to medRxiv on 23 February 2021 [277] and Biber et al. posted to medRxiv on 31 May 2021 [511]).

**Removal of studies**
Version 44: Due to inconsistencies which have been identified in the data reported in the studies by Abd-Elsalam et al. (J Med Virol, 7 Jun 2021) [512] and Niaee et al. (Asian Pacific J Trop Med, 25 June 2021) [586], these studies have been removed from our analyses. Both studies contributed data to all-cause mortality, and Abd-Elsalam et al. also contributed data to mechanical ventilation and duration of hospitalisation. The removal of these data did not change the strength or direction of the recommendation.

Version 45: The study by Samaha (Viruses, 26 May 2021) [513] was retracted by the journal on 26 Oct 2021 at the request of the authors following an error between files used for the statistical analysis. The study contributed data to the outcome hospitalisation and removal of these data did not change the strength or direction of the recommendation.

**Study characteristics**
Mean/median age of participants across the studies ranged from 26 to 56 years and the proportion of women ranged from 27 to 61% (with the exception of two studies, in which the proportion of women ranged from 10 to 20% [278][564]). Pregnant and breastfeeding women were ineligible in all trials.

**What are the main results?**
We are uncertain whether ivermectin increases or decreases death, patients requiring invasive mechanical ventilation or oxygen, adverse or serious adverse events, admission to ICU, rate of viral clearance, discharge from hospital, clinical progression or clinical improvement, time to clinical recovery or duration of hospital stay.

**Our confidence in the results**
Certainty of the evidence is low for mortality, invasive mechanical ventilation, adverse or serious adverse events, discharge from hospital, admission to ICU and clinical improvement all due to very serious imprecision (based on reliance on a single study, limited number of patients, and/or wide confidence intervals). Certainty is very low for viral clearance, time to clinical recovery and duration of hospital stay due to very serious imprecision (reliance on a single study, limited number of patients, and/or wide confidence intervals) and serious risk of bias (based on inadequate randomisation).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Common side effects and harms associated with ivermectin are diarrhoea, nausea and dizziness [269].

**Pregnant and breastfeeding women**
Limited information suggests that ivermectin is not associated with an increased risk of congenital abnormalities. Ivermectin may be used in women who are breastfeeding [270].
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.79 (CI 95% 0.35 – 1.78) Based on data from 1,236 participants in 5 studies.</td>
<td>Standard care</td>
<td>Ivermectin</td>
<td>Low</td>
<td>Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ivermectin may have little impact on death (23 events).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>End of follow-up</td>
<td>Relative risk 0.86 (CI 95% 0.24 – 3.04) Based on data from 834 participants in 4 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ivermectin may have little impact on invasive mechanical ventilation (16 events).</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 21 days of commencing treatment</td>
<td>Relative risk 1.04 (CI 95% 0.94 – 1.15) Based on data from 398 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether ivermectin increases or decreases clinical recovery (320 events).</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>End of follow-up</td>
<td>Relative risk 1.08 (CI 95% 0.5 – 2.32) Based on data from 114 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether ivermectin increases or decreases requirement of supplemental oxygen (19 events).</td>
</tr>
<tr>
<td>ICU admission</td>
<td>End of follow-up</td>
<td>Relative risk 0.53 (CI 95% 0.11 – 2.51) Based on data from 143 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether ivermectin increases or decreases admission to ICU (13 events)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.95 (CI 95% 0.86 – 1.05) Based on data from 1,306 participants in 8 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ivermectin may have little or no difference on adverse events</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>---------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.12 (CI 95% 0.21 — 5.88) Based on data from 1,165 participants in 6 studies.</td>
<td>Standard care</td>
<td>Ivermectin</td>
<td>Low</td>
<td>Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td>Discontinuation due to adverse event</td>
<td>End of treatment</td>
<td>Relative risk 2.97 (CI 95% 1.1 — 8.02) Based on data from 899 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>End of follow-up</td>
<td>Relative risk 0.63 (CI 95% 0.34 — 1.17) Based on data from 590 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td>Discharge from hospital (end of follow-up)</td>
<td></td>
<td>Relative risk 1.06 (CI 95% 0.99 — 1.12) Based on data from 342 participants in 4 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td>Clinical progression</td>
<td>End of follow-up</td>
<td>Based on data from 24 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Ivermectin may increase discharge from hospital slightly</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>End of follow-up</td>
<td>Relative risk 1.07 (CI 95% 0.94 — 1.22) Based on data from 125 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>No participants progressed to severe disease.</td>
</tr>
</tbody>
</table>

13 Based on data from 1,165 participants in 6 studies. 14 Due to serious risk of bias and serious imprecision 15 Due to very serious imprecision 16 Due to very serious imprecision 18 Due to serious risk of bias and serious imprecision 20 Due to serious risk of bias and serious imprecision 21 Based on data from 24 participants in 1 studies. 22 No participants progressed to severe disease. 23 Based on data from 125 participants in 1 studies. 24 Based on data from 125 participants in 1 studies. 25 Due to very serious imprecision.
## Outcome Timeframe

<table>
<thead>
<tr>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral clearance 7-12 days after treatment</td>
<td>Relative risk 1.19 (CI 95% 0.94 — 1.52) Based on data from 833 participants in 5 studies.</td>
<td>752 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision.</td>
<td>We are uncertain whether ivermectin increases or decreases viral clearance.</td>
</tr>
<tr>
<td>Time to clinical recovery [onset to resolution] 28 Days</td>
<td>Lower better Based on data from: 62 participants in 1 studies.</td>
<td>11.5 (Mean)</td>
<td>Very low Due to very serious risk of bias and very serious imprecision.</td>
<td>We are uncertain whether ivermectin increases or decreases time to clinical recovery (from onset of illness).</td>
</tr>
<tr>
<td>Time to clinical recovery [randomisation to resolution] Days</td>
<td>Lower better Based on data from: 62 participants in 1 studies.</td>
<td>6.3 (Mean)</td>
<td>Very low Due to very serious risk of bias and very serious imprecision.</td>
<td>We are uncertain whether ivermectin increases or decreases time to clinical recovery (from randomisation).</td>
</tr>
<tr>
<td>Time to recovery 31 Days</td>
<td>Lower better Based on data from: 398 participants in 1 studies.</td>
<td>12 (Median)</td>
<td>Low Due to very serious imprecision.</td>
<td>We are uncertain whether ivermectin increases or decreases time to recovery.</td>
</tr>
<tr>
<td>Duration of hospitalisation Days</td>
<td>Lower better Based on data from: 69 participants in 1 studies.</td>
<td>8.3 (Mean)</td>
<td>Low Due to very serious imprecision.</td>
<td>We are uncertain whether ivermectin increases or decreases duration of hospitalisation.</td>
</tr>
</tbody>
</table>

2. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision: serious.** due to few events.
4. **Imprecision: very serious.** Wide confidence intervals, due to few events.
6. **Imprecision: very serious.** Wide confidence intervals. Only data from one study, due to few events.


8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Imprecision: serious.** Low number of patients, due to few events, Wide confidence intervals.


10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Wide confidence intervals, Low number of patients.


12. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Wide confidence intervals.


14. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Imprecision: serious.** due to few events.


16. **Imprecision: very serious.** Wide confidence intervals, due to few events.


18. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Imprecision: serious.** Wide confidence intervals, due to few events.


20. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Wide confidence intervals.


22. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, due to no events, Only data from one study.

23. Based on a decrease of two or more points on the WHO ordinal scale.


25. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.


27. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance
bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Incomplete data and/or large loss to follow up. **Imprecision: serious.** Wide confidence intervals.

28. Measured as time to clinical recovery from onset of illness to complete resolution of symptoms

29. **Risk of Bias: very serious. Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.

30. **Risk of Bias: very serious. Imprecision: very serious.** Low number of patients, Only data from one study.

31. Defined as sustained resolution of symptoms

32. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.


34. **Imprecision: very serious.** Only data from one study, Low number of patients.

### 6.3.3.4 Ivermectin plus doxycycline

**Only in research settings**

Do not use ivermectin plus doxycycline for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Ivermectin plus doxycycline should still be considered for other evidence-based indications in people who have COVID-19.

 Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ivermectin plus doxycycline to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

### Evidence To Decision

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with both ivermectin and doxycycline including gastrointestinal disorders (such as diarrhoea, vomiting, nausea and abdominal pain), rash, fever, headache and photosensitivity.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence is very low for all outcomes due to very serious imprecision (low patient numbers, few events and the reliance on a single study) and serious risk of bias (incomplete outcome data).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.
Preference and values

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Resources and other considerations

**General adult population**
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

**General adult population, children and adolescents, pregnant and breastfeeding women**
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

**General adult population**
There is currently limited evidence about the impact of ivermectin plus doxycycline on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that ivermectin plus doxycycline should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living**
with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of ivermectin plus doxycycline to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Ivermectin plus doxycycline</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary
There remains significant uncertainty whether ivermectin plus doxycycline is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials that compared ivermectin plus doxycycline with standard care in 447 adults with COVID-19 [273][522].

Study characteristics
Mean age of participants ranged from 42 to 48 years and the proportion of women ranged from 48 to 54%. Patients received ivermectin 12 mg on day one and doxycycline 100 mg twice daily for five days. Pregnant and breastfeeding women were ineligible.

What are the main results?
There were too few who died (three deaths) to determine whether ivermectin plus doxycycline makes a difference. We are uncertain if ivermectin plus doxycycline increases or decreases adverse or serious adverse events, negative PCR, clinical improvement or clinical deterioration.

Our confidence in the results
Certainty of the evidence is very low for all outcomes due to very serious risk of bias and very serious imprecision (reliance on a single study, low patient numbers and few events).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Common side effects and harms associated with ivermectin are diarrhoea, nausea and dizziness [269]. Common side effects and harms associated with doxycycline are nausea, vomiting, diarrhoea, epigastric burning, tooth discolouration, enamel dysplasia and photosensitivity [288].

Pregnant and breastfeeding women
Limited information suggests that ivermectin is not associated with an increased risk of congenital abnormalities. Ivermectin may be used in women who are breastfeeding [270]. Doxycycline is safe if used during the first 18 weeks of pregnancy. After 16 weeks post-conception, doxycycline use is contraindicated as it can inhibit bone growth in the fetus [270].
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>End of treatment</td>
<td>Relative risk 4.92 (CI 95% 0.24 — 101.74) Based on data from 411 participants in 2 studies.³ (Randomized controlled)</td>
<td>Standard care</td>
<td>Ivermectin plus doxycycline</td>
<td>Very low Due to serious risk of bias and very serious imprecision ⁴</td>
<td>There were too few who experienced serious adverse events to determine whether ivermectin plus doxycycline makes a difference (2 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of treatment</td>
<td>Relative risk 14.76 (CI 95% 0.85 — 256.46) Based on data from 363 participants in 1 studies.³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision ⁵</td>
<td>There were too few who experienced adverse events to determine whether ivermectin plus doxycycline makes a difference (7 events).</td>
</tr>
<tr>
<td>Virological clearance</td>
<td>End of treatment</td>
<td>Relative risk 1.15 (CI 95% 1.06 — 1.26) Based on data from 363 participants in 1 studies.³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision ⁶</td>
<td>We are uncertain whether ivermectin plus doxycycline increases or decreases virological clearance (negative PCR).</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>End of treatment</td>
<td>Relative risk 1.36 (CI 95% 1.12 — 1.67) Based on data from 363 participants in 1 studies.³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision ⁷</td>
<td>We are uncertain whether ivermectin plus doxycycline increases or decreases clinical improvement.</td>
</tr>
<tr>
<td>Clinical deterioration</td>
<td>End of treatment</td>
<td>Relative risk 0.49 (CI 95% 0.28 — 0.86) Based on data from 363 participants in 1 studies.³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision ⁸</td>
<td>We are uncertain whether ivermectin plus doxycycline improves or worsens clinical deterioration.</td>
</tr>
</tbody>
</table>

2. **Risk of Bias: serious.** The large loss to follow up. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, Low number of patients. **Publication bias:** no serious.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Wide confidence intervals, Wide confidence intervals, Only data from one study, due to few events.
6.3.3.5 Nitazoxanide

**Only in research settings**

Do not use nitazoxanide for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Nitazoxanide should still be considered for other evidence-based indications in people who have COVID-19.

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use nitazoxanide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.**

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**Evidence To Decision**

**Benefits and harms**

**General adult population**

As the safety profile for nitazoxanide is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There are additional concerns regarding harms as nitazoxanide has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

General adult population

Very low
Certainty of the evidence is very low for all outcomes due to very serious risk of bias and very serious imprecision (reliance on a single study, low patient numbers and few events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

### Preference and values

#### General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

#### Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of nitazoxanide in pregnancy are unknown.

### Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

#### General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

#### Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

#### People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

#### General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

#### People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

**General adult population**

There is currently limited evidence about the impact of nitazoxanide on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that nitazoxanide should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of nitazoxanide to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical Question/ PICO

- **Population:** Patients with COVID-19
- **Intervention:** Nitazoxanide
- **Comparator:** Standard care

### Summary

There remains significant uncertainty whether nitazoxanide is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from three randomised trials that compared nitazoxanide with placebo in 1363 adults with mild or moderate COVID-19 [296][298][299].

We have found one new study comparing nitazoxanide with placebo (Fontanesi Blum et al. SSRN doi: 10.2139/ssrn.3763773). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Publication status**

Two studies are only available as preprints (Silva et al. posted to medRxiv on 5 March 2021 and Rossignol et al. posted to medRxiv on 20 April 2021) and have therefore not been peer reviewed.

**Study characteristics**

Median age of participants ranged from 37 to 53 years and 28 to 55% were women. Pregnant and breastfeeding women were ineligible. In Rocco et al. patients received nitazoxanide 500 mg oral solution, 20 mg/mL (25 mL) three times a day for 5 days, Rossignol et al. two nitazoxanide 300 mg extended release tablets (600 mg per dose) daily for 5 days, and Silva et al. 500 mg (1 film-coated tablet) every 6 hours (2 g/day) for 14 days.

**What are the main results?**

There were four deaths among the three studies. We are uncertain if nitazoxanide increases or decreases clinical recovery, clinical deterioration, hospitalisation, or the risk of adverse or serious adverse events.

**Our confidence in the results**

Certainty of the evidence is very low for all outcomes due to very serious risk of bias and very serious imprecision (low patient numbers and few events).
For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

In Australia nitazoxanide is only available under the special access scheme for the treatment of giardiasis, cryptosporidiosis and blastocystis. Common side effects and harms associated with nitazoxanide are stomach pain, headache, vomiting and discoloured urine.

**Pregnant and breastfeeding women**

Limited information suggests that nitazoxanide is not associated with an increased risk of congenital abnormalities.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td>Standard care</td>
<td>Nitazoxanide</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether nitazoxanide impacts death (4 events).</td>
</tr>
<tr>
<td>End of treatment</td>
<td>Relative risk 1.46 (CI 95% 0.2 — 10.92) Based on data from 1,363 participants in 3 studies.</td>
<td>9 Critical</td>
<td>5 per 1000</td>
<td>12 per 1000 Difference: 7 fewer per 1000 (CI 95% 11 fewer — 6 more)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.38 (CI 95% 0.1 — 1.5) Based on data from 1,327 participants in 2 studies. (Randomized controlled)</td>
<td>6 Important</td>
<td>188 per 1000</td>
<td>204 per 1000 Difference: 16 fewer per 1000 (CI 95% 53 fewer — 29 more)</td>
<td></td>
</tr>
<tr>
<td>End of follow up</td>
<td></td>
<td></td>
<td>123 per 1000</td>
<td>141 per 1000 Difference: 18 fewer per 1000 (CI 95% 36 fewer — 5 more)</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 0.92 (CI 95% 0.74 — 1.14) Based on data from 1,327 participants in 2 studies. (Randomized controlled)</td>
<td>6 Important</td>
<td>188 per 1000</td>
<td>204 per 1000 Difference: 16 fewer per 1000 (CI 95% 53 fewer — 29 more)</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to an adverse event</td>
<td>Relative risk 6.12 (CI 95% 0.74 — 50.4) Based on data from 392 participants in 1 studies. (Randomized controlled)</td>
<td>6 Important</td>
<td>6.12 per 1000</td>
<td>1.46 per 1000 Difference: 5.4 fewer per 1000 (CI 95% 12 fewer — 1 more)</td>
<td></td>
</tr>
<tr>
<td>End of follow up</td>
<td></td>
<td></td>
<td>123 per 1000</td>
<td>141 per 1000 Difference: 18 fewer per 1000 (CI 95% 36 fewer — 5 more)</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>Relative risk 0.21 (CI 95% 0.02 — 1.8) Based on data from 379 participants in 1 studies.</td>
<td>6 Important</td>
<td>0.21 per 1000</td>
<td>0.38 per 1000 Difference: 0.17 fewer per 1000 (CI 95% 0.30 fewer — 0.05 more)</td>
<td></td>
</tr>
<tr>
<td>End of follow up</td>
<td></td>
<td></td>
<td>123 per 1000</td>
<td>141 per 1000 Difference: 18 fewer per 1000 (CI 95% 36 fewer — 5 more)</td>
<td></td>
</tr>
</tbody>
</table>
### 6.3.4 Antihypertensives

#### 6.3.4.1 Telmisartan

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Nitazoxanide</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical deterioration End of follow-up</td>
<td>Relative risk 0.15 (CI 95% 0.02 – 1.22) Based on data from 379 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether nitazoxanide increases or decreases clinical deterioration (8 events).</td>
</tr>
<tr>
<td>Clinical recovery End of follow-up</td>
<td>Relative risk 0.94 (CI 95% 0.83 – 1.07) Based on data from 392 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether nitazoxanide increases or decreases clinical recovery (281 events).</td>
</tr>
</tbody>
</table>

3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision: serious.** due to few events.
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision: serious.** Wide confidence intervals.
7. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
11. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting. **Imprecision: very serious.** Low number of patients, Only data from one study.

### 6.3.4 Antihypertensives
Only in research settings

Do not use telmisartan for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Telmisartan should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use telmisartan to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

General adult population
Although there are no significant harms associated with telmisartan, there is uncertainty around the benefits and harms for patients with COVID-19.

Certainty of the Evidence

General adult population
Certainty of the evidence is low for all outcomes due to serious imprecision (low patient numbers and the reliance on a single study).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.
Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of telmisartan on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that telmisartan should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of telmisartan for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Telmisartan</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary
There remains significant uncertainty whether telmisartan is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared telmisartan with standard care in 78 adults hospitalised with confirmed COVID-19 [328].
Publication status
The study is only available as a preprint paper (posted to medRxiv on 13 August 2020) and has therefore not been peer reviewed.

Study characteristics
Median age of participants was 62 years and 38% were women. Pregnant and breastfeeding women were ineligible.

What are the main results?
For the outcomes of death, invasive mechanical ventilation and admission to intensive care, there were too few events (six deaths, four who required invasive ventilation and nine who were admitted to ICU) to determine whether telmisartan makes a difference. Telmisartan may increase the likelihood of patients being discharged from hospital and may reduce the time to discharge. No adverse events related to telmisartan were reported.

Our confidence in the results
Certainty of the evidence is low for all outcomes due to very serious imprecision (low patient numbers and reliance on a single study).

Additional information
According to the Therapeutic Goods Administration, common adverse effects related to telmisartan use include pain, fatigue, headache and upper respiratory tract infections. However, the incidence of these adverse effects was equivalent in patients receiving placebo [329].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>15 days after commencing</td>
<td>Relative risk 0.95 (CI 95% 0.14 — 6.41) Based on data from 78 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>53</td>
<td>50</td>
<td>Low Due to very serious imprecision ²</td>
<td>There were too few who had died by day 15 to determine whether telmisartan makes a difference (4 events).</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 3 fewer per 1000 (CI 95% 46 fewer — 287 more)</td>
<td>53</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>30 days after commencing</td>
<td>Relative risk 0.48 (CI 95% 0.09 — 2.44) Based on data from 78 participants in 1 studies. ² (Randomized controlled)</td>
<td>105</td>
<td>50</td>
<td>Low Due to very serious imprecision ³</td>
<td>There were too few who had died by day 30 to determine whether telmisartan makes a difference (6 events).</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 55 fewer per 1000 (CI 95% 96 fewer — 151 more)</td>
<td>105</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical</td>
<td>15 days after commencing</td>
<td>Relative risk 0.32 (CI 95% 0.03 — 2.91) Based on data from 78 participants in 1 studies. ³ (Randomized controlled)</td>
<td>79</td>
<td>25</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>There were too few who required mechanical ventilation at day 15 to determine whether telmisartan makes a difference (4 events).</td>
</tr>
<tr>
<td>mechanical ventilation</td>
<td>treatment</td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 54 fewer per 1000 (CI 95% 77 fewer — 151 more)</td>
<td>79</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical</td>
<td></td>
<td>Relative risk 0.32 (CI 95% 0.03 — 2.91)</td>
<td>79</td>
<td>25</td>
<td>Low Due to very</td>
<td>There were too few who required invasive</td>
</tr>
<tr>
<td>mechanical</td>
<td></td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Outcome

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Telmisartan</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ventilation</strong></td>
<td>Based on data from 78 participants in 1 studies.</td>
<td>per 1000</td>
<td>per 1000</td>
<td>serious imprecision</td>
<td>mechanical ventilation at day 30 to determine whether telmisartan makes a difference (4 events).</td>
</tr>
<tr>
<td>30 days after commencing treatment</td>
<td><strong>9 Critical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>Relative risk 0.76 (CI 95% 0.22 – 2.62) Based on data from 78 participants in 1 studies.</td>
<td>132 per 1000</td>
<td>100 per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>There were too few who were admitted to intensive care to determine whether telmisartan makes a difference (9 events).</td>
</tr>
<tr>
<td>30 days after commencing treatment</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Relative risk 1.43 (CI 95% 1.01 – 2.02) Based on data from 68 participants in 1 studies.</td>
<td>563 per 1000</td>
<td>805 per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>Telmisartan may increase discharge from hospital (47 events).</td>
</tr>
<tr>
<td>15 days after commencing treatment</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to discharge from hospital</td>
<td>Based on data from: 78 participants in 1 studies.</td>
<td>15 (Median)</td>
<td>9 (Median)</td>
<td>Low Due to very serious imprecision</td>
<td>Telmisartan may decrease time to discharge from hospital.</td>
</tr>
<tr>
<td>Days</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision: very serious.** Low number of patients, Only data from one study.
4. **Imprecision: very serious.** Low number of patients, Only data from one study.
6. **Imprecision: very serious.** Low number of patients, Only data from one study.
8. **Imprecision: very serious.** Low number of patients, Only data from one study.
10. **Imprecision: very serious.** Low number of patients, Only data from one study.
12. **Imprecision: very serious.** Low number of patients, Only data from one study.
13. Systematic review [330]. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: very serious.** Low number of patients, Only data from one study.
Clinical Question/ PICO

**Population:** Special populations with COVID-19  
**Intervention:** Telmisartan  
**Comparator:** Standard care

**Summary**
There remains significant uncertainty whether telmisartan is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared telmisartan with standard care in 78 adults hospitalised with confirmed COVID-19 [328].

**Publication status**
The study is only available as a preprint paper (posted to medRxiv on 13 August 2020) and has therefore not been peer reviewed.

**Study characteristics**
Median age of participants was 62 years and 38% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
For the outcomes of death, invasive mechanical ventilation and admission to intensive care, there were too few events (six deaths, four who required invasive ventilation and nine who were admitted to ICU) to determine whether telmisartan makes a difference. Telmisartan may increase the likelihood of patients being discharged from hospital and may reduce the time to discharge. No adverse events related to telmisartan were reported.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to very serious imprecision (low patient numbers and reliance on a single study) and serious indirectness (limited inclusion of these populations).

**Additional information**
According to the Therapeutic Goods Administration, common adverse effects related to telmisartan use include pain, fatigue, headache and upper respiratory tract infections. However, the incidence of these adverse effects was equivalent in patients receiving placebo [329].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>15 days after commencing treatment</td>
<td>Relative risk 0.95 (CI 95% 0.14 – 6.41) Based on data from 78 participants in 1 studies.</td>
<td></td>
<td>53 per 1000</td>
<td>50 per 1000</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Standard care</td>
<td>Telmisartan</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>30 days after commencing treatment</td>
<td>Relative risk 0.48 (CI 95% 0.09 – 2.44) Based on data from 78 participants in 1 studies.</td>
<td></td>
<td>40 of 734</td>
<td>40 of 734</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<tr>
<td>Mechanical ventilation</td>
<td>15 days after commencing treatment</td>
<td>Relative risk 0.32 (CI 95% 0.03 — 2.91) Based on data from 78 participants in 1 studies. 7 (Randomized controlled)</td>
<td>Standard care</td>
<td>Telmisartan</td>
<td>Very low Due to very serious imprecision and serious indirectness 6</td>
</tr>
<tr>
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<td></td>
<td>Very low Due to very serious imprecision and serious indirectness 8</td>
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<td></td>
<td></td>
<td>Very low Due to very serious imprecision and serious indirectness 12</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>30 days after commencing treatment</td>
<td>Relative risk 0.76 (CI 95% 0.22 — 2.62) Based on data from 78 participants in 1 studies. 9 (Randomized controlled)</td>
<td>Standard care</td>
<td></td>
<td>Very low Due to very serious imprecision and serious indirectness 10</td>
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<td></td>
<td></td>
<td></td>
<td>Very low Due to very serious imprecision and serious indirectness 14</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>15 days after commencing treatment</td>
<td>Relative risk 1.43 (CI 95% 1.01 — 2.02) Based on data from 68 participants in 1 studies. 11 (Randomized controlled)</td>
<td>Standard care</td>
<td></td>
<td>Very low Due to very serious imprecision and serious indirectness 12</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Very low Due to very serious imprecision and serious indirectness 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to discharge from hospital</td>
<td>Days</td>
<td>Based on data from: 78 participants in 1 studies. 13 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to very serious imprecision and serious indirectness 14</td>
</tr>
</tbody>
</table>

2. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients. Only data from one study.
4. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients. Only data from one study.
6. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients. Only data from one study.

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6.3.5 Antithrombotic, antiplatelets and related therapies

6.3.5.1 Sulodexide

**Only in research settings**

Do not use sulodexide for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Sulodexide should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sulodexide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

**Benefits and harms**

There is uncertainty around the benefits and harms associated with the use of sulodexide in patients with COVID-19. As of 16 February 2021, sulodexide is not approved for use in Australia.

**Certainty of the Evidence**

Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single study, wide confidence intervals and few events for the outcomes of death, invasive mechanical ventilation and discontinuation due to adverse events).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).
### Preference and values

#### General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

### Resources and other considerations

#### General adult population
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

#### General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

#### Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

#### People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

#### General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

#### People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

#### General adult population
There is currently limited evidence about the impact of sulodexide on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that sulodexide should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

#### Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living...
with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of sulodexide for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

| Population: | Sulodexide for COVID-19 |
| Intervent: | Sulodexide |
| Comparator: | Placebo |

Summary
There remains significant uncertainty whether sulodexide is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared sulodexide with placebo in 243 adult outpatients with mild COVID-19, who were at high risk of severe clinical progression due to chronic comorbidities [327].

Study characteristics
Mean age of participants was 55 years and the proportion of women was 53%. Of note, the minimum age at enrolment was 40 years. Patients received either sulodexide 500 mg twice daily (4 x 250 mg capsules) or placebo equivalent for 3 weeks. Pregnant and breastfeeding women were ineligible.

What are the main results?
It is unclear whether sulodexide increases or decreases incidence of death, requirement of invasive mechanical ventilation, supplemental oxygen or duration of supplemental oxygen, number of patients who require hospitalisation and duration of hospitalisation, adverse events, or number of patients who discontinued due to adverse events.

Our confidence in the results
Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single study, wide confidence intervals and few events for the outcomes of death, invasive mechanical ventilation and discontinuation due to adverse events).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As the safety profile for sulodexide is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19. As of 16 February 2021, sulodexide is not approved for use in Australia.

Pregnant and breastfeeding women
There are additional concerns regarding harms, as sulodexide has not been sufficiently tested in this population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.41 (CI 95% 0.11 — 1.55) Based on data from 243 participants in 1 studies. 1 (Randomized controlled)</td>
<td>Placebo</td>
<td>Sulodexide</td>
<td>Very low Due to very serious imprecision and serious risk of bias 2</td>
<td>We are uncertain whether sulodexide impacts death (10 events).</td>
</tr>
<tr>
<td>Within 21 days of commencing treatment</td>
<td>59 per 1000</td>
<td>24 per 1000</td>
<td>35 fewer per 1000 (CI 95% 53 fewer — 32 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of Evidence</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>---------------------------------</td>
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</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Within 21 days of commencing treatment</td>
<td>Relative risk 0.48  (CI 95% 0.12 — 1.87) Based on data from 243 participants in 1 studies.</td>
<td>50 per 1000</td>
<td>24 per 1000</td>
<td>Very low Due to very serious imprecision and serious risk of bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 26 fewer per 1000 (CI 95% 44 fewer — 44 more)</td>
<td></td>
<td></td>
<td>We are uncertain whether sulodexide increases or decreases need for invasive mechanical ventilation (9 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>Within 21 days of commencing treatment</td>
<td>Relative risk 0.71  (CI 95% 0.5 — 1) Based on data from 243 participants in 1 studies.</td>
<td>420 per 1000</td>
<td>298 per 1000</td>
<td>Very low Due to very serious imprecision and serious risk of bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 122 fewer per 1000 (CI 95% 210 fewer — 0 fewer)</td>
<td></td>
<td></td>
<td>We are uncertain whether sulodexide increases or decreases need for supplemental oxygen (87 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 Important</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>Within 21 days of commencing treatment</td>
<td>Relative risk 0.6  (CI 95% 0.38 — 0.97) Based on data from 243 participants in 1 studies.</td>
<td>294 per 1000</td>
<td>176 per 1000</td>
<td>Very low Due to very serious imprecision and serious risk of bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 118 fewer per 1000 (CI 95% 182 fewer — 9 fewer)</td>
<td></td>
<td></td>
<td>We are uncertain whether sulodexide increases or decreases need for hospitalisation (57 events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 Important</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Within 21 days of commencing treatment</td>
<td>Relative risk 1.08  (CI 95% 0.93 — 1.26) Based on data from 243 participants in 1 studies.</td>
<td>714 per 1000</td>
<td>771 per 1000</td>
<td>Very low Due to very serious imprecision and serious risk of bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 57 more per 1000 (CI 95% 50 fewer — 186 more)</td>
<td></td>
<td></td>
<td>We are uncertain whether sulodexide increases or decreases adverse events (181 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 Important</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>Within 21 days of commencing treatment</td>
<td>Relative risk 1.28  (CI 95% 0.46 — 3.58) Based on data from 243 participants in 1 studies.</td>
<td>50 per 1000</td>
<td>64 per 1000</td>
<td>Very low Due to very serious imprecision and serious risk of bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 14 more per 1000 (CI 95% 27 fewer — 129 more)</td>
<td></td>
<td></td>
<td>We are uncertain whether sulodexide increases or decreases discontinuation due to adverse events (14 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 Important</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of supplemental oxygen</td>
<td>Days</td>
<td>Based on data from: 243 participants in 1 studies.</td>
<td>11.5 (Mean)</td>
<td>9 (Mean)</td>
<td>Very low Due to very serious imprecision and serious risk of bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: MD 2.5 lower (CI 95% 4.64 lower — 0.36 lower)</td>
<td></td>
<td></td>
<td>We are uncertain whether sulodexide increases or decreases duration of supplemental oxygen.</td>
</tr>
</tbody>
</table>

Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce
### 6.3.6 Antivirals

#### 6.3.6.1 Baloxavir marboxil

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of hospitalisation Days</strong></td>
<td>Based on data from: 243 participants in 1 studies.</td>
<td><strong>7.8 (Mean)</strong></td>
<td><strong>6.2 (Mean)</strong></td>
<td>Very low Due to very serious imprecision and serious risk of bias</td>
<td>We are uncertain whether sulodexide increases or decreases duration of hospitalisation.</td>
</tr>
<tr>
<td><strong>6 Important</strong></td>
<td></td>
<td><strong>Difference:</strong> MD 1.6 lower (CI 95% 2.68 lower — 0.52 lower)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, due to few events.
4. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, due to few events.
6. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Only data from one study, Low number of patients.
8. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
10. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
12. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
14. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
16. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.

**6.3.6.1 Baloxavir marboxil**
Evidence To Decision

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as baloxavir marboxil has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of baloxavir marboxil in pregnancy are unknown.
### Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

**General adult population**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

**General adult population, children and adolescents, pregnant and breastfeeding women**

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

**General adult population**

There is currently limited evidence about the impact of baloxavir marboxil on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that baloxavir marboxil should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of baloxavir marboxil to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical Question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Baloxavir marboxil  
**Comparator:** Standard care

**Summary**
There remains significant uncertainty whether baloxavir marboxil is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared baloxavir marboxil with standard care in 20 adults hospitalised with COVID-19 [195].

**Study characteristics**
Mean age of participants was 50 years and 30% were women. It is unclear whether pregnant and breastfeeding women were eligible. Patients concomitantly used lopinavir-ritonavir, darunavir-cobicistat and/or arbidol.

**What are the main results?**
For the critical outcomes of death and mechanical invasive ventilation there were too few events (one death and one requiring ventilation) to determine whether baloxavir marboxil makes a difference. We are uncertain whether baloxavir marboxil increases or decreases respiratory support or likelihood of clinical improvement after 14 days. No data were reported on adverse or serious adverse events.

**Our confidence in the results**
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding and very serious imprecision due to low patient numbers, few observed events and reliance on a single study.

**Additional information**
The Therapeutic Goods Administration highlights several mild side effects associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache. In addition, post-marketing surveillance has identified cases of anaphylactic reactions, angioedema, vomiting and other gastrointestinal and skin/subcutaneous tissue disorders [194].

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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
</table>
| **Mortality**  
During treatment (14 days)  | Based on data from 20 participants in 1 studies. ¹ | Standard care | Baloxavir marboxil | Very low  
Due to serious risk of bias and very serious imprecision ² | There were no deaths in the study. |
| **Respiratory support and ARDS**  
During treatment (14 days)  | Odds Ratio 2.25  
(CI 95% 0.38 – 13.47)  
Based on data from 20 participants in 1 studies. ³ (Randomized controlled) | Standard care | Baloxavir marboxil | Very low  
We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (10 events). |
| **Invasive mechanical ventilation or ECMO** | Odds Ratio 3.32  
(CI 95% 0.12 – 91.6)  
Based on data from 20 participants in 1 | Standard care | Baloxavir marboxil | Very low  
Due to serious risk of bias and very serious | There were too few who required invasive mechanical ventilation or ECMO to determine |
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Baloxavir marboxil</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment (14 days)</td>
<td>studies. ¹ (Randomized controlled)</td>
<td></td>
<td></td>
<td>imprecision ⁵</td>
<td>whether baloxavir marboxil makes a difference (1 event).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data for number of patients experiencing one or more events were not reported.</td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data for number of patients experiencing one or more events were not reported.</td>
</tr>
<tr>
<td>Adverse events</td>
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<tr>
<td>During treatment (14 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Odds Ratio 1.5 (CI 95% 0.26 – 8.82) Based on data from 20 participants in 1 studies. ⁶ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (11 events).</td>
</tr>
<tr>
<td>End of treatment (14 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. **Risk of Bias:** serious. **Imprecision:** very serious. Low number of patients, Only data from one study.
5. **Risk of Bias:** serious. **Imprecision:** very serious. Low number of patients, Only data from one study.
7. Systematic review [192] with included studies: [193]. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Risk of Bias:** serious. **Imprecision:** very serious. Low number of patients, Only data from one study.

**Clinical Question/ PICO**

**Population:** Special populations with COVID-19
Summary
There remains significant uncertainty whether baloxavir marboxil is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared baloxavir marboxil with standard care in 20 adults hospitalised with COVID-19 [195].

Study characteristics
Mean age of participants was 50 years and 30% were women. It is unclear whether pregnant and breastfeeding women were eligible. Patients concomitantly used lopinavir-ritonavir, darunavir-cobicistat and/or arbidol.

What are the main results?
For the critical outcomes of death and mechanical ventilation there were too few events (one death and one requiring ventilation) to determine whether baloxavir marboxil makes a difference. We are uncertain whether baloxavir marboxil increases or decreases respiratory support or likelihood of clinical improvement after 14 days. No data were reported on adverse or serious adverse events.

Our confidence in the results
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, serious indirectness due to limited inclusion of these populations, and very serious imprecision due to low patient numbers, few observed events and reliance on a single study.

Additional information
The Therapeutic Goods Administration highlights several mild side effects associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache. In addition, post-marketing surveillance has identified cases of anaphylactic reactions, angioedema, vomiting and other gastrointestinal and skin/subcutaneous tissue disorders [194].

Children and adolescents
There is insufficient safety data on the use of baloxavir marboxil in children or adolescents for other indications.

Pregnant and breastfeeding women
No studies pertained to the safety of baloxavir marboxil (for any indication) when used in pregnant or breastfeeding women.

### Outcome Timeframe
<table>
<thead>
<tr>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Standard care</td>
<td>Baloxavir marboxil</td>
<td>Very low Due to serious risk of bias, serious indirectness and very serious imprecision</td>
<td>There were no deaths in the study.</td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td>Based on data from 20 participants in 1 studies.</td>
<td></td>
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</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory support and ARDS</td>
<td>Standard care</td>
<td>Baloxavir marboxil</td>
<td></td>
<td>We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (10 events).</td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td>Odds Ratio 2.25 (CI 95% 0.38 – 13.47) Based on data from 20 participants in 1 studies.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

[1] [195]
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Invasive mechanical ventilation or ECMO During treatment (14 days)</td>
<td>Odds Ratio 3.32 (CI 95% 0.12 – 91.6) Based on data from 20 participants in 1 studies.</td>
<td>Standard care</td>
<td>Baloxavir marboxil</td>
<td>Very low Due to serious risk of bias, serious indirectness and very serious imprecision</td>
<td>There were too few who required mechanical ventilation or ECMO (1 event) to determine whether baloxavir marboxil makes a difference.</td>
</tr>
<tr>
<td>Serious adverse events During treatment (14 days)</td>
<td>6</td>
<td>Control arm of reference used for intervention.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td>7</td>
<td>Control arm of reference used for intervention.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical improvement End of treatment (14 days)</td>
<td>Odds Ratio 1.5 (CI 95% 0.26 – 8.82) Based on data from 20 participants in 1 studies.</td>
<td>Control arm of reference used for intervention.</td>
<td></td>
<td>Very low Due to serious risk of bias, serious indirectness and very serious imprecision</td>
<td>We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (11 events).</td>
</tr>
</tbody>
</table>

3. **Risk of Bias:** serious. **Indirectness:** serious. **Imprecision:** very serious. Low number of patients, Only data from one study.
5. **Risk of Bias:** serious. **Indirectness:** serious. **Imprecision:** very serious. Low number of patients, Only data from one study.
7. Systematic review [192] with included studies: [193]. **Baseline/comparator:** Control arm of reference used for intervention.
6.3.6.2 Darunavir-cobicistat

Only in research settings

Do not use darunavir-cobicistat for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

**Darunavir-cobicistat should still be considered for other evidence-based indications in people who have COVID-19.**

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use darunavir-cobicistat to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.**

**This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.**

Evidence To Decision

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known short-term harms associated with darunavir-cobicistat including severe skin reactions. There are several known and potential interactions with drugs that inhibit CYP3A4 and anti-arrhythmic drugs.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

The benefits and harms associated with darunavir-cobicistat in pregnant women and young children with COVID-19 are not well established. Darunavir plus cobicistat is not recommended for the treatment of HIV in pregnant women because of inadequate safety data for cobicistat. Caution should be taken when prescribing darunavir-cobicistat to children, adolescents or elderly patients.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence for each outcome is very low due to serious risk of bias and very serious imprecision (low number of patients and/or observed events and reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.
Rationale
General adult population

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of darunavir-cobicistat in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.
There is currently limited evidence about the impact of darunavir-cobicistat on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that darunavir-cobicistat should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of darunavir-cobicistat to treat COVID-19 in these populations should be avoided until evidence becomes available.

**Clinical Question/ PICO**

| Population: | Darunavir-cobicistat for COVID-19 |
| Intervention: | Darunavir-cobicistat |
| Comparator: | Standard care |

**Summary**
There remains significant uncertainty whether darunavir-cobicistat is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared darunavir-cobicistat with standard care in 30 adults hospitalised with mild-to-moderate symptoms of laboratory-confirmed COVID-19 [230].

**Study characteristics**
Mean age was 47 years and 40% were women. Patients considered unlikely to complete the study (e.g. severely or critically ill) or deemed not suitable by the investigators were excluded. It is unlikely that pregnant and breastfeeding women were eligible.

**What are the main results?**
There were no deaths and only one patient progressed to critical illness. We are uncertain whether darunavir-cobicistat makes a difference to viral clearance (days 3, 5 or 7) or to the likelihood of patients experiencing adverse events.

**Our confidence in the results**
Certainty of the evidence for viral clearance and adverse events is very low. This judgement is based on very serious imprecision (low patient numbers, few observed events and reliance on a single study) and serious risk of bias (patients, personnel and outcome assessors not blinded).

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Darunavir-cobicistat</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Based on data from 30 participants in 1 studies.</td>
<td>Standard care</td>
<td>Darunavir-cobicistat</td>
<td>2</td>
<td>There were no deaths in the study.</td>
</tr>
<tr>
<td>14 days after commencing treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression to critical illness</td>
<td>Based on data from 30 participants in 1</td>
<td></td>
<td></td>
<td>4</td>
<td>There were too few who experienced progression to critical illness to determine</td>
</tr>
<tr>
<td>14 days after commencing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>Within 14 days of commencing treatment</td>
<td>Odds Ratio 1.31 (CI 95% 0.31 – 5.48) Based on data from 30 participants in 1 studies.</td>
<td>Control arm of reference used for intervention.</td>
<td>Darunavir-cobicistat</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (15 events).</td>
</tr>
<tr>
<td>Viral clearance</td>
<td>Day 7 of treatment</td>
<td>Relative risk 0.78 (CI 95% 0.39 – 1.54) Based on data from 30 participants in 1 studies.</td>
<td>Control arm of reference used for intervention.</td>
<td>Darunavir-cobicistat</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 7 (16 events).</td>
</tr>
<tr>
<td>Viral clearance</td>
<td>Day 5 of treatment</td>
<td>Odds Ratio 1.45 (CI 95% 0.26 – 8.01) Based on data from 30 participants in 1 studies.</td>
<td>Control arm of reference used for intervention.</td>
<td>Darunavir-cobicistat</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 5 (5 events).</td>
</tr>
<tr>
<td>Viral clearance</td>
<td>Day 3 of treatment</td>
<td>Odds Ratio 1 (CI 95% 0.17 – 5.98) Based on data from 30 participants in 1 studies.</td>
<td>Control arm of reference used for intervention.</td>
<td>Darunavir-cobicistat</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 3 (6 events).</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study, due to no events. **Publication bias:** no serious.
4. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study, due to no events. **Publication bias:** no serious.
5. Primary study[230]. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study, due to no events. **Publication bias:** no serious.
8. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study, due to no events. **Publication bias:** no serious.
patients, Only data from one study.
10. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study. **Publication bias:** no serious.
12. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study. **Publication bias:** no serious.

**Clinical Question/ PICO**

<table>
<thead>
<tr>
<th>Population</th>
<th>Special populations with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Darunavir-cobicistat</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

**Summary**

There remains significant uncertainty whether darunavir-cobicistat is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from a single randomised trial that compared darunavir-cobicistat with standard care in 30 adults hospitalised with mild-to-moderate symptoms of laboratory-confirmed COVID-19 [230].

**Study characteristics**

Mean age was 47 years and 40% were women. Patients considered unlikely to complete the study (e.g. severely or critically ill) or deemed not suitable by the investigators were excluded. It is unlikely that pregnant and breastfeeding women were eligible.

**What are the main results?**

There were no deaths and only one patient progressed to critical illness. We are uncertain whether darunavir-cobicistat makes a difference to viral clearance (days 3, 5 or 7) or to the likelihood of patients experiencing adverse events.

**Our confidence in the results**

Certainty of the evidence for viral clearance and adverse events is very low. This judgement is based on very serious imprecision (low patient numbers, few observed events and reliance on a single study), serious indirectness (limited inclusion of these populations) and serious risk of bias (patients, personnel and outcome assessors not blinded).

**Children and adolescents**

Paediatricians have limited experience of darunavir-cobicistat in children and adolescents for other indications. To date, no specific information on its benefits or harms for children and adolescents has been collected for treating COVID-19 in this population.

**Pregnant and breastfeeding women**

Darunavir plus cobicistat is not recommended for the treatment of HIV in pregnant women because of inadequate safety data for cobicistat [231].
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>14 days after commencing treatment</td>
<td>Based on data from 30 participants in 1 studies. 2 (Randomized controlled)</td>
<td>Standard care</td>
<td>Darunavir-cobicistat</td>
<td>Very low</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (15 events).</td>
</tr>
<tr>
<td>Progression to critical illness</td>
<td>14 days after commencing treatment</td>
<td>Based on data from 30 participants in 1 studies. 2 (Randomized controlled)</td>
<td></td>
<td></td>
<td>There were too few who experienced progression to critical illness to determine whether darunavir-cobicistat makes a difference (1 event).</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Within 14 days of commencing treatment</td>
<td>Odds Ratio 1.31 (CI 95% 0.31 — 5.48) Based on data from 30 participants in 1 studies. 2 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (15 events).</td>
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<td></td>
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</tr>
<tr>
<td>Viral clearance</td>
<td>Day 3 of treatment</td>
<td>Odds Ratio 1 (CI 95% 0.17 — 5.98) Based on data from 30 participants in 1 studies. 2 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 3 (6 events).</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for
enitamium should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use enitamium to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

General adult population
As the safety profile for enitamium is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people
living with frailty or cognitive impairment
There are additional concerns regarding harms as enisamium has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

Certainty of the Evidence

General adult population
Certainty of the evidence is very low for time to recovery due to very serious risk of bias (issues with randomisation, blinding and loss to follow-up) and serious imprecision (reliance on a single study, wide confidence intervals and few events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Preference and values

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of enisamium in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.
Rationale

General adult population
There is currently limited evidence about the impact of enisamium on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that enisamium should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of enisamium to treat COVID-19 in these populations should be avoided until evidence becomes available.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Clinical Question/ PICO

| Population: | Patients with COVID-19 |
| Intervention: | Enisamium |
| Comparator: | Placebo |

Summary
There remains significant uncertainty whether enisamium is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared enisamium with standard care in 373 adults with moderate COVID-19 [235].

Publication status
The included study is only available as a preprint (posted to medRxiv on 21 January 2021) and has therefore not been peer reviewed.

Study characteristics
Median age of participants was not reported, nor was the proportion of female patients. Patients received either 500 mg enisamium iodide or matching placebo 4 times daily every 6 hours for 7 days. Pregnant and breastfeeding women were ineligible.

What are the main results?
The study primarily focused on pharmacokinetic analyses and the only reported clinical outcome of relevance was time to recovery, in which we are uncertain whether enisamium makes a difference.

Our confidence in the results
Certainty of the evidence is very low for time to recovery due to very serious risk of bias (issues with
randomisation, blinding and loss to follow-up) and serious imprecision (reliance on a single study, wide confidence intervals and few events).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Enisamium is not approved for use in Australia and, as of 16 March 2021, there are no reliable safety data to inform treatment.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to recovery</td>
<td>Lower better</td>
<td>Placebo</td>
<td>Enisamium</td>
<td>Very low</td>
<td>We are uncertain whether enisamium increases or decreases time to recovery.</td>
</tr>
<tr>
<td>Days</td>
<td>Based on data from:</td>
<td></td>
<td></td>
<td>Due to very serious risk of bias and serious imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>373 participants in 1 studies.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. **Risk of Bias: very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision: serious.** Only data from one study.

### 6.3.6.4 Favipiravir

*Only in research settings*

Do not use favipiravir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

**Favipiravir should still be considered for other evidence-based indications in people who have COVID-19.**

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use favipiravir to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.**

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**Evidence To Decision**

**Benefits and harms**

**General adult population**
As the safety profile for favipiravir is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.
Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There are additional concerns regarding harms as favipiravir has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

Certainty of the Evidence

General adult population
Certainty of the evidence for all-cause mortality, respiratory failure or ARDS, serious adverse events, adverse events and negative PCR is low based on very serious imprecision due to low patient numbers and few events. Certainty for the remaining outcomes is very low based on serious risk of bias due to lack of blinding and very serious imprecision due to low patient numbers, wide confidence intervals, few events and/or reliance on a single study.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of favipiravir in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment).
Rationale

General adult population
There is currently limited evidence about the impact of favipiravir on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that favipiravir should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Acceptability

General adult population
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of favipiravir on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that favipiravir should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of favipiravir to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Favipiravir
Comparator: Standard care

Summary
There remains significant uncertainty whether favipiravir is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from four randomised trials that compared favipiravir with standard care in 395 adults hospitalised with COVID-19 [195][236][240][241].

We have found two new studies comparing favipiravir with standard care or placebo (Balykova et al. Infectious Diseases doi: 10.33029/2305-3496-2020-9-3-16-29 and Shinkai et al. Infect Dis Ther doi: 10.1007/s40121-021-00517-4). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.
Study characteristics
Mean age of participants ranged from 42 to 58 years and 43 to 56% were women (with the exception of Udwadia et al. in which 27% were women). Pregnant and breastfeeding women were ineligible.

What are the main results?
For the critical outcomes of death, respiratory failure and mechanical ventilation there were too few events (three deaths, eight experiencing respiratory failure and none requiring ventilation) to determine whether favipiravir makes a difference. We are uncertain whether favipiravir increases or decreases adverse or serious adverse events, discontinuation due to adverse events, clinical improvement, negative PCR and discharge from hospital.

Our confidence in the results
Certainty of the evidence for mortality, respiratory failure or ARDS, adverse or serious adverse events, and negative PCR is low based on very serious imprecision due to low patient numbers and few events. Certainty for the remaining outcomes is very low based on serious risk of bias due to lack of blinding and very serious imprecision due to low patient numbers, wide confidence intervals, few events and/or reliance on a single study.

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As of 3 December 2020, favipiravir (Avigan) is not approved for use in Australia. The safety profile for favipiravir is incompletely characterised in humans.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.34 (CI 95% 0.01 – 8.27) Based on data from 316 participants in 2 studies. ① (Randomized controlled)</td>
<td>Standard care</td>
<td>Favipiravir</td>
<td>Low Due to very serious imprecision ①</td>
<td>We are uncertain whether favipiravir impacts death (1 event).</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>8 per 1000 Difference: 5 fewer per 1000 ( CI 95% 8 fewer – 58 more )</td>
<td>3 per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 2.56 (CI 95% 0.13 – 50.95) Based on data from 79 participants in 2 studies. ② (Randomized controlled)</td>
<td>Standard care</td>
<td>Favipiravir</td>
<td>Low Due to very serious imprecision ②</td>
<td>There were too few who died to determine whether favipiravir makes a difference (2 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>9 Critical</td>
<td>3 per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Relative risk 1.11 (CI 95% 0.39 – 3.19) Based on data from 19 participants in 1 studies. ③ (Randomized controlled)</td>
<td>Standard care</td>
<td>Favipiravir</td>
<td>Very low Due to serious risk of bias and very serious imprecision ③</td>
<td>There were too few who experienced respiratory failure or ARDS to determine whether favipiravir makes a difference (8 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>9 Critical</td>
<td>3 per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Based on data from 19 participants in 1 studies. ④ (Randomized controlled)</td>
<td>Standard care</td>
<td>Favipiravir</td>
<td></td>
<td>8 No patients required mechanical ventilation.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Favipiravir</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>--------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.38 (CI 95% 0.24 – 8.08) Based on data from 371 participants in 3 studies.</td>
<td></td>
<td>7 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.92 (CI 95% 0.83 – 4.43) Based on data from 371 participants in 3 studies.</td>
<td></td>
<td>10 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td><strong>Discontinuation due to adverse events</strong></td>
<td>End of treatment</td>
<td>Relative risk 1.24 (CI 95% 0.25 – 6.25) Based on data from 376 participants in 3 studies.</td>
<td></td>
<td>563 per 1000</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.11 (CI 95% 0.47 – 2.6) Based on data from 19 participants in 1 studies.</td>
<td></td>
<td>293 per 1000</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td><strong>Discharge from hospital</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.05 (CI 95% 0.97 – 1.13) Based on data from 188 participants in 2 studies.</td>
<td></td>
<td>882 per 1000</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td><strong>Negative PCR</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.09 (CI 95% 1.01 – 1.18) Based on data from 315 participants in 2 studies.</td>
<td></td>
<td>809 per 1000</td>
<td>Low Due to serious risk of bias and very serious imprecision</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** no serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. The direction of the effect is not consistent between the included studies. **Imprecision:** very serious. Low number of patients, Wide confidence intervals.


4. **Imprecision:** very serious. Low number of patients, Only data from one study, few events.


6. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** very serious. Low number of patients, Only data from one study, few events.


8. **Imprecision:** very serious. Low number of patients, Only data from one study.


10. **Risk of Bias:** no serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Wide confidence intervals, Low number of patients.


12. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** serious. Wide confidence intervals, Low number of patients.


14. **Risk of Bias:** very serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** very serious. Low number of patients, Only data from one study.


16. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** very serious. Low number of patients, Only data from one study.


18. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** very serious. Wide confidence intervals, Low number of patients.


20. **Imprecision:** very serious. Wide confidence intervals, Low number of patients.

**6.3.6.5 Sofosbuvir-daclatasvir**
Evidence To Decision

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with sofosbuvir, including fatigue, insomnia, anaemia and irritability, and with daclatasvir, including fatigue, diarrhoea, nausea and headache.

**Certainty of the Evidence**

Certainty of the evidence is low for mechanical ventilation, adverse events, clinical recovery, time to hospital discharge, incidence of hospitalisation and dyspnoea due to very serious imprecision (low patient numbers, wide confidence intervals and/or reliance on a single study). Certainty is very low for mortality (days 14 and 28) and ICU admission due to very serious imprecision (based on aforementioned reasons with the addition of few events).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

**General adult population**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.
**Rationale**

**General adult population**
There is currently limited evidence about the impact of sofosbuvir-daclatasvir on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that sofosbuvir-daclatasvir should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of combination sofosbuvir-daclatasvir to treat COVID-19 in these populations should be avoided until evidence becomes available.

---

**Clinical Question/ PICO**

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Sofosbuvir-daclatasvir</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

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**Summary**

There remains significant uncertainty whether sofosbuvir-daclatasvir is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from two randomised trials that compared sofosbuvir-daclatasvir with standard care in 66 adults hospitalised with moderate or severe COVID-19 [318] and 89 adults hospitalised with mild to severe COVID-19 [323]. A third study compared sofosbuvir-daclatasvir plus hydroxychloroquine with hydroxychloroquine alone in 55 adult outpatients with confirmed COVID-19 [325].

We have found one new study comparing sofosbuvir-daclatasvir with placebo (Mobarak et al. J Antimicrob Chemother doi: 10.1093/jac/dkab433). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Publication status**
One study is only available as a preprint (Yakoot et al. posted to SSRN on 6 October 2020 [323]) and has therefore not been peer reviewed.

**Study characteristics**
Across the studies, median age of participants ranged from 43 to 58 years, and the proportion of women ranged from 48 to 56%. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
There were too few deaths (eight deaths at 14 days and seven deaths at 28 days) to determine whether sofosbuvir-daclatasvir makes a difference. We are uncertain if sofosbuvir-daclatasvir decreases the requirement for invasive mechanical ventilation, increases or decreases admission to hospital or ICU, or whether it impacts adverse events or dyspnoea. However, sofosbuvir-daclatasvir may improve clinical recovery slightly (154 more
Our confidence in the results
Certainty of the evidence is low for mechanical ventilation, adverse events, clinical recovery, time to hospital discharge, incidence of hospitalisation and dyspnoea due to very serious imprecision (low patient numbers, wide confidence intervals and/or reliance on a single study). Certainty is very low for mortality (days 14 and 28) and ICU admission due to very serious imprecision (based on the aforementioned reasons with the addition of few events).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known acute harms for sofosbuvir include fatigue, insomnia, anaemia and irritability [319], and known acute harms for daclatasvir include fatigue, diarrhoea, nausea and headache. There are several known and potential interactions with other drugs [320].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality Within 28 days of commencing treatment</td>
<td>Relative risk 0.41 (CI 95% 0.08 — 2) Based on data from 89 participants in 1 studies.</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Very low Due to very serious imprecision</td>
<td>We are uncertain whether sofosbuvir-daclatasvir increases or decreases risk of dying (7 deaths).</td>
</tr>
<tr>
<td>All-cause mortality Within 14 days of commencing treatment</td>
<td>Relative risk 0.6 (CI 95% 0.16 — 2.31) Based on data from 66 participants in 1 studies.</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Very low Due to very serious imprecision</td>
<td>We are uncertain whether sofosbuvir-daclatasvir increases or decreases risk of dying (8 deaths).</td>
</tr>
<tr>
<td>Mechanical ventilation Within 14 days of commencing treatment</td>
<td>Relative risk 0.42 (CI 95% 0.16 — 1.13) Based on data from 155 participants in 2 studies.</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Low Due to very serious imprecision</td>
<td>We are uncertain whether sofosbuvir-daclatasvir decreases mechanical ventilation (17 events).</td>
</tr>
<tr>
<td>ICU admission Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.15 — 6.94) Based on data from 89 participants in 1 studies.</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Very low Due to very serious imprecision</td>
<td>We are uncertain whether sofosbuvir-daclatasvir increases or decreases ICU admission (4 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>-------------------------------------------------------------------------------------------------</td>
<td>----------------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.36 – 2.93) Based on data from 89 participants in 1 studies. 7 (Randomized controlled)</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Low Due to very serious imprecision 10</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.21 (CI 95% 1.04 – 1.41) Based on data from 155 participants in 2 studies. 11 (Randomized controlled)</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Low</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>End of follow-up</td>
<td>Relative risk 0.26 (CI 95% 0.03 – 2.17) Based on data from 55 participants in 1 studies. 13 (Randomized controlled)</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Low Due to very serious imprecision 14</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>End of follow-up</td>
<td>Relative risk 0.38 (CI 95% 0.14 – 1.04) Based on data from 55 participants in 1 studies. 15 (Randomized controlled)</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Low Due to very serious imprecision 16</td>
</tr>
<tr>
<td>Time to hospital discharge</td>
<td>Days</td>
<td>Based on data from: 66 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Sofosbuvir-daclatasvir</td>
<td>Low</td>
</tr>
</tbody>
</table>

2. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
4. **Imprecision:** very serious. Low number of patients, Wide confidence intervals, Only data from one study.
6. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
8. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
10. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
12. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
14. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
16. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to [reason].
17. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study.

### 6.3.6.6 Triazavirin

**Only in research settings**

Do not use triazavirin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

**Triazavirin should still be considered for other evidence-based indications in people who have COVID-19.**

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use triazavirin for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.**

This is a **low priority** recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

---

**Evidence To Decision**

**Benefits and harms**

**General adult population**
As the safety profile for triazavirin is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as triazavirin has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.
Certainty of the Evidence

General adult population
Certainty of the evidence is very low for all outcomes due to very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals) and very serious risk of bias.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is further considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of triazavirin during pregnancy and breastfeeding are unknown in the context of COVID-19.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.
People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale
General adult population
There is currently limited evidence about the impact of triazavirin on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that triazavirin should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of triazavirin for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO
- **Population:** Patients with COVID-19
- **Intervention:** Triazavirin
- **Comparator:** Placebo

Summary
There remains significant uncertainty whether triazavirin is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared triazavirin with placebo in 52 adults hospitalised with mild, severe or critical COVID-19 [332].

Study characteristics
Mean age of participants was 58 years and 50% were women. Patients received 250 mg triazavirin three times a day (mild patients) or four times a day (severe or critical patients) for seven days. Pregnant and breastfeeding women were ineligible.

What are the main results?
There were too few who died (one death) or suffered adverse or serious adverse events to determine whether triazavirin makes a difference. It is unclear whether triazavirin increases or decreases viral clearance at day 28 or time to clinical improvement.

Our confidence in the results
Certainty of the evidence is very low for all outcomes due to very serious risk of bias (trial stopped early, selective outcome reporting) and very serious imprecision (reliance on a single study with low patient numbers and few events).

Additional information
As the safety profile for triazavirin is incompletely characterised in humans, there is uncertainty around the...
benefits and harms for patients with COVID-19.

**Pregnant and breastfeeding women**
There are additional concerns regarding harms, as triazavirin has not been sufficiently tested in this population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.33 (CI 95% 0.01 – 7.82) Based on data from 52 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>Placebo</td>
<td>Triazavirin</td>
<td>Very low Due to very serious risk of bias and very serious imprecision ²</td>
<td>There were too few who died to determine whether triazavirin makes a difference (1 death).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Relative risk 0.8 (CI 95% 0.24 – 2.65) Based on data from 52 participants in 1 studies. ³ (Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td>Data for patients requiring mechanical ventilation were not reported.</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.6 (CI 95% 0.26 – 1.41) Based on data from 52 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to very serious risk of bias and very serious imprecision ⁴</td>
<td>There were too few who experienced one or more serious adverse events to determine whether triazavirin makes a difference (9 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 1.14 (CI 95% 0.92 – 1.42) Based on data from 52 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to very serious risk of bias and very serious imprecision ⁸</td>
<td>There were too few who experienced one or more adverse events to determine whether triazavirin made a difference (6 events).</td>
</tr>
<tr>
<td>Virological clearance (Negative PCR)</td>
<td></td>
<td></td>
<td></td>
<td>Very low We are uncertain whether triazavirin increases virological clearance.</td>
<td></td>
</tr>
</tbody>
</table>
**Outcome Timeframe** | **Study results and measurements** | **Comparator** | **Intervention** | **Certainty of the Evidence (Quality of evidence)** | **Plain language summary**
--- | --- | --- | --- | --- | ---
Time to improvement Within 28 days of commencing treatment | Lower better 9 (Randomized controlled) | Placebo | Triazavirin | Very low Due to very serious risk of bias and very serious imprecision. | We are uncertain whether triazavirin decreases time to improvement.

<p>| | | | | | |</p>
<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Days (Median)</td>
<td>Days (Median)</td>
<td>CI 95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria. Selective outcome reporting, due to [reason]. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Selective outcome reporting. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, due to [reason]. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Only data from one study, Low number of patients, Wide confidence intervals, Wide confidence intervals, Low number of patients, Only data from one study. Publication bias: no serious.
4. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria, Selective outcome reporting. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Only data from one study, Low number of patients, Wide confidence intervals. Publication bias: no serious.
6. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria, Selective outcome reporting. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study. Publication bias: no serious.
8. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria, Selective outcome reporting. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Wide confidence intervals, Low number of patients, Only data from one study. Publication bias: no serious.
10. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria, Selective outcome reporting. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Wide confidence intervals, Low number of patients, Only data from one study. Publication bias: no serious.

**6.3.6.7 Umifenovir**
Only in research settings

Do not use umifenovir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

*Umifenovir should still be considered for other evidence-based indications in people who have COVID-19.*

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use umifenovir for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**Evidence To Decision**

**Benefits and harms**

**General adult population**

As the safety profile for umifenovir is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Certainty of the Evidence**

Certainty of the evidence is low for all outcomes. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study (clinical improvement and negative PCR) and few events (adverse events and clinical progression).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.
### Rationale

#### General adult population

There is currently limited evidence about the impact of umifenovir on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that umifenovir should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

#### Children and adolescents, pregnant and breastfeeding women

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

#### People requiring palliative care and older people living with frailty or cognitive impairment

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Important issues, or potential issues not investigated

#### Equity

**General adult population**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

### Acceptability

**General adult population**

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

#### General adult population

There is currently limited evidence about the impact of umifenovir on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that umifenovir should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

#### Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of umifenovir for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Umifenovir</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Summary

There remains significant uncertainty whether umifenovir is more effective and safer than standard care in treating patients with COVID-19.
What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared umifenovir with standard care in 135 adults hospitalised with mild or moderate COVID-19 [130][333][335].

Publication status
One study is only available as a preprint (Ghaderkhani et al. posted to Res Sq on 18 October 2020) and has therefore not been peer reviewed.

Study characteristics
In Li et al. mean age was 51 years in the umifenovir group (54% women) and 44 years in the standard care group (59% women). In Yethindra et al. mean age was 36 years (40% women)—patients over 60 years were excluded. In Ghaderkhani et al. median age was 47 years in the umifenovir group (68% women) and 42 years in the standard care group (52% women). In all three studies, pregnant and breastfeeding women were ineligible.

What are the main results?
No patients died or experienced a serious adverse event in any of the three studies. There were too few patients experiencing an adverse event or clinical deterioration to determine whether umifenovir makes a difference to these outcomes. It is unclear whether umifenovir increases the rate of negative PCR at day 14, however umifenovir may be less effective than standard care alone in facilitating clinical improvement based on chest CT scans at day 14.

Our confidence in the results
Certainty of the evidence is low for all outcomes. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study (clinical improvement and negative PCR) and few events (adverse events and clinical progression).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As of 21 September 2020, umifenovir (Arbidol) is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. The safety profile for umifenovir is incompletely characterised in humans.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Based on data from 52 participants in 1 studies.</td>
<td>Standard care</td>
<td>Umifenovir</td>
<td>Low due to very serious imprecision ²</td>
<td>No patients died.</td>
</tr>
<tr>
<td>Within 21 days of commencing treatment</td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 4.18 (CI 95% 0.51 – 34.19) Based on data from 135 participants in 3 studies. ²</td>
<td>Standard care</td>
<td>Umifenovir</td>
<td>Low due to very serious imprecision ²</td>
<td>There were too few who experienced one or more adverse events to determine whether umifenovir makes a difference (6 events).</td>
</tr>
<tr>
<td>Within 21 days of commencing treatment</td>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Based on data from 82</td>
<td></td>
<td></td>
<td></td>
<td>No patients experienced a serious adverse event.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>-----------------------------------------------------------------------------------------------</td>
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<td>------------------------------------------------</td>
</tr>
<tr>
<td>Clinical deterioration</td>
<td>Within 21 days of commencing treatment</td>
<td>Clinical deterioration (mild/mod to sev/crit) 5&lt;br&gt;Within 21 days of commencing treatment</td>
<td>63 per 1000</td>
<td>46 per 1000</td>
<td>Low Due to very serious imprecision 7&lt;br&gt;There were too few who experienced clinical deterioration to determine whether umifenovir makes a difference (5 events).</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Based on chest CT scan 14 days after commencing treatment</td>
<td>Clinical improvement 8&lt;br&gt;Based on chest CT scan 14 days after commencing treatment</td>
<td>929 per 1000</td>
<td>697 per 1000</td>
<td>Low Due to very serious imprecision 10&lt;br&gt;Umifenovir may decrease clinical improvement slightly at day 14 (36 events).</td>
</tr>
<tr>
<td>Negative PCR</td>
<td>Within 14 days of commencing treatment</td>
<td>Negative PCR 1.2&lt;br&gt;Based on data from 52 participants in 1 study. 11&lt;br&gt;(Randomized controlled)</td>
<td>765 per 1000</td>
<td>918 per 1000</td>
<td>Low Due to very serious imprecision 12&lt;br&gt;Umifenovir may have little impact on negative PCR (45 events).</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 21 days of commencing treatment</td>
<td>Discharge from hospital&lt;br&gt;Within 21 days of commencing treatment</td>
<td>1,000 per 1000</td>
<td>1,000 per 1000</td>
<td>Low Due to very serious imprecision 14&lt;br&gt;Umifenovir may have little impact on discharge from hospital (30 events).</td>
</tr>
</tbody>
</table>

2. Systematic review [334] with included studies: Li 2020, Yethindra 2020, [335]. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision:** very serious. Low number of patients, due to few events.
5. The number of patients who deteriorated from a mild or moderate form of disease to a severe or critical form.

7. **Imprecision: very serious.** Low number of patients, due to few events.

8. Criteria of chest CT improvement included: 1) no new exudative lesions; 2) decreasing size of exudative lesions; 3) decreasing densities of lesions.


10. **Imprecision: very serious.** Only data from one study, Low number of patients.


12. **Imprecision: very serious.** Only data from one study, Low number of patients.


14. **Imprecision: very serious.** Only data from one study, Low number of patients.

6.3.7 Corticosteroids

6.3.8 Human and blood derived products

6.3.8.1 Human umbilical cord mesenchymal stem cells

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**Only in research settings**

Do not use human umbilical cord mesenchymal stem cells for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

*Human umbilical cord mesenchymal stem cells should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use human umbilical cord mesenchymal stem cells (hUC-MSCs) to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

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**Evidence To Decision**

**Benefits and harms**

**General adult population**

There is uncertainty around benefits and harms associated with human umbilical cord mesenchymal stem cells (hUC-MSCs) in patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as hUC-MSCs have not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. There is insufficient evidence pertaining to the safety of hUC-MSCs for pregnant or breastfeeding women (for any indication) [245].
In Australia, stem cell therapy is only approved for haematopoietic stem cell (HPC) transplantation (using stem cells from umbilical cord blood or bone marrow), which is standard practice for the treatment of disorders of the blood and immune system, such as leukaemia [245].

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence is low for all-cause mortality and adverse events due to very serious imprecision (low patient numbers, few events and wide confidence intervals). Certainty is very low for all other outcomes due to very serious risk of bias (incomplete randomisation, lack of blinding, deviation from intended intervention and selective outcome reporting) and very serious imprecision (low patient numbers, few events, wide confidence intervals and reliance on a single study for four outcomes).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is downgraded for indirectness due to limited inclusion (or absence) of these populations in the study.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of hUC-MSCs in pregnancy are unknown.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications. There is very limited capacity to produce stem cell-related products, which would limit implementation of this treatment if effective.

**Equity**

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage
trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, treatment may be acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Stem cell therapies outside very specific settings and diseases remain a very experimental treatment and difficult to implement as a wide-use treatment.

Rationale

General adult population
There is currently limited evidence about the impact of human umbilical cord mesenchymal stem cells (hUC-MSCs) on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that human umbilical cord mesenchymal stem cells should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of hUC-MSCs to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Interventions</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with COVID-19</td>
<td>Human umbilical cord mesenchymal stem cells (hUC-MSC)</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary

There remains significant uncertainty whether therapy with human umbilical cord mesenchymal stem cells (hUC-MSCs) is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from four randomised trials that compared hUC-MSC therapy with standard care in 181 adults hospitalised with severe or critical COVID-19 [246][250][507] and 24 adults with mild to severe disease [249].

Study characteristics
Median age of patients was ~60 years and 44% were women. Standard care across the studies included
supplemental oxygen (non-invasive or invasive ventilation), antiviral agents (abidom/oseltamivir), antibiotic agents and glucocorticoid therapy. Pregnant and breastfeeding women were ineligible in three studies; in one study their eligibility was unclear.

Patients in the intervention groups received either: $2 \times 10^6$ cells/kg on day 0, $100 \times 10^6$ cells on days 0 and 3, $4 \times 10^7$ cells on days 0, 3 and 6, or $1 \times 10^6$ cells/kg on day 0.

What are the main results?

Preliminary results demonstrate that hUC-MSC therapy may reduce the incidence of death. There were too few events to determine whether hUC-MSC had an impact on mechanical ventilation or serious adverse events. hUC-MSC therapy may decrease adverse events slightly. We are uncertain whether hUC-MSC therapy decreases time to clinical improvement and duration of hospital stay, or increases clinical improvement and hospital discharge.

Our confidence in the results

Certainty of the evidence is low for all-cause mortality and adverse events due to very serious imprecision (low patient numbers, few events and wide confidence intervals). Certainty is very low for all other outcomes due to very serious risk of bias (incomplete randomisation, lack of blinding, deviation from intended intervention and selective outcome reporting) and very serious imprecision (low patient numbers, few events, wide confidence intervals and reliance on a single study for four outcomes).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information

Stem cell therapies outside of specific settings and diseases are very experimental and highly regulated in Australia.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.56 (CI 95% 0.36 — 0.89) Based on data from 205 participants in 4 studies.</td>
<td>Standard care</td>
<td>hU-MSC</td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td></td>
<td>271 per 1000</td>
<td>152 per 1000</td>
<td>119 fewer per 1000 (CI 95% 173 fewer — 30 fewer)</td>
<td>hU-MSC may decrease death (38 events).</td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Relative risk 0.26 (CI 95% 0.01 — 4.43) Based on data from 41 participants in 1 studies.</td>
<td>Standard care</td>
<td>hU-MSC</td>
<td>Very low</td>
<td>Due to very serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>9 Critical</td>
<td>9 Critical</td>
<td>There were too few who required invasive mechanical ventilation to determine whether hU-MSC makes a difference (4 patients).</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.25 (CI 95% 0.07 — 0.94) Based on data from 24 participants in 1 studies.</td>
<td>Standard care</td>
<td>hU-MSC</td>
<td>Very low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>9 Critical</td>
<td>9 Critical</td>
<td>There were too few who experienced serious adverse events to determine whether hU-MSC makes a difference (10 events).</td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention hU-MSC</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
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<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Relative risk 0.86 (CI 95% 0.65 — 1.12) Based on data from 124 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>hU-MSC may decrease adverse events slightly (77 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hospital discharge</strong></td>
<td>Relative risk 2.42 (CI 95% 0.85 — 6.85) Based on data from 41 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether hU-MSC increases hospital discharge.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>(Randomized controlled)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>6 Important</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>Relative risk 1.13 (CI 95% 0.94 — 1.36) Based on data from 41 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether hU-MSC increases clinical improvement.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>(Randomized controlled)</td>
<td></td>
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<tr>
<td>6 Important</td>
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<tr>
<td><strong>Duration of hospital stay</strong> Days</td>
<td>Lower better Based on data from: 40 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether hU-MSC increases or decreases duration of hospital stay.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
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<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of hospital stay</strong></td>
<td>Based on data from: 41 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether hU-MSC decreases duration of hospital stay.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
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<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Time to clinical improvement</strong></td>
<td>Based on data from: 41 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether hU-MSC decreases time to clinical improvement.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

2. **Imprecision**: very serious. Wide confidence intervals, Low number of patients.
4. **Risk of Bias**: very serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in
potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, only data from one study, due to few events. **Publication bias:** no serious.


6. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, low number of patients, only data from one study, few events. **Publication bias:** no serious.


8. **Imprecision:** very serious. Wide confidence intervals, due to few events, low number of patients. **Publication bias:** no serious.


10. **Risk of Bias:** very serious. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, only data from one study, due to few events. **Publication bias:** no serious.


12. **Risk of Bias:** very serious. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, low number of patients, only data from one study, due to few events. **Publication bias:** no serious.


14. **Imprecision:** very serious. Wide confidence intervals, low number of patients, only data from one study.

15. Primary study **Supporting references:** [246].

16. **Risk of Bias:** very serious. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, low number of patients, only data from one study, due to few events. **Publication bias:** no serious.

17. 2-point change on a 7-point ordinal scale

18. Primary study **Supporting references:** [246].

19. **Risk of Bias:** very serious. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, low number of patients, only data from one study, due to few events. **Publication bias:** no serious.

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**6.3.8.2 Intravenous immunoglobulin**
Evidence To Decision

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with intravenous immunoglobulin including flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury.

**Children and adolescents, pregnant and breastfeeding women**
Intravenous immunoglobulin is used in these populations for other medical conditions.

**People requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms, as intravenous immunoglobulin has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence is very low for all outcomes due to very serious imprecision (reliance on a single study and few events) and serious risk of bias (missing data).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people**
General adult population

There is currently limited evidence about the impact of intravenous immunoglobulin on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that intravenous immunoglobulin should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of intravenous immunoglobulin in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women

Because the benefit to harm ratio is uncertain, this recommendation may protect these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment

Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population

There is currently limited evidence about the impact of intravenous immunoglobulin on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that intravenous immunoglobulin should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of intravenous immunoglobulin to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

**Population:** Patients with COVID-19  
**Intervention:** Immunoglobulin  
**Comparator:** Placebo

**Summary**

There remains significant uncertainty whether intravenous immunoglobulin is more effective and safer than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from a single randomised trial that compared intravenous immunoglobulin with placebo in 64 hospitalised adults with severe COVID-19 [263].

Additional data were provided for the patients excluded from the analysis (two in the IVIg arm and three in the placebo arm) who died in the 72 hours following randomisation.

We have found two new studies comparing intravenous immunoglobulin with standard care or placebo (Raman et al. J Infect Dis doi: 10.1093/infdis/jiab098 and Mazeraud et al. Lancet Respir Med doi: 10.1016/S2213-2600(21)00440-9). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**

Mean age of participants was 56 years in both groups and 31% were women. Pregnant women were ineligible.

**What are the main results?**

Only two outcomes—mortality and duration of hospital stay—were reported. Significant uncertainty remains as to whether intravenous immunoglobulin affects either of these outcomes.

**Our confidence in the results**

Certainty of the evidence is very low for mortality and duration of hospital stay. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study, and serious risk of bias due to missing data.

For children & adolescents and pregnant & breastfeeding women, certainty is downgraded to very low due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

Adverse effects associated with intravenous immunoglobulin include flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury [265].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Placebo</th>
<th>Intervention Immunoglobulin</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality End of treatment</td>
<td>Relative risk 0.47 (CI 95% 0.24 – 0.93) Based on data from 64 participants in 1 studies.</td>
<td>7</td>
<td>9</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether immunoglobulin increases or decreases risk of death (25 events).</td>
</tr>
<tr>
<td>Duration of</td>
<td></td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether</td>
</tr>
</tbody>
</table>
### Evidence To Decision

#### Benefits and harms

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with immunoglobulin including flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury.

**Children and adolescents, pregnant and breastfeeding women**

Intravenous immunoglobulin and methylprednisolone are used in these populations for other medical conditions.

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**6.3.8.3 Intravenous immunoglobulin plus methylprednisolone**

*Only in research settings*

Do not use immunoglobulin plus methylprednisolone for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

*Intravenous immunoglobulin plus methylprednisolone should still be considered for other evidence-based indications in people who have COVID-19.*

*This recommendation does not apply to the use of immunoglobulin plus methylprednisolone in children and adolescents when managing PIMS-TS, Kawasaki disease or toxic shock syndrome related to COVID-19 [see section for specific guidance]. The Taskforce is currently developing recommendations for the management of these conditions in children and adolescents with COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use combination immunoglobulin plus methylprednisolone to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

---


**2. Risk of Bias: very serious.** Missing intention-to-treat analysis, Selective outcome reporting, Incomplete data and/or large loss to follow up. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Low number of patients, Only data from one study. Publication bias: no serious.

**3. Risk of Bias: serious.** Incomplete data and/or large loss to follow up, due to exclusion of patients who died within 72 hours of commencing treatment. Imprecision: very serious. Low number of patients, Only data from one study.

---

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>hospital stay</td>
<td>Based on data from: 59 participants in 1 studies. (Randomized controlled)</td>
<td>Placebo (Median)</td>
<td>Immunoglobulin (Median)</td>
<td>Due to serious risk of bias and very serious imprecision ³</td>
<td>Immunoglobulin increases or decreases duration of hospital stay.</td>
</tr>
</tbody>
</table>

---

Due to serious risk of bias and very serious imprecision, immunoglobulin increases or decreases duration of hospital stay.
People requiring palliative care and older people living with frailty or cognitive impairment
There are additional concerns regarding harms as intravenous immunoglobulin and methylprednisolone has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

Certainty of the Evidence
General adult population
Certainty of the evidence is very low for all outcomes based on very serious imprecision due to the low number of trial participants, low number of events and reliance on a single study.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values
General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of immunoglobulin in pregnancy are unknown.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity
General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation may protect these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.
Rationale
General adult population
There is currently limited evidence about the impact of immunoglobulin plus methylprednisolone on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that immunoglobulin plus methylprednisolone should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Acceptability
General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale
General adult population
There is currently limited evidence about the impact of immunoglobulin plus methylprednisolone on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that immunoglobulin plus methylprednisolone should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of immunoglobulin plus methylprednisolone to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO
Population: Patients with COVID-19
Intervention: Immunoglobulin plus methylprednisolone
Comparator: Standard care

Summary
There remains significant uncertainty whether intravenous immunoglobulin plus methylprednisolone is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared combination intravenous immunoglobulin plus methylprednisolone with standard care in 34 patients with moderate or severe COVID-19 [266].

We have found one new study comparing intravenous immunoglobulin with standard care (Tabarsi et al. Int Immunopharmacol doi: 10.1016/j.intimp.2020.107205). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
Mean age of participants was 54 years in both groups and 39% were women. It is unclear if pregnant and breastfeeding women were eligible.

What are the main results?
For the critical outcomes of death and invasive mechanical ventilation, there were too few events (four deaths and eight requiring ventilation) to determine whether combination immunoglobulin plus methylprednisolone makes a difference. No patient experienced an adverse event.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes. This judgement is based on very serious imprecision due to low patient numbers, few events and reliance on a single study.

**Additional information**
Adverse effects associated with immunoglobulin include flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury [265].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>30 days after commencing treatment</td>
<td>Relative risk 0.33 (CI 95% 0.04 – 2.89) Based on data from 34 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>Standard care</td>
<td>Immunoglobulin in plus methylprednisolone</td>
<td>Very low Due to very serious imprecision ²</td>
<td>There were too few who died to determine whether combination immunoglobulin plus methylprednisolone makes a difference (4 events).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>30 days after commencing treatment</td>
<td>Relative risk 0.29 (CI 95% 0.07 – 1.18) Based on data from 34 participants in 1 studies. ³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to very serious imprecision ⁴</td>
<td>There were too few who experienced invasive mechanical ventilation to determine whether combination immunoglobulin plus methylprednisolone makes a difference (9 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Within 30 days of commencing treatment</td>
<td>Based on data from 34 participants in 1 studies. ⁵</td>
<td></td>
<td></td>
<td>⁶</td>
<td>No patients experienced an adverse event.</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Within 30 days of commencing treatment</td>
<td></td>
<td></td>
<td></td>
<td>⁶</td>
<td>No studies were found that looked at serious adverse events.</td>
</tr>
</tbody>
</table>

2. **Imprecision: very serious.** Low number of patients, Only data from one study, low events.

4. **Imprecision**: very serious. Low number of patients, Only data from one study, few events.


---

**Clinical Question/ PICO**

- **Population**: Special populations with COVID-19
- **Intervention**: Immunoglobulin plus methylprednisolone
- **Comparator**: Standard care

---

**Summary**

There remains significant uncertainty whether immunoglobulin is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from a single randomised trial that compared combination immunoglobulin plus methylprednisolone with standard care in 34 patients with moderate or severe COVID-19 [266].

We have found one new study comparing intravenous immunoglobulin with standard care (Tabarsi et al. Int Immunopharmacol doi: 10.1016/j.intimp.2020.107205). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**

Mean age of participants was 54 years in both groups and 39% were women. It is unclear if pregnant and breastfeeding women were eligible.

**What are the main results?**

For the critical outcomes of death and mechanical ventilation there were too few events (four deaths and eight requiring ventilation) to determine whether combination immunoglobulin plus methylprednisolone makes a difference. No patient experienced an adverse event.

**Our confidence in the results**

Certainty of the evidence is very low for all outcomes. This judgement is based on serious indirectness and very serious imprecision due to low patient numbers, few events and reliance on a single study.

**Additional information**

Adverse effects associated with immunoglobulin include flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury [265].

---

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality 30 days after commencing treatment</td>
<td>Relative risk 0.33 (CI 95% 0.04 – 2.89) Based on data from 34 participants in 1 studies.</td>
<td>Standard care</td>
<td>Immunoglobulin plus methylprednisolone</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>There were too few who died to determine whether combination immunoglobulin plus methylprednisolone makes a difference (4 events).</td>
</tr>
</tbody>
</table>
### 6.3.9 Immunomodulating drugs

#### 6.3.9.1 Anakinra

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Immunoglobulin plus methylprednisolone</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation 30 days after commencing treatment</td>
<td>Relative risk 0.29 (CI 95% 0.07 – 1.18) Based on data from 34 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Standard care</td>
<td>Immunoglobulin plus methylprednisolone</td>
<td>Very low Due to very serious imprecision and serious indirectness ⁴</td>
<td>There were too few who experienced invasive mechanical ventilation to determine whether combination immunoglobulin plus methylprednisolone makes a difference (9 events).</td>
</tr>
</tbody>
</table>

**Adverse events**

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Immunoglobulin plus methylprednisolone</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 30 days of commencing treatment</td>
<td>Based on data from 34 participants in 1 studies. ⁵</td>
<td>Standard care</td>
<td>Immunoglobulin plus methylprednisolone</td>
<td></td>
<td>No patients experienced an adverse event.</td>
</tr>
</tbody>
</table>

**Serious adverse events**

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Immunoglobulin plus methylprednisolone</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 30 days of commencing treatment</td>
<td></td>
<td>Standard care</td>
<td>Immunoglobulin plus methylprednisolone</td>
<td></td>
<td>No studies were found that looked at serious adverse events.</td>
</tr>
</tbody>
</table>

2. **Indirectness:** serious. **Imprecision:** very serious. Low number of patients. Only data from one study, low events.
4. **Indirectness:** serious. **Imprecision:** very serious. Low number of patients. Only data from one study, few events.
6. Systematic review [264]. **Baseline/comparator:** Control arm of reference used for intervention.

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---
Do not use anakinra for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

**Anakinra should still be considered for other evidence-based indications in people who have COVID-19.**

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use anakinra to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.**

This is a **moderate priority** recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

### Evidence To Decision

#### Benefits and harms

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, common side effects include headache, injection site reactions, serious infections, neutropaenia and thrombocytopaenia [186]. It remains unclear if anakinra is safe for the treatment of COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as anakinra has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. There is insufficient evidence pertaining to the safety of anakinra for pregnant or breastfeeding women.

#### Certainty of the Evidence

**General adult population**

Certainty of the evidence is low for mortality, the composite outcome of mortality or mechanical ventilation, respiratory failure or ARDS, and sepsis due to very serious imprecision (reliance on a single study and wide confidence intervals). Certainty is very low for remaining outcomes due to serious risk of bias (lack of blinding), in addition to very serious imprecision.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

#### Preference and values

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the
potential effects of anakinra in pregnancy are unknown.

**Resources and other considerations**  
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**  
**General adult population**  
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**  
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**  
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability**  
**General adult population, children and adolescents, pregnant and breastfeeding women**  
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**  
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**  
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**  
**General adult population**  
There is currently limited evidence about the impact of anakinra on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that anakinra should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**  
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of anakinra to treat COVID-19 in these populations should be avoided until evidence becomes available.
Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Anakinra
Comparator: Standard care

Summary
There remains significant uncertainty whether anakinra is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared anakinra with usual care in 116 adults hospitalised with mild-to-moderate COVID-19 [187].

We have found two new studies comparing anakinra with placebo: 594 hospitalised patients with moderate–severe COVID-19 (Kyriazopoulou et al. doi: 10.1101/2021.05.16.21257283) and 796 hospitalised patients with critical COVID-19 (Derde et al. (REMAP-CAP), medRxiv doi: 10.1101/2021.06.18.21259133). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
Mean age of participants was 66 years and 30% were women. Patients received a median of 11 infusions of anakinra with a cumulative median dose of 1900 mg. Pregnant and breastfeeding women were ineligible.

What are the main results?
Anakinra may decrease slightly the number of deaths and the need for invasive mechanical ventilation or ECMO. We are uncertain whether anakinra increases or decreases NIV/HFNO, clinical recovery and adverse or serious adverse events.

Our confidence in the results
Certainty of the evidence is low for mortality, the composite outcome of mortality or mechanical ventilation, respiratory failure or ARDS, and sepsis due to very serious imprecision (reliance on a single study and wide confidence intervals). Certainty is very low for remaining outcomes due to serious risk of bias (lack of blinding), in addition to very serious imprecision.

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, common side effects associated with anakinra include headache, injection site reactions, serious infections, neutropaenia and thrombocytopenia [186].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Anakinra</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality Within 28 days of commencing treatment</td>
<td>Relative risk 0.93 (CI 95% 0.47 – 1.83)</td>
<td>236 per 1000</td>
<td>219 per 1000</td>
<td>Low Due to very serious imprecision ²</td>
<td>We are uncertain whether anakinra impacts death (26 events).</td>
</tr>
<tr>
<td>Critical</td>
<td>Difference: 17 fewer per 1000 (CI 95% 125 fewer – 196 more)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality or Relative risk 0.98 (CI 95% 0.59 – 1.63)</td>
<td>345 per 1000</td>
<td>338 per 1000</td>
<td>Low Due to very</td>
<td>We are uncertain whether anakinra</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>mechanical ventilation [composite]</td>
<td>Within 14 days of commencing treatment</td>
<td>Based on data from 114 participants in 1 studies.</td>
<td>Standard care</td>
<td>Anakinra</td>
<td>9 Critical</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.79 (CI 95% 0.39 — 1.61) Based on data from 114 participants in 1 studies.</td>
<td>Standard care</td>
<td></td>
<td>Low Due to very serious imprecision</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 2.33 (CI 95% 0.78 — 7) Based on data from 114 participants in 1 studies.</td>
<td>Standard care</td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.18 (CI 95% 0.78 — 1.76) Based on data from 114 participants in 1 studies.</td>
<td>Standard care</td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.2 (CI 95% 0.77 — 1.85) Based on data from 114 participants in 1 studies.</td>
<td>Standard care</td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.93 (CI 95% 0.69 — 1.26) Based on data from 114 participants in 1 studies.</td>
<td>Standard care</td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
</tr>
</tbody>
</table>

**Table Notes:**
- Each outcome has a specified timeframe for its measurement.
- **Comparator** refers to the standard care group.
- **Intervention** refers to the anakinra treatment group.
- **Certainty of the Evidence** indicates the level of confidence in the results, ranging from "Critical" to "Very low".
- **Plain language summary** provides a human-readable interpretation of the scientific findings.

**Study Details:**
- Values are based on data from 114 participants in studies.
- Differences are calculated per 1000 participants, with confidence intervals (CI) provided.
- "Randomized controlled" studies imply randomized clinical trials with controlled conditions.

**Quality Considerations:**
- "Serious adverse events" section includes a note on serious risk of bias and very serious imprecision.
- "Sepsis" section also notes a very low level of certainty due to risk of bias and very serious imprecision.
- "Hospital discharge" section indicates an uncertain level of certainty due to risk of bias and very serious imprecision.
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anakinra</td>
<td></td>
<td>more )</td>
</tr>
</tbody>
</table>

2. **Risk of Bias: no serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
4. **Risk of Bias: no serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study.
6. **Risk of Bias: no serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
8. **Risk of Bias: serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Low number of patients, Only data from one study.
10. **Risk of Bias: serious.** Adequate/lack of blinding of participants and personnel, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, Low number of patients.
12. **Risk of Bias: serious.** Adequate/lack of blinding of participants and personnel, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
14. **Risk of Bias: serious.** Adequate/lack of blinding of participants and personnel, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

**6.3.9.2 Lenzilumab**
Do not use lenzilumab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use lenzilumab for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms
There is insufficient information to determine whether lenzilumab is safe for the treatment of COVID-19. As lenzilumab is not listed in the Australian Register of Therapeutic Goods and is currently not approved for use in Australia, there are no reliable safety data to inform treatment with lenzilumab.

Certainty of the Evidence
Certainty of the evidence is low for adverse and serious adverse events and time to recovery due to very serious imprecision (wide confidence intervals and reliance on a single study), and very low for septic shock (few events).

Preference and values
General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of lenzilumab during pregnancy and breastfeeding are unknown in the context of COVID-19.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity
General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.
People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability
General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale
General adult population
There is currently limited evidence about the impact of lenzilumab on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that lenzilumab should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of lenzilumab to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO
- **Population:** Patients with COVID-19
- **Intervention:** Lenzilumab
- **Comparator:** Placebo

Summary
We are uncertain if lenzilumab is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared lenzilumab with placebo in 479 adults hospitalised with moderate to severe COVID-19 [291].

Publication status
The study is only available as a preprint (posted to medRxiv on 5 May 2021) and has therefore not been peer
reviewed.

Study characteristics
Median age of participants was 61 years and 35% were women. Pregnant and breastfeeding women were ineligible.

What are the main results?
No critical outcomes (mortality, invasive mechanical ventilation or respiratory failure or ARDS) were reported. For the important outcomes, lenzilumab may decrease the incidence of adverse and serious adverse events slightly. It is unclear whether lenzilumab increases or decreases the incidence of septic shock and time to recovery.

Our confidence in the results
Certainty of the evidence is low for adverse and serious adverse events and time to recovery due to very serious imprecision (wide confidence intervals and reliance on a single study), and very low for septic shock (wide confidence intervals, reliance on a single study and few events).

Additional information
As of 14 May 2021, lenzilumab is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. There are no reliable safety data to inform treatment with lenzilumab.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.84 (CI 95% 0.63 – 1.11) Based on data from 512 participants in 1 studies.</td>
<td>Placebo</td>
<td>Lenzilumab</td>
<td>Low Due to very serious imprecision</td>
<td>Lenzilumab may decrease serious adverse events slightly (139 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.82 (CI 95% 0.62 – 1.07) Based on data from 512 participants in 1 studies.</td>
<td>Placebo</td>
<td>Lenzilumab</td>
<td>Low Due to very serious imprecision</td>
<td>Lenzilumab may decrease adverse events slightly (152 events).</td>
</tr>
<tr>
<td>Septic shock</td>
<td>End of follow-up</td>
<td>Relative risk 0.56 (CI 95% 0.19 – 1.63) Based on data from 512 participants in 1 studies.</td>
<td>Placebo</td>
<td>Lenzilumab</td>
<td>Very low Due to very serious imprecision</td>
<td>We are uncertain whether lenzilumab increases or decreases septic shock (14 events).</td>
</tr>
<tr>
<td>Time to recovery</td>
<td>Median (Days)</td>
<td>Lower better Based on data from: 479 participants in 1 studies.</td>
<td>Placebo</td>
<td>Lenzilumab</td>
<td>Low Due to very serious imprecision</td>
<td>Lenzilumab may make little or no difference to time to recovery.</td>
</tr>
</tbody>
</table>

2. **Imprecision:** very serious. Wide confidence intervals. Only data from one study.
4. **Imprecision:** very serious. Wide confidence intervals. Only data from one study.
6. **Imprecision:** very serious. Only data from one study, Wide confidence intervals, due to few events.
7. **Imprecision:** very serious. Only data from one study, Wide confidence intervals.

**6.3.9.3 Ruxolitinib**
Evidence To Decision

Benefits and harms

General adult population
In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms of ruxolitinib. Although most of the information on side effects and harms is derived from long-term use, potential harms include thrombocytopenia and other haematological adverse reactions, and increased incidence of bacterial and other infections.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There are additional concerns regarding harms as ruxolitinib has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. No studies pertained to the safety of ruxolitinib (for any indication) for pregnant or breastfeeding women.

Certainty of the Evidence

General adult population
Certainty of the evidence is low for mortality and very low for all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (low number of patients and observed events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of ruxolitinib in pregnancy are unknown.
## Rationale

### General adult population

There is currently limited evidence about the impact of ruxolitinib on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that ruxolitinib should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

### Children and adolescents, pregnant and breastfeeding women

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of ruxolitinib to treat COVID-19 in these populations should be avoided until evidence becomes available.

## Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

## Equity

### General adult population

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Children and adolescents, pregnant and breastfeeding women

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

### People requiring palliative care and older people living with frailty or cognitive impairment

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

## Acceptability

### General adult population, children and adolescents, pregnant and breastfeeding women

We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

### People requiring palliative care and older people living with frailty or cognitive impairment

Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

## Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

## Clinical Question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Ruxolitinib  
**Comparator:** Placebo

### Summary
We are uncertain if ruxolitinib is more effective and safer than standard care in treating patients with COVID-19.

### What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared ruxolitinib with placebo (vitamin C) in 41 adults hospitalised with severe COVID-19 [311].

### Study characteristics
Median age of participants was 63 years and 42% were women. Pregnant and breastfeeding women were ineligible.

### What are the main results?
For the critical outcomes, there were too few events (three deaths, nine who required invasive mechanical ventilation and two who experienced septic shock) to determine whether ruxolitinib makes a difference. We are uncertain whether ruxolitinib increases or decreases the likelihood of clinical improvement, time to discharge from hospital or adverse events. Four patients in the control group experienced serious adverse events.

### Our confidence in the results
Certainty of the evidence is low for mortality and very low for all other outcomes. This judgement is based on serious risk of bias (unblinded outcome assessors) and very serious imprecision (low patient numbers, few observed events and reliance on a single study). Mortality was not downgraded for risk of bias as this outcome is unlikely to be affected by lack of blinding.

### Additional information
The Therapeutic Goods Administration highlights several potential side effects associated with ruxolitinib, including thrombocytopaenia and other haematological adverse reactions, and increased incidence of bacterial and other infections. Cases of progressive multifocal leukoencephalopathy and non-melanoma skin cancer have also been reported in patients treated with ruxolitinib [310].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Placebo</th>
<th>Intervention Ruxolitinib</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
</table>
| **All-cause mortality (Day 28)**  
Within 28 days of commencing treatment  
9 Critical | Odds Ratio 0.13 (CI 95% 0.01 – 2.67) Based on data from 41 participants in 1 studies. ² (Randomized controlled) | 143 per 1000 | 21 per 1000 | Low  
Due to very serious imprecision ² | There were too few who died to determine whether ruxolitinib makes a difference (3 events). |
| **Invasive mechanical ventilation**  
Within 28 days of commencing treatment  
9 Critical | Odds Ratio 0.22 (CI 95% 0.04 – 1.24) Based on data from 41 participants in 1 studies. ² (Randomized controlled) | 122 fewer per 1000 (CI 95% 141 fewer – 165 more) |  
Very low  
Due to serious risk of bias and very serious imprecision ⁴ | There were too few who required invasive mechanical ventilation to determine whether ruxolitinib makes a difference (9 events). |
| **Septic shock**  
Within 28 days | Odds Ratio 0.19 (CI 95% 0.01 – 4.22) |  
Very low  
Due to serious | There were too few who experienced |
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>of commencing treatment</td>
<td>Based on data from 41 participants in 1 studies.</td>
<td>Placebo</td>
<td>Ruxolitinib</td>
<td>risk of bias and very serious imprecision ⁸</td>
<td>septic shock to determine whether ruxolitinib makes a difference (2 events).</td>
</tr>
<tr>
<td>9 Critical</td>
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</tr>
<tr>
<td>Clinical improvement</td>
<td>Odds Ratio 2 (CI 95% 0.58 — 6.94)</td>
<td>Placebo</td>
<td>Ruxolitinib</td>
<td>Very low</td>
<td>We are uncertain whether ruxolitinib improves or worsens clinical improvement (21 events).</td>
</tr>
<tr>
<td>At day 14 of treatment</td>
<td>Based on data from 41 participants in 1 studies.</td>
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<tr>
<td>6 Important</td>
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</tr>
<tr>
<td>Adverse events</td>
<td>Odds Ratio 1.35 (CI 95% 0.36 — 5.04)</td>
<td>Placebo</td>
<td>Ruxolitinib</td>
<td>Very low</td>
<td>We are uncertain whether ruxolitinib increases or decreases adverse events (13 events).</td>
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<tr>
<td>Within 28 days of commencing treatment</td>
<td>Based on data from 41 participants in 1 studies.</td>
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<td>6 Important</td>
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</tr>
<tr>
<td>Serious adverse events</td>
<td>Odds Ratio 0.09 (CI 95% 0 — 1.89)</td>
<td>Placebo</td>
<td>Ruxolitinib</td>
<td>Very low</td>
<td>There were too few who experienced serious adverse events to determine whether ruxolitinib makes a difference (4 events).</td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td>Based on data from 41 participants in 1 studies.</td>
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<tr>
<td>6 Important</td>
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<tr>
<td>Clinical deterioration</td>
<td>Odds Ratio 0.09 (CI 95% 0 — 1.89)</td>
<td>Placebo</td>
<td>Ruxolitinib</td>
<td>Very low</td>
<td>We are uncertain whether ruxolitinib improves or worsens clinical deterioration (4 events).</td>
</tr>
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<td>At day 14 of treatment</td>
<td>Based on data from 41 participants in 1 studies.</td>
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<tr>
<td>6 Important</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Time to improvement</td>
<td>Lower better (Median)</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether ruxolitinib decreases time to improvement.</td>
</tr>
<tr>
<td>Median days to improvement</td>
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<tr>
<td>6 Important</td>
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<td></td>
</tr>
<tr>
<td>Time to discharge</td>
<td>Lower better (Median)</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether ruxolitinib increases or decreases time to discharge.</td>
</tr>
<tr>
<td>Median days to discharge</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Clinical Question/ PICO

Population: Special populations with COVID-19
Intervention: Ruxolitinib
Comparator: Placebo

Summary
We are uncertain if ruxolitinib is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared ruxolitinib with placebo (vitamin C) in 41 adults hospitalised with severe COVID-19 [311].

Study characteristics
Median age of participants was 63 years and 42% were women. Pregnant and breastfeeding women were ineligible.

What are the main results?
For the critical outcomes, there were too few events (three deaths, nine who required invasive mechanical
ventilation and two who experienced septic shock) to determine whether ruxolitinib makes a difference. We are uncertain whether ruxolitinib increases or decreases the likelihood of clinical improvement, time to discharge from hospital or adverse events. Four patients in the control group experienced serious adverse events.

**Our confidence in the results**

Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias (unblinded outcome assessors), serious indirectness (limited inclusion or absence of these populations) and very serious imprecision (low patient numbers, few observed events and reliance on a single study). Mortality was not downgraded for risk of bias as this outcome is unlikely to be affected by lack of blinding.

**Additional information**

The Therapeutic Goods Administration highlights several potential side effects associated with ruxolitinib, including thrombocytopenia and other haematological adverse reactions, and increased incidence of bacterial and other infections. Cases of progressive multifocal leukoencephalopathy and non-melanoma skin cancer have also been reported in patients treated with ruxolitinib.[310]

**Children and adolescents**

There is insufficient safety data on the use of ruxolitinib in children and adolescents for other indications.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator Placebo</th>
<th>Intervention Ruxolitinib</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 28)</td>
<td>Odds Ratio 0.13 (CI 95% 0.01 – 2.67) Based on data from 41 participants in 1 studies. ² (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious indirectness and very serious imprecision ²</td>
<td>There were too few who died to determine whether ruxolitinib makes a difference (3 events).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Odds Ratio 0.22 (CI 95% 0.04 – 1.24) Based on data from 41 participants in 1 studies. ³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and indirectness, and very serious imprecision ³</td>
<td>There were too few who required invasive mechanical ventilation to determine whether ruxolitinib makes a difference (9 events).</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Odds Ratio 0.19 (CI 95% 0.01 – 4.22) Based on data from 41 participants in 1 studies. ⁴ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and indirectness, and very serious imprecision ⁴</td>
<td>There were too few who experienced septic shock to determine whether ruxolitinib makes a difference (2 events).</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Odds Ratio 2 (CI 95% 0.58 – 6.94) Based on data from 41 participants in 1 studies. ⁶ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and indirectness, and very serious imprecision ⁶</td>
<td>We are uncertain whether ruxolitinib improves or worsens clinical improvement (21 events).</td>
</tr>
</tbody>
</table>
### Outcome

<table>
<thead>
<tr>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention Ruxolitinib</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome Timeframe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Odds Ratio 1.35 (CI 95% 0.36 – 5.04) Based on data from 41 participants in 1 studies.</td>
<td>Very low Due to serious risk of bias and indirectness, and very serious imprecision.</td>
<td>We are uncertain whether ruxolitinib increases or decreases adverse events (13 events).</td>
<td></td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>Odds Ratio 0.09 (CI 95% 0 – 1.89) Based on data from 41 participants in 1 studies.</td>
<td>Very low Due to serious risk of bias and indirectness, and very serious imprecision.</td>
<td>There were too few who experienced serious adverse events to determine whether ruxolitinib makes a difference (4 events).</td>
<td></td>
</tr>
<tr>
<td>Within 28 days of commencing treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical deterioration</strong></td>
<td>Odds Ratio 0.09 (CI 95% 0 – 1.89) Based on data from 41 participants in 1 studies.</td>
<td>Very low Due to serious risk of bias and indirectness, and very serious imprecision.</td>
<td>We are uncertain whether ruxolitinib improves or worsens clinical deterioration (4 events).</td>
<td></td>
</tr>
<tr>
<td>At day 14 of treatment</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Time to improvement</strong></td>
<td>Lower better (Median)</td>
<td>15 (Median)</td>
<td>Very low Due to serious risk of bias and indirectness, and very serious imprecision.</td>
<td>We are uncertain whether ruxolitinib decreases time to improvement.</td>
</tr>
<tr>
<td>Median days to improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time to discharge</strong></td>
<td>Lower better (Median)</td>
<td>16 (Median)</td>
<td>Very low Due to serious risk of bias and indirectness, and very serious imprecision.</td>
<td>We are uncertain whether ruxolitinib increases or decreases time to discharge.</td>
</tr>
<tr>
<td>Median days to discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Indirectness**: serious. **Imprecision**: very serious. Low number of patients. Only data from one study.
4. **Risk of Bias**: serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness**: serious. **Imprecision**: very serious. Low number of patients. Only data from one study.
7. Systematic review [309] with included studies: Cao Y 2020. **Baseline/comparator**: Control arm of reference used
for intervention.

8. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** Imprecision: **very serious.** Low number of patients, Only data from one study.


10. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** Imprecision: **very serious.** Low number of patients, Only data from one study.


12. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** Imprecision: **very serious.** Low number of patients, Only data from one study.


14. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** Imprecision: **very serious.** Low number of patients, Only data from one study.

15. Systematic review [309] with included studies: [311]. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** Imprecision: **very serious.** Low number of patients, Only data from one study.

17. Systematic review [309] with included studies: [311]. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** Imprecision: **very serious.** Low number of patients, Only data from one study.

### 6.3.9.4 Tofacitinib

**Only in research settings**

Do not use tofacitinib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Tofacitinib should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use tofacitinib for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a **low priority** recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

#### Evidence To Decision

<table>
<thead>
<tr>
<th>Benefits and harms</th>
<th>Small net benefit, or little difference between alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General adult population</strong></td>
<td>In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with tofacitinib, including thrombosis and increased risk of serious infection.</td>
</tr>
</tbody>
</table>
Certainty of the Evidence

General adult population
Certainty of the evidence for all outcomes is low due to very serious imprecision (reliance on a single study and wide confidence intervals and/or few events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of tofacitinib in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

**General adult population**

There is currently limited evidence about the impact of tofacitinib on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that tofacitinib should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of tofacitinib to treat COVID-19 in these populations should be avoided until evidence becomes available.

**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** Tofacitinib
- **Comparator:** Placebo

**Summary**

There remains significant uncertainty whether tofacitinib is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from one randomised trial that compared tofacitinib with placebo in 289 adults hospitalised with moderate to critical COVID-19 [515].

**Study characteristics**

Mean age of participants was 56 years and 35% were women. Most patients received concomitant corticosteroids (90%) and prophylactic anticoagulation (78%). Pregnant women were ineligible.

**What are the main results?**

We are uncertain whether tofacitinib makes a difference to mortality, adverse or serious adverse events, discontinuation due to adverse events or discharge from hospital.

**Our confidence in the results**

Certainty of the evidence for all outcomes is low due to very serious imprecision (reliance on a single study, wide confidence intervals and/or few events).

For children & adolescents and pregnant & breastfeeding women, certainty is very low due to serious indirectness (absence of inclusion of these populations in the included study).

**Additional information**

According to the Therapeutic Goods Administration, potential side effects of tofacitinib include an increased risk of serious infections and thrombosis. It is noted that tofacitinib must not be used in combination with biological agents or other potent immunosuppressive agents.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.49 (CI 95% 0.14 — 1.66) Based on data from 289 participants in 1 studies.</td>
<td>Placebo</td>
<td>Tofacitinib</td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.21 (CI 95% 0.6 — 2.41) Based on data from 284 participants in 1 studies.</td>
<td>Placebo</td>
<td>Tofacitinib</td>
<td>Low</td>
<td>We are uncertain whether tofacitinib impacts risk of death (12 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 1.21 (CI 95% 0.7 — 2.09) Based on data from 284 participants in 1 studies.</td>
<td>Placebo</td>
<td>Tofacitinib</td>
<td>Low</td>
<td>We are uncertain whether tofacitinib increases or decreases serious adverse events (37 events).</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>During treatment</td>
<td>Relative risk 3.2 (CI 95% 1.2 — 8.5) Based on data from 284 participants in 1 studies.</td>
<td>Placebo</td>
<td>Tofacitinib</td>
<td>Low</td>
<td>Tofacitinib may increase discontinuation due to adverse events slightly (21 events).</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.05 (CI 95% 0.97 — 1.12) Based on data from 289 participants in 1 studies.</td>
<td>Placebo</td>
<td>Tofacitinib</td>
<td>Low</td>
<td>Tofacitinib may increase discharge from hospital slightly (134 events).</td>
</tr>
</tbody>
</table>

6.3.10 Interferons

6.3.10.1 Interferon β-1a (inhaled)

**Only in research settings**

Do not use inhaled interferon β-1a for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Inhaled interferon β-1a should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use inhaled interferon β-1a to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

### Evidence To Decision

#### Benefits and harms

**General adult population**

Although there remains uncertainty about the effects of inhaled interferon β-1a on adverse or serious adverse events in patients with COVID-19, there are well-known side effects and harms associated with interferon β-1a including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

**Children and adolescents, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as interferon β-1a has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Pregnant and breastfeeding women**

Evidence suggests that interferon β-1a in pregnant women is not associated with an increase in early pregnancy loss, stillbirths or congenital anomalies.

#### Certainty of the Evidence

Certainty of the evidence is low for adverse and serious adverse events, discharge from hospital and the composite outcome of invasive mechanical ventilation or death. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study.

Certainty is very low for mortality based on very serious imprecision (due to the aforementioned issues, with the addition of low event numbers). Certainty was also very low for clinical recovery and clinical improvement, as many of these values were derived using the last observation carried forward method.
Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment

Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.
Rationale

General adult population
There is currently limited evidence about the impact of inhaled interferon β-1a on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that inhaled interferon β-1a should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of inhaled interferon β-1a to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

- **Population:** Patients with COVID-19
- **Intervention:** Inhaled interferon β-1a
- **Comparator:** Standard care

Summary
There remains significant uncertainty whether inhaled interferon β-1a is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared inhaled interferon β-1a with placebo in 98 adults hospitalised with moderate or severe COVID-19 [252].

**Study characteristics**
Mean age of patients was 58 years and 41% were women. Patients in the intervention group received 6 mIU of nebulised interferon β-1a a day for 14 days. Pregnant women were ineligible.

**What are the main results?**
We are uncertain whether inhaled interferon β-1a has an impact on death, the composite outcome of invasive mechanical ventilation or death, discharge from hospital, adverse or serious adverse events, or the number of patients who experience clinical recovery or clinical improvement.

**Our confidence in the results**
Certainty of the evidence is low for adverse or serious adverse events, discharge from hospital and the composite outcome of invasive mechanical ventilation or death. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study. Certainty is very low for mortality based on very serious imprecision (due to the aforementioned issues, with the addition of low event numbers). Certainty was also very low for clinical recovery and clinical improvement, as many of these values were derived using the last observation carried forward method.

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
The Therapeutic Goods Administration highlights several potential side effects associated with the use of interferon β-1a, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation. Interferon β-1a is also associated with immune reactions that can produce flu-like symptoms [160][161].

**Children and adolescents**
Paediatricians have limited experience with interferon β-1a in children and adolescents for other indications. To
date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population.

**Pregnant and breastfeeding women**

Interferon β-1a is used in pregnancy for the treatment of multiple sclerosis. Evidence has shown no correlation between the use of interferon β-1a and increases in early pregnancy loss, stillbirths or congenital anomalies [162].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Inhaled interferon β-1a</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
</table>
| **All-cause mortality**          | Relative risk 0.15 (CI 95% 0.01 – 2.8) Based on data from 98 participants in 1 studies. | Standard care | Inhaled interferon β-1a | Very low Due to very serious imprecision
| Within 28 days of commencing treatment | 9 Critical                   |                           |                                      |                                                 |
| **Invasive mechanical ventilation or death [composite]** | Relative risk 0.63 (CI 95% 0.16 – 2.47) Based on data from 98 participants in 1 studies. | Standard care | Inhaled interferon β-1a | Low Due to very serious imprecision
| Within 28 days of commencing treatment | 9 Critical                   |                           |                                      |                                                 |
| **Discharge from hospital**      | Relative risk 1.1 (CI 95% 0.85 – 1.44) Based on data from 98 participants in 1 studies. | Standard care | Inhaled interferon β-1a | Low Due to very serious imprecision
| Within 28 days of commencing treatment | 6 Important                  |                           |                                      |                                                 |
| **Serious adverse events**       | Relative risk 0.49 (CI 95% 0.22 – 1.09) Based on data from 98 participants in 1 studies. | Standard care | Inhaled interferon β-1a | Low Due to very serious imprecision
| Within 28 days of commencing treatment | 6 Important                  |                           |                                      |                                                 |
| **Adverse events**               | Relative risk 0.9 (CI 95% 0.64 – 1.27) Based on data from 98 participants in 1 studies. | Standard care | Inhaled interferon β-1a | Low Due to very serious imprecision
<p>| Within 28 days of commencing treatment | 6 Important                  |                           |                                      |                                                 |</p>
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Inhaled interferon β-1a</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical recovery</strong> Within 28 days of commencing treatment</td>
<td>Relative risk 1.99 (CI 95% 1.08 – 3.67) Based on data from 98 participants in 1 study.</td>
<td>Control arm of reference used for intervention.</td>
<td>( CI 95% 216 fewer – 162 more )</td>
<td><strong>Very low</strong> Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether inhaled interferon β-1a increases or decreases clinical recovery.</td>
</tr>
<tr>
<td><strong>Clinical improvement</strong> Within 28 days of commencing treatment</td>
<td>Relative risk 1.43 (CI 95% 1.01 – 2.02) Based on data from 98 participants in 1 study.</td>
<td>Control arm of reference used for intervention.</td>
<td></td>
<td><strong>Very low</strong> Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether inhaled interferon β-1a increases or decreases clinical improvement.</td>
</tr>
</tbody>
</table>

2. **Imprecision: very serious**. Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
4. **Imprecision: very serious**. Wide confidence intervals, Low number of patients, Only data from one study.
6. **Imprecision: very serious**. Wide confidence intervals, Low number of patients.
8. **Imprecision: very serious**. Low number of patients, Only data from one study, Wide confidence intervals.
10. **Imprecision: very serious**. Low number of patients, Wide confidence intervals, Only data from one study.
12. **Risk of Bias: serious**. due to LOCF used for 28 days for clinical recovery. **Imprecision: very serious**. Low number of patients, Only data from one study, Wide confidence intervals.
14. **Risk of Bias: serious**. due to LOCF being used at day 28 of improvement. **Imprecision: very serious**. Low number of patients, Wide confidence intervals, Only data from one study.

**6.3.10.2 Interferon β-1b**
Evidence To Decision

Benefits and harms

General adult population
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with interferon β-1b, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

Children and adolescents, people requiring palliative care and older people living with frailty or cognitive impairment
There are additional concerns regarding harms as interferon β-1b has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

Pregnant and breastfeeding women
Evidence suggests that interferon β-1b in pregnant women is not associated with an increase in early pregnancy loss, stillbirths or congenital anomalies.

Certainty of the Evidence

Certainty of the evidence is low for discharge from hospital (days 14 and 28) and clinical deterioration (admission to ICU) due to very serious imprecision (low patient numbers and reliance on a single study). Certainty for the remaining outcomes is additionally downgraded due to few observed events.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for...
Rationale

**General adult population**

There is currently limited evidence about the impact of interferon β-1b on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that interferon β-1b should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of interferon β-1b to treat COVID-19 in these populations should be done with caution.

Resources and other considerations

**Important issues, or potential issues not investigated**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

**Important issues, or potential issues not investigated**

**General adult population**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

**Important issues, or potential issues not investigated**

**General adult population**

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

**General adult population**

There is currently limited evidence about the impact of interferon β-1b on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that interferon β-1b should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of interferon β-1b to treat COVID-19 in these populations should
be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Interferon β-1b
Comparator: Standard care

Summary
There remains significant uncertainty whether interferon β-1b is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared interferon β-1b with standard care in 66 adults hospitalised with severe COVID-19 [253].

We have found one new study comparing interferon β-1b with standard care (Darazam et al. Sci Rep doi: 10.1038/s41598-021-86859-y. This study is currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
Median age of patients was ~60 years in both groups and ~40% were women.

What are the main results?
For the critical outcomes, there were too few events (eight deaths and eight who experienced respiratory failure) to determine whether interferon β-1b makes a difference. We are uncertain whether interferon β-1b reduces septic shock, clinical deterioration, discharge from hospital or time to discharge from hospital. Data for adverse and serious events were not reported.

Our confidence in the results
Certainty of the evidence is low for discharge from hospital (days 14 and 28) and clinical deterioration (admission to ICU) due to very serious imprecision (low patient numbers and reliance on a single study). Certainty for the remaining outcomes is additionally downgraded due to few observed events.

Additional information
According to the Therapeutic Goods Administration, there are well-known side effects and harms associated with interferon β-1b, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation [256].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong>&lt;br&gt;Within 14 days of commencing treatment</td>
<td>Relative risk 0.33 (CI 95% 0.04 – 3.04)&lt;br&gt;Based on data from 66 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Very low&lt;br&gt;Due to very serious imprecision ²</td>
<td>There were too few events to determine whether interferon β-1b increases or decreases death at 14 days (4 events).</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong>&lt;br&gt;Within 28 days of commencing treatment</td>
<td>Relative risk 0.33 (CI 95% 0.07 – 1.53)&lt;br&gt;Based on data from 66 participants in 1 studies. ² (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Very low&lt;br&gt;Due to very serious imprecision ²</td>
<td>There were too few events to determine whether interferon β-1b increases or decreases death at 28 days (8 events).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Critical Respiratory failure or ARDS</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 0.33 (CI 95% 0.07 – 1.53) Based on data from 66 participants in 1 studies. 5 (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Very low Due to very serious imprecision 6</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.25 (CI 95% 0.03 – 2.12) Based on data from 66 participants in 1 studies. 7 (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Very low Due to very serious imprecision 8</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.44 (CI 95% 1.01 – 2.07) Based on data from 66 participants in 1 studies. 11 (Randomized controlled)</td>
<td>Standard care</td>
<td></td>
<td>Very low Due to very serious imprecision and serious risk of bias 12</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.15 (CI 95% 0.96 – 1.38) Based on data from 66 participants in 1 studies. 13 (Randomized controlled)</td>
<td>Standard care</td>
<td></td>
<td>Very low Due to very serious imprecision and serious risk of bias 14</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td>Relative risk 0.64</td>
<td></td>
<td></td>
<td>Very low</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
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<td>-----------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>deterioration (admission to ICU) Within 28 days of commencing treatment</td>
<td>(CI 95% 0.4 – 1.01) Based on data from 66 participants in 1 studies.</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Due to very serious imprecision and serious risk of bias</td>
<td>interferon β-1b decreases clinical deterioration (based on admission to ICU; 36 events).</td>
</tr>
<tr>
<td>Time to discharge from hospital</td>
<td>Based on data from: 66 participants in 1 studies.</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

2. **Imprecision:** very serious. Low number of patients, Only data from one study, due to few events.
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17. Primary study[253]. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** very serious. Low number of patients, Only data from one study.
Clinical Question/ PICO

**Population:** Special populations with COVID-19  
**Intervention:** Interferon β-1b  
**Comparator:** Standard care

**Summary**

There remains significant uncertainty whether interferon β-1b is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from a single randomised trial that compared interferon β-1b with standard care in 66 adults hospitalised with severe COVID-19 [253].

We have found one new study comparing interferon β-1b with standard care (Darazam et al. Res Sq doi: 10.21203/rs.3.rs-136499/v1). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**

Median age of patients was ~60 years in both groups and ~40% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**

For the critical outcomes, there were too few events (eight deaths and eight who experienced respiratory failure) to determine whether interferon β-1b makes a difference. We are uncertain whether interferon β-1b reduces septic shock, clinical deterioration, discharge from hospital or time to discharge from hospital. Data for adverse and serious events were not reported.

**Our confidence in the results**

Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias (lack of blinding), very serious imprecision (low patient numbers, few observed events and reliance on a single study) and serious indirectness (limited inclusion of these populations). Mortality, respiratory failure or ARDS and septic shock were not downgraded for risk of bias as these outcomes are unlikely to be affected by lack of blinding.

**Additional information**

According to the Therapeutic Goods Administration, there are well-known side effects and harms associated with interferon β-1b, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation [256].

**Children and adolescents**

Efficacy and safety of interferon β-1b has not been investigated in children and adolescents for other indications. To date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population.

**Pregnant and breastfeeding women**

Interferon β-1b is used in pregnancy for the treatment of multiple sclerosis. Evidence has shown no correlation between the use of Interferon β-1b and increases in early pregnancy loss, stillbirths or congenital anomalies [162].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
</table>
| All-cause mortality  
Within 14 days of commencing treatment | Relative risk 0.33  
(CI 95% 0.04 - 3.04)  
Based on data from 66 participants in 1 studies. 1 (Randomized controlled) | Standard care | Interferon β-1b | Very low  
Due to very serious imprecision and serious | We are uncertain whether interferon β-1b increases or decreases death at 14 days (4 events). |
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.33 (CI 95% 0.07 — 1.53) Based on data from 66 participants in 1 studies.⁹ (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether interferon β-1b increases or decreases death at 28 days (8 events).</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 0.33 (CI 95% 0.07 — 1.53) Based on data from 66 participants in 1 studies.⁹ (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether interferon β-1b increases or decreases respiratory failure or ARDS (8 events).</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.25 (CI 95% 0.03 — 2.12) Based on data from 66 participants in 1 studies.⁷ (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether interferon β-1b increases or decreases septic shock (5 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data for adverse events were not reported.</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data for serious adverse events were not reported.</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 14 days of commencing treatment</td>
<td>Relative risk 1.44 (CI 95% 1.01 — 2.07) Based on data from 66 participants in 1 studies.¹¹ (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon β-1b</td>
<td>Very low Due to very serious imprecision, serious risk of bias and serious indirectness</td>
<td>We are uncertain whether interferon β-1b may increases discharge from hospital within 14 days (44 events).</td>
</tr>
<tr>
<td>Discharge from</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain</td>
</tr>
<tr>
<td>Outcome/Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator/Study Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
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</tr>
<tr>
<td><strong>Hospital</strong> Within 28 days of commencing treatment</td>
<td>(CI 95% 0.96 – 1.38) Based on data from 66 participants in 1 studies. 13 (Randomized controlled)</td>
<td>Standard care Interferon β-1b</td>
<td>Due to very serious imprecision, serious risk of bias and serious indirectness 14</td>
<td>whether interferon β-1b has any impact on discharge from hospital within 28 days (58 events).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical deterioration (admission to ICU)</strong> Within 28 days of commencing treatment</td>
<td>Relative risk 0.64 (CI 95% 0.4 – 1.01) Based on data from 66 participants in 1 studies. 15 (Randomized controlled)</td>
<td></td>
<td>Very low Due to very serious imprecision, serious risk of bias and serious indirectness 16</td>
<td>We are uncertain whether interferon β-1b has any impact on clinical deterioration (based on admission to ICU; 36 events).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time to discharge from hospital</strong> Days</td>
<td>Based on data from: 66 participants in 1 studies. 17 (Randomized controlled)</td>
<td></td>
<td>Very low Due to very serious imprecision, serious risk of bias and serious indirectness 18</td>
<td>We are uncertain whether interferon β-1b increases or decreases time to discharge from hospital.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients. Only data from one study, due to few events.
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6.3.10.3 Interferon gamma

Only in research settings

Do not use interferon gamma for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Interferon gamma should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use interferon gamma to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

General adult population
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with interferon gamma including gastrointestinal disorders (such as diarrhoea, vomiting, nausea and abdominal pain), rash, fever and headache, and depression.

Certainty of the Evidence

General adult population
Certainty of the evidence is very low for all outcomes due to serious imprecision (low patient numbers and the reliance on a single study) and risk of bias (missing outcome data for negative PCR and adverse events, and lack of blinding for discharge from hospital).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because
of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Preference and values

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of interferon gamma during pregnancy and breastfeeding are unknown in the context of COVID-19.

### Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

**General adult population**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

**General adult population, children and adolescents, pregnant and breastfeeding women**

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.
Rationale

General adult population
There is currently limited evidence about the impact of interferon gamma on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that interferon gamma should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of interferon gamma to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Interferon gamma</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary
There remains significant uncertainty whether interferon gamma is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared interferon gamma with standard care in 63 adults hospitalised with mild or moderate COVID-19 [258].

We have found one new study comparing interferon gamma with control (Myasnikov et al. Vopr Virusol doi: 10.36233/0507-4088-24). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

Publication status
The study is only available as a preprint (posted to medRxiv on 4 August 2020) and has therefore not been peer reviewed.

Study characteristics
Median age was 42 years in the interferon gamma group and 31 years in the control group; the proportion of women was 53% and 39% respectively. Pregnant and breastfeeding women were ineligible.

What are the main results?
No patients died or experienced serious adverse events. We are uncertain whether interferon gamma increases or decreases the likelihood of negative PCR at days 3 and 5, discharge from hospital or adverse events.

Our confidence in the results
Certainty of the evidence is very low for all outcomes due to serious imprecision (low patient numbers and reliance on a single study) and serious risk of bias (missing outcome data for negative PCR and adverse events, and lack of blinding for discharge from hospital).

Additional information
According to the Therapeutic Goods Administration, common adverse effects related to interferon gamma include gastrointestinal disorders (such as diarrhoea, vomiting, nausea and abdominal pain), rash, depression, fever and headache [259].
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<tr>
<th>Outcome</th>
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<tr>
<td>All-cause mortality</td>
<td>21 days after commencing treatment</td>
<td>Based on data from 63 participants in 1 studies.</td>
<td>Standard care</td>
<td>Interferon gamma</td>
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<tr>
<td>Adverse events</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>No patients had serious adverse events.</td>
</tr>
<tr>
<td>Negative PCR (Day 3)</td>
<td>3 days after commencing treatment</td>
<td>Relative risk 1.84 (CI 95% 1.04 – 3.25)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 3 (29 events).</td>
</tr>
<tr>
<td>Negative PCR (Day 5)</td>
<td>5 days after commencing treatment</td>
<td>Relative risk 1.3 (CI 95% 1 – 1.68)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events).</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>14 days after commencing treatment</td>
<td>Relative risk 1.1 (CI 95% 0.97 – 1.24)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether interferon gamma increases discharge from hospital (60 events).</td>
</tr>
</tbody>
</table>

used for intervention.


3. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Imprecision:** very serious. Low number of patients, Only data from one study.


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**Clinical Question/ PICO**

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**Summary**

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**Our confidence in the results**

Certainty of the evidence is very low for all outcomes due to serious imprecision (low patient numbers and reliance on a single study), serious risk of bias (missing outcome data for negative PCR and adverse events, and lack of blinding for discharge from hospital) and serious indirectness (absence of these populations from the included studies).
### Additional information

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<td>Standard care</td>
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<td>Very low</td>
<td>No patients died in the study.</td>
</tr>
<tr>
<td>21 days after commencing treatment</td>
<td>Relative risk 1.21 (CI 95% 0.56 — 2.61) Based on data from 57 participants in 1 studies. ² (Randomized controlled)</td>
<td></td>
<td></td>
<td>Due to serious risk of bias, very serious imprecision and serious indirectness ³</td>
<td>We are uncertain whether interferon gamma increases or decreases adverse events (18 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td>Very low</td>
<td>No patients had serious adverse events.</td>
</tr>
<tr>
<td>21 days after commencing treatment</td>
<td>Relative risk 1.3 (CI 95% 1 — 1.68) Based on data from 47 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Due to serious risk of bias, very serious imprecision and serious indirectness ⁸</td>
<td>We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Based on data from 63 participants in 1 studies. ⁴</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 3 (29 events).</td>
</tr>
<tr>
<td>21 days after commencing treatment</td>
<td>Relative risk 1.84 (CI 95% 1.04 — 3.25) Based on data from 59 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Due to serious risk of bias, very serious imprecision and serious indirectness ⁶</td>
<td>We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events).</td>
</tr>
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<td>Negative PCR (Day 3)</td>
<td>Relative risk 1.3 (CI 95% 1 — 1.68) Based on data from 47 participants in 1 studies. ⁷ (Randomized controlled)</td>
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<td>Very low</td>
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<td>3 days after commencing treatment</td>
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<td></td>
<td></td>
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<tr>
<td>5 days after commencing treatment</td>
<td>Relative risk 1.3 (CI 95% 1 — 1.68) Based on data from 47 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Due to serious risk of bias, very serious imprecision and serious indirectness ⁸</td>
<td>We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events).</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Relative risk 1.1 (CI 95% 0.97 — 1.24) Based on data from 63 participants in 1 studies. ³</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events).</td>
</tr>
</tbody>
</table>
**Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)**

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 days after commencing treatment</td>
<td>participants in 1 studies. 9 (Randomized controlled)</td>
<td>Standard care</td>
<td>Interferon gamma</td>
<td>risk of bias, very serious imprecision and serious indirectness 10</td>
<td>discharge from hospital (60 events).</td>
</tr>
</tbody>
</table>

3. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.
6. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.
8. **Risk of Bias:** serious. Incomplete data and/or large loss to follow up. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.
10. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Only data from one study.

**6.3.10.4 Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)**

**Only in research settings**

Do not use IFN-κ plus TFF2 for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

IFN-κ plus TFF2 should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use IFN-κ plus TFF2 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Evidence To Decision

Benefits and harms

General adult population
Data for deaths, adverse events or serious adverse events were not reported in the study. There remains uncertainty regarding the benefits of IFN-κ plus TFF2 in patients with COVID-19, as well as uncertainty regarding the safety profile of this combination therapy.

Certainty of the Evidence

Certainty of the evidence is very low for all reported outcomes due to serious risk of bias (lack of blinding of patients and personnel) and very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals).

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of IFN-κ plus TFF2 during pregnancy and breastfeeding are unknown in the context of COVID-19.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.
### Rationale

**General adult population**

There is currently limited evidence about the impact of IFN-κ plus TFF2 on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that IFN-κ plus TFF2 should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of IFN-κ plus TFF2 for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>IFN-κ plus TFF2</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Summary

There remains significant uncertainty whether therapy with interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2) is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from one randomised trial that compared IFN-κ plus TFF2 with standard care in 80 adults hospitalised with COVID-19 [261].

**Study characteristics**

Mean age of patients was 35 years in both groups and 36% were women. IFN-κ (2 mg) and TFF2 (5 mg) were dissolved in 5 ml of water and administered via aerosol inhalation once every 24 hours for six days. Standard care included hydroxychloroquine, antibiotics, vasopressors, antifever medicine, vitamin C, immune enhancers and/or traditional Chinese medicine. Pregnant and breastfeeding women were ineligible.

**What are the main results?**

There were no deaths or serious adverse events in either group. Compared with standard care, we are uncertain if IFN-κ plus TFF2 leads to clinical improvement based on chest CT scans, or increases or decreases time to discharge from hospital or time to negative PCR.

**Our confidence in the results**

Certainty of the evidence is very low for all reported outcomes due to serious risk of bias (lack of blinding of patients and personnel) and very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals).
### Additional information
As of 5 October 2020, IFN-κ plus TFF2 is not listed on the Australian Register of Therapeutic Goods and is not available for use in Australia.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 12 days of commencing treatment</td>
<td>Based on data from 80 participants in 1 studies.</td>
<td>Standard care</td>
<td>IFN-κ plus TFF2</td>
<td>Very low</td>
<td>No patients died.</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Within 12 days of commencing treatment</td>
<td>Based on data from 80 participants in 1 studies.</td>
<td>Standard care</td>
<td>IFN-κ plus TFF2</td>
<td>Very low</td>
<td>No patients experienced a serious adverse event.</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Within 12 days of commencing treatment</td>
<td>Relative risk 1.21 (CI 95% 0.96 – 1.51) Based on data from 80 participants in 1 studies.</td>
<td>Standard care</td>
<td>IFN-κ plus TFF2</td>
<td>Very low</td>
<td>We are uncertain whether IFN-κ plus TFF2 increases or decreases clinical improvement based on chest CT scan (64 events).</td>
</tr>
<tr>
<td>Time to discharge from hospital</td>
<td>Days</td>
<td>Lower better Based on data from: 80 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>IFN-κ plus TFF2</td>
<td>Very low</td>
<td>We are uncertain whether IFN-κ plus TFF2 increases or decreases time to discharge from hospital.</td>
</tr>
<tr>
<td>Time to negative PCR</td>
<td>Days</td>
<td>Lower better Based on data from: 80 participants in 1 studies.</td>
<td>Standard care</td>
<td>IFN-κ plus TFF2</td>
<td>Very low</td>
<td>We are uncertain whether IFN-κ plus TFF2 increases or decreases time to negative PCR.</td>
</tr>
</tbody>
</table>

3. Based on chest CT imaging; reduction in the size and density of lesions.
6.3.10.5 Peginterferon lambda

We have found two new studies comparing peginterferon lambda with placebo (Jagannathan et al. medRxiv doi: 10.1101/2020.11.18.20234161 and Feld et al. medRxiv doi: 10.1101/2020.11.09.20228098). These studies are currently under review and a recommendation will be included in a future version of the guideline.

**Evidence To Decision**

**Benefits and harms**

**General adult population**

As the safety profile for peginterferon lambda is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as peginterferon lambda has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

Certainty of the evidence is low for all outcomes due to very serious imprecision (wide confidence intervals, low patient numbers and/or low number of events).
### Preference and values

#### General adult population
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

#### Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of peginterferon lambda during pregnancy and breastfeeding are unknown in the context of COVID-19.

### Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered, but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

#### General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

#### Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

#### People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

#### General adult population
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

#### People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

### Feasibility
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

#### General adult population
There is currently limited evidence about the impact of peginterferon lambda on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that peginterferon lambda should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of peginterferon lambda to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Peginterferon lambda</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary
There remains significant uncertainty whether therapy with peginterferon lambda is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials that compared a single 180 microgram dose of subcutaneously delivered peginterferon lambda with placebo in 180 adult outpatients with mild or moderate COVID-19 [302][303].

Study characteristics
Median age of participants was 36 years in Jagannathan et al. and 46 years in Feld et al. In both studies, 42% were women. Pregnant and breastfeeding women were ineligible.

What are the main results?
Reporting of critical outcomes was minimal across both studies due to the inclusion of outpatients with mild or moderate illness. There were no deaths in either study. We are uncertain whether peginterferon lambda increases or decreases the incidence of serious adverse events (six events) or adverse events, or whether it improves or worsens hospitalisation or time to clinical progression.

Our confidence in the results
Certainty of the evidence is low for all outcomes due to very serious imprecision (wide confidence intervals, low patient numbers and/or low number of events).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Whereas peginterferon alpha and beta are listed on the Australian Register of Therapeutic Goods, as of 11 December 2020, peginterferon lambda is not listed. The safety profile of peginterferon lambda is incompletely characterised in humans.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Based on data from 60</td>
<td>Standard</td>
<td>Peginterferon</td>
<td></td>
<td>There were no deaths</td>
</tr>
<tr>
<td></td>
<td>participants in 1</td>
<td>care</td>
<td>lambda</td>
<td></td>
<td>in the study that</td>
</tr>
<tr>
<td></td>
<td>studies. ¹</td>
<td></td>
<td></td>
<td></td>
<td>reported this outcome.</td>
</tr>
</tbody>
</table>

¹ Including data from the study by Feld et al., where the comparator was placebo in 30 patients.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1 (CI 95% 0.21 — 4.82) Based on data from 180 participants in 2 studies. ^2 (Randomized controlled)</td>
<td>Standard care</td>
<td>Peginterferon lambda</td>
<td>Low Due to very serious imprecision ^3</td>
<td>We are uncertain whether peginterferon lambda increases or decreases serious adverse events (6 events).</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.21 (CI 95% 0.77 — 1.9) Based on data from 180 participants in 2 studies. ^4 (Randomized controlled)</td>
<td>Standard care</td>
<td>Peginterferon lambda</td>
<td>Low Due to very serious imprecision ^5</td>
<td>We are uncertain whether peginterferon lambda increases or decreases adverse events (49 events).</td>
</tr>
<tr>
<td><strong>Hospitalisation</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1 (CI 95% 0.21 — 4.82) Based on data from 180 participants in 2 studies. ^6 (Randomized controlled)</td>
<td>Standard care</td>
<td>Peginterferon lambda</td>
<td>Low Due to very serious imprecision ^7</td>
<td>We are uncertain whether peginterferon lambda increases or decreases incidence of hospitalisation (6 events).</td>
</tr>
<tr>
<td><strong>Time to clinical progression</strong></td>
<td>Days</td>
<td>Based on data from: 120 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Peginterferon lambda</td>
<td>Low Due to very serious imprecision ^8</td>
<td>We are uncertain whether peginterferon lambda increases or decreases time to clinical progression.</td>
</tr>
</tbody>
</table>

3. **Imprecision: very serious**. Low number of patients, Wide confidence intervals, due to few events.
5. **Imprecision: very serious**. Low number of patients, Wide confidence intervals.
7. **Imprecision: very serious**. Low number of patients, Wide confidence intervals, due to few events.
8. **Imprecision: very serious**. Low number of patients, Wide confidence intervals, Only data from one study.
6.3.11 Other antibody related therapies

6.3.11.1 Bamlanivimab

**Evidence To Decision**

**Benefits and harms**

**General adult population**

Although preliminary evidence suggests that compared with standard care bamlanivimab does not result in more adverse or serious adverse events, it remains unclear if bamlanivimab is safe for the treatment of COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as bamlanivimab has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. There is insufficient evidence pertaining to the safety of bamlanivimab for pregnant or breastfeeding women.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence for all outcomes is low due to very serious imprecision (either reliance on a single study and wide confidence intervals, or few events). Certainty for serious adverse events is very low.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of bamlanivimab in pregnancy are unknown.
Rationale

General adult population
There is currently limited evidence about the impact of bamlanivimab on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that bamlanivimab should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of bamlanivimab to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO
Population: Patients with COVID-19
**Summary**
There remains significant uncertainty whether the neutralising antibody bamlanivimab is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials. BLAZE-1 compared bamlanivimab with standard care in 465 adult outpatients with mild COVID-19 [199], and ACTIV-3/TICO compared bamlanivimab with placebo in 314 patients with moderate to severe illness [200].

**Study characteristics**
In BLAZE-1 mean age of participants was 45 years and 55% were women. Patients allocated bamlanivimab were assigned to three different dosage groups (700 mg, 2800 mg and 7000 mg); however, results were similar and were pooled for analysis. In ACTIV-3/TICO median age was ~60 years and 44% were women. Pregnant women were ineligible in both studies.

**What are the main results?**
We are uncertain whether bamlanivimab makes a difference with regards to death, adverse events, hospitalisation, discharge from hospital, virological clearance (defined as negative PCR) or rate of clinical recovery/clinical improvement. No patients experienced a serious adverse event.

**Our confidence in the results**
Certainty of the evidence for all outcomes is low due to very serious imprecision (either reliance on a single study and wide confidence intervals, or few events). Certainty for serious adverse events is very low.

For children & adolescents and pregnant & breastfeeding women, certainty is downgraded to very low due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Bamlanivimab was developed as a highly specific treatment for COVID-19. The treatment is not approved for use in Australia and, as of 16 November 2020, there are no reliable safety data to inform treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Bamlanivimab</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.67 (CI 95% 0.57 — 4.86) Based on data from 779 participants in 2 studies. ¹ (Randomized controlled)</td>
<td>16 per 1000</td>
<td>27 per 1000</td>
<td>Low Due to very serious imprecision ²</td>
<td>We are uncertain whether bamlanivimab impacts death (19 events).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Within 30 days of commencing treatment</td>
<td>Based on data from 465 participants in 1 studies. ³ (Randomized controlled)</td>
<td>9 Critical</td>
<td>16 per 1000</td>
<td>Very low Due to very serious imprecision ⁴</td>
<td>No patients experienced a serious adverse event.</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td>Relative risk 0.9 (CI 95% 0.65 — 1.25)</td>
<td>269</td>
<td>242</td>
<td>Low Due to very</td>
<td>We are uncertain whether bamlanivimab</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
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<td>------------------------------------------------</td>
<td>---------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>Within 30 days of commencing treatment</td>
<td>Relative risk 0.28 (CI 95% 0.1 – 0.82) Based on data from 465 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Bamlanivimab  per 1000 per 1000 Difference: 27 fewer per 1000 (CI 95% 94 fewer – 67 more )</td>
<td>Low Due to very serious imprecision 6 We are uncertain whether bamlanivimab increases or decreases adverse events (117 events).</td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Within 30 days of commencing treatment</td>
<td>Relative risk 0.97 (CI 95% 0.9 – 1.05) Based on data from 314 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Bamlanivimab  58 per 1000 per 1000 Difference: 42 fewer per 1000 (CI 95% 52 fewer – 10 fewer )</td>
<td>Low Due to very serious imprecision 8 We are uncertain whether bamlanivimab increases or decreases hospitalisation (14 events).</td>
<td></td>
</tr>
<tr>
<td>Virological clearance</td>
<td>(negative PCR) End of follow-up</td>
<td>Relative risk 0.85 (CI 95% 0.67 – 1.08) Based on data from 431 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Bamlanivimab  459 per 1000 per 1000 Difference: 69 fewer per 1000 (CI 95% 151 fewer – 37 more )</td>
<td>Low Due to very serious imprecision 12 We are uncertain whether bamlanivimab increases or decreases negative PCR (177 events).</td>
<td></td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 30 days of commencing treatment</td>
<td>Relative risk 1.03 (CI 95% 0.89 – 1.2) Based on data from 168 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Bamlanivimab  790 per 1000 per 1000 Difference: 24 more per 1000 (CI 95% 87 fewer – 158 more )</td>
<td>Low Due to very serious imprecision 14 We are uncertain whether bamlanivimab improves or worsens clinical recovery (135 events).</td>
<td></td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Within 30 days of commencing treatment</td>
<td>Relative risk 1.11 (CI 95% 0.93 – 1.33) Based on data from 253 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Bamlanivimab  632 per 1000 per 1000 Difference: 70 more per 1000 (CI 95% 44 fewer – 209 more )</td>
<td>Low Due to very serious imprecision 16 We are uncertain whether bamlanivimab improves or worsens clinical improvement (167 events).</td>
<td></td>
</tr>
</tbody>
</table>
6.3.11.2 Bamlanivimab plus etesevimab

**Evidence To Decision**

**Benefits and harms**

**General adult population**

As the safety profile for bamlanivimab plus etesevimab is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There are additional concerns regarding harms as bamlanivimab plus etesevimab has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

**General adult population**

Certainty is low for all outcomes due to very serious imprecision (reliance on a single study, wide confidence intervals and few events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

In addition to the concerns in the general adult population, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of bamlanivimab plus etesevimab in pregnancy are unknown.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

**General adult population**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.
Acceptability
General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale
General adult population
There is currently limited evidence about the impact of bamlanivimab plus etesevimab on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that bamlanivimab plus etesevimab should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of bamlanivimab plus etesevimab to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO
- Population: Patients with COVID-19
- Intervention: Bamlanivimab plus etesevimab
- Comparator: Placebo

Summary
There remains significant uncertainty whether bamlanivimab plus etesevimab is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials (phase II and III of the BLAZE-1 trial) that compared bamlanivimab plus etesevimab with placebo in 248 adults with mild COVID-19 [199] and 1033 adults with mild or moderate COVID-19 who were at high risk for progression to severe disease [535].

Study characteristics
Median age of participants in phase II (Gottlieb et al.) and phase III (Dougan et al.) of BLAZE-1 was 45 and 54 years, respectively. Across both phases 52% were women. Patients received either a single one-hour infusion of 2,800 mg bamlanivimab plus 2,800 mg etesevimab or placebo solution. Pregnant and breastfeeding women were ineligible.

What are the main results?
There were too few who died or experienced a serious adverse event or required hospitalisation to determine whether bamlanivimab plus etesevimab makes a difference. We are uncertain if bamlanivimab plus etesevimab increases or decreases adverse events, clinical improvement, clinical recovery or negative PCR.

Our confidence in the results
Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single study, low
patient numbers and few events) or serious imprecision and serious inconsistency (point estimates do not overlap or inconsistency in direction of effect).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

Bamlanivimab and etesevimab were developed as highly specific treatments for COVID-19. These treatments are not approved for use in Australia and, as of 1 August 2021, there are no reliable safety data to inform treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>End of treatment</td>
<td>Relative risk 0.05 (CI 95% 0 – 0.81) Based on data from 1,303 participants in 2 studies. ¹ (Randomized controlled)</td>
<td>Placebo</td>
<td>Bamlanivimab plus etesevimab</td>
<td>Low</td>
<td>Due to serious inconsistency and serious imprecision ²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 per 1000</td>
<td>1 per 1000</td>
<td>14 fewer per 1000 (CI 95% 15 fewer – 3 fewer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 1.4 (CI 95% 0.49 – 4.01) Based on data from 1,303 participants in 2 studies. ³ (Randomized controlled)</td>
<td></td>
<td>Bamlanivimab plus etesevimab</td>
<td>Low</td>
<td>Due to serious inconsistency and serious imprecision ³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 per 1000</td>
<td>13 per 1000</td>
<td>4 more per 1000 (CI 95% 5 fewer – 27 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>End of follow-up</td>
<td>Relative risk 0.87 (CI 95% 0.49 – 1.57) Based on data from 1,303 participants in 2 studies. ⁴ (Randomized controlled)</td>
<td></td>
<td>Bamlanivimab plus etesevimab</td>
<td>Low</td>
<td>Due to very serious imprecision ⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>152 per 1000</td>
<td>132 per 1000</td>
<td>20 fewer per 1000 (CI 95% 78 fewer – 87 more)</td>
<td></td>
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</tr>
<tr>
<td><strong>Hospitalisation</strong></td>
<td>Within 29 days of commencing treatment</td>
<td>Relative risk 0.15 (CI 95% 0.02 – 1.21) Based on data from 261 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td></td>
<td>Bamlanivimab plus etesevimab</td>
<td>Low</td>
<td>Due to very serious inconsistency, Due to serious imprecision ⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59 per 1000</td>
<td>9 per 1000</td>
<td>50 fewer per 1000 (CI 95% 58 fewer – 12 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>Within 22 days of commencing treatment</td>
<td>Relative risk 1.13 (CI 95% 0.96 – 1.34) Based on data from 261 participants in 1 studies. ⁶ (Randomized controlled)</td>
<td></td>
<td>Bamlanivimab plus etesevimab</td>
<td>Low</td>
<td>Due to very serious imprecision ⁶</td>
</tr>
<tr>
<td></td>
<td></td>
<td>632 per 1000</td>
<td>714 per 1000</td>
<td>82 more per 1000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# 6.3.11.3 Regdanvimab

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention Bam+etesevimab</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical recovery</td>
<td>Relative risk 1.19 (CI 95% 0.99 – 1.43) Based on data from 261 participants in 1 studies.</td>
<td>Placebo</td>
<td>Bam+etesevimab</td>
<td>Low</td>
<td>We are uncertain whether bamlanivimab plus etesevimab improves or worsens clinical recovery (163 events).</td>
</tr>
<tr>
<td>6 Important</td>
<td>controlled)</td>
<td></td>
<td>( CI 95% 25 fewer — 215 more )</td>
<td></td>
<td>(174 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>579 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 10 more per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( CI 95% 22 fewer — 249 more )</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative risk 1 (CI 95% 0.72 – 1.38) Based on data from 261 participants in 1 studies.</td>
<td>Low</td>
<td>We are uncertain whether bamlanivimab plus etesevimab improves or worsens negative PCR (96 events).</td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td>368 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: 0 fewer per 1000</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>( CI 95% 103 fewer — 140 more )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Systematic review [529] with included studies: Gottlieb 2021, BLAZE-1 pIII. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Imprecision:** serious, due to few events.
4. **Imprecision:** very serious, due to few events.
6. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Imprecision:** serious. Wide confidence intervals.
7. Systematic review [201] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision:** very serious. Low number of patients, Only data from one study, Wide confidence intervals, due to few events.
10. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
12. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
14. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
Evidence To Decision

**Benefits and harms**
Based on the available evidence, it is unclear if regdanvimab is safer or more effective than standard care for the treatment of COVID-19. The safety profile for regdanvimab is incompletely characterised in humans and it is not approved for use in Australia.

**Certainty of the Evidence**
Certainty of the evidence is very low for all outcomes due to very serious imprecision (low patient numbers, wide confidence intervals and reliance on a single study).

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability**

*General adult population, children and adolescents, pregnant and breastfeeding women*
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

*People requiring palliative care and older people living with frailty or cognitive impairment*
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

*General adult population*
There is currently limited evidence about the impact of regdanvimab on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that regdanvimab should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

*Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment*
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of regdanvimab to treat COVID-19 in these populations should be avoided until evidence becomes available.

**Clinical Question/ PICO**

| Population: | Patients with COVID-19 |
| Intervention: | Regdanvimab monoclonal antibody |
| Comparator: | Standard care |

**Summary**
There remains significant uncertainty whether regdanvimab (CT-P59) is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared regdanvimab with standard care in 327 adult outpatients with mild or moderate COVID-19 [226].
**Publication status**  
The study is only available as a preprint (posted to Res Sq on 15 March 2021) and has therefore not been peer reviewed.

**Study characteristics**  
Median age of participants was ~51 years and 56% were women. Ninety-four per cent had laboratory-confirmed COVID-19.

**What are the main results?**  
No deaths had occurred in either group by day 28. Invasive mechanical ventilation occurred in one patient. Supplemental oxygen (17 events) and hospitalisation (18 events) were infrequently reported. There were similar numbers of adverse events in the regdanvimab group (27%) compared with the placebo group (31%). By day 28 clinical recovery was higher with regdanvimab (87%) compared with placebo (71%).

**Our confidence in the results**  
Certainty of the evidence is very low for all outcomes due to very serious imprecision (low patient numbers, wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included study).

**Additional information**  
As of 30 March 2021, regdanvimab is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. The safety profile for regdanvimab is incompletely characterised in humans.

**Pregnant and breastfeeding women**  
There are additional concerns regarding harms, as regdanvimab has not been sufficiently tested in this population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Based on data from 307 participants in 1 studies.</td>
<td>Standard care</td>
<td>Regdanvimab monoclonal antibody</td>
<td>2</td>
<td>There were no deaths.</td>
</tr>
<tr>
<td>Day 28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Relative risk 1.52 (CI 95% 0.06 — 37.04) Based on data from 307 participants in 1 studies.</td>
<td>Standard care</td>
<td>Regdanvimab monoclonal antibody</td>
<td>Very low due to very serious imprecision and serious publication bias</td>
<td>There were too few who required invasive mechanical ventilation to determine whether regdanvimab makes a difference (1 event).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>Relative risk 0.45 (CI 95% 0.18 — 1.13) Based on data from 307 participants in 1 studies.</td>
<td>Standard care</td>
<td>Regdanvimab monoclonal antibody</td>
<td>Very low due to very serious imprecision and serious publication bias</td>
<td>We are uncertain whether regdanvimab increases or decreases requirement for supplemental oxygen (17 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
</tr>
<tr>
<td>---------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>ICU admission</td>
<td>End of follow-up</td>
<td>Based on data from 307 participants in 1 studies.</td>
<td>Control arm of reference used for intervention.</td>
<td>Regdanvimab monoclonal antibody</td>
<td>Very low</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.87 (CI 95% 0.61 — 1.25) Based on data from 325 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>End of follow-up</td>
<td>Relative risk 0.5 (CI 95% 0.21 — 1.23) Based on data from 307 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>End of follow-up</td>
<td>Relative risk 1.21 (CI 95% 1.06 — 1.39) Based on data from 285 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
</tr>
</tbody>
</table>

2. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Low number of patients, Only data from one study, due to no events. **Publication bias**: no serious. Mostly commercially funded studies.
4. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Wide confidence intervals, Only data from one study. **Publication bias**: serious. Mostly commercially funded studies.
6. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias**: serious. Mostly commercially funded studies.
8. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias**: serious. Mostly commercially funded studies.
10. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias**: serious. Mostly commercially funded studies.
6.3.12 Other therapies

6.3.12.1 Aprepitant

Only in research settings

Do not use aprepitant for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

**Aprepitant should still be considered for other evidence-based indications in people who have COVID-19.**

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use aprepitant to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.**

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with aprepitant, including fatigue, muscle weakness, headache or dizziness, gastrointestinal symptoms and rash.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence is very low for both outcomes. This judgement is based on very serious risk of bias (patients and personnel not blinded, deviation from intended intervention [20 mg dexamethasone provided to both groups compared to 6 mg as stated in the ClinicalTrials.gov entry] and selective outcome reporting), serious indirectness (due to insufficient timeframe), and very serious imprecision (results based on only one study with low patient numbers and few events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trial.
### Preference and values

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

### Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

**General adult population, children and adolescents, pregnant and breastfeeding women**
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

**General adult population**
There is currently limited evidence about the impact of aprepitant on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that aprepitant should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of aprepitant to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

| Population: | Patients with COVID-19 |
| Intervention: | Aprepitant |
| Comparator: | Standard care |

Summary

There remains significant uncertainty whether aprepitant is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?

Evidence comes from a single randomised trial that compared aprepitant with standard care in 18 adults hospitalised with laboratory-confirmed COVID-19 [189].

Publication status

The study is only available as a preprint paper (posted to medRxiv on 4 August 2020) and has therefore not been peer reviewed. In addition to our daily evidence surveillance processes, we follow up with the corresponding author every two months to request an update on the study's publication status.

Study characteristics

Median age was 61 years in the aprepitant group and 48 years in the control group; the proportion of women was 20% and 63% respectively. Both groups received 20 mg of dexamethasone daily, and standard care included treatment with azithromycin, remdesivir and tocilizumab. Pregnant and breastfeeding women were ineligible.

What are the main results?

Preliminary results were presented for death and discharge from hospital within five days of starting treatment. For both outcomes, there were too few events (two deaths and two discharged from hospital) to determine whether aprepitant makes a difference. No data were reported on adverse or serious adverse events.

Our confidence in the results

Certainty of the evidence is very low for both outcomes. This judgement is based on very serious risk of bias (patients and personnel not blinded, deviation from intended intervention and selective outcome reporting), serious indirectness (insufficient timeframe), and very serious imprecision (results based on only one study with low patient numbers and few events).

Additional information

According to the Therapeutic Goods Administration, known acute harms for aprepitant include fatigue, muscle weakness, headache or dizziness, gastrointestinal symptoms, chills, hot flushes, hiccups and rash [190]. There are several known and potential interactions with other drugs, including hormonal contraceptives [190].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Aprepitant</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.8 (CI 95% 0.06 — 10.89) Based on data from 18</td>
<td></td>
<td></td>
<td>Very low Due to very serious risk of</td>
<td>There were too few who died to determine whether aprepitant</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care</td>
<td>Intervention Aprepitant</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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<tr>
<td>commencing treatment</td>
<td>participants in 1 study. ¹ (Randomized controlled)</td>
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<td></td>
<td>bias, very serious imprecision and serious indirectness ²</td>
<td>makes a difference (2 events).</td>
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<tr>
<td>Invasive mechanical ventilation</td>
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<tr>
<td>No studies were found that looked at patients requiring invasive mechanical ventilation.</td>
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<tr>
<td>Adverse events</td>
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<td>Within 5 days of commencing treatment</td>
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<td>No studies were found that looked at adverse events.</td>
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<tr>
<td>Serious adverse events</td>
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<tr>
<td>No studies were found that looked at serious adverse events.</td>
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<tr>
<td>Discharge from hospital</td>
<td>Relative risk 0.8 (CI 0.95% 0.06 – 10.89) Based on data from 18 participants in 1 study. ³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to very serious risk of bias, very serious imprecision and serious indirectness ⁴</td>
<td>There were too few who were discharged from hospital (2 events) to determine whether aprepitant makes a difference.</td>
</tr>
</tbody>
</table>
outcome time frame in studies were insufficient. **Imprecision: very serious.** Only data from one study, Low number of patients, due to few events.

### Clinical Question/ PICO

**Population:** Special populations with COVID-19  
**Intervention:** Aprepitant  
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether aprepitant is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from a single randomised trial that compared aprepitant with standard care alone in 18 adults hospitalised with laboratory confirmed COVID-19 [189].

**Publication status**

The study is only available as a preprint paper (posted to medRxiv on 4 August 2020) and has therefore not been peer-reviewed. In addition to our daily evidence surveillance processes, we also follow up with the corresponding author every two months to request an update on the study's publication status.

**Study characteristics**

Median age was 61 in the aprepitant group and 48 in the control group; the proportion of women was 20% and 63% respectively. Both groups received 20 mg dexamethasone daily, and standard care included treatment with azithromycin, remdesivir and tocilizumab. Pregnant and breastfeeding women were ineligible.

**What are the main results?**

Preliminary results were presented for death and discharge from hospital within five days of starting treatment. For both outcomes, there were too few events (two deaths and two discharged from hospital) to determine whether aprepitant makes a difference. No data were reported on adverse or serious adverse events.

**Our confidence in the results**

Certainty of the evidence is very low for both outcomes. This judgement is based on very serious risk of bias (patients and personnel not blinded, deviation from intended intervention and selective outcome reporting), serious indirectness (insufficient timeframe and limited inclusion of these populations), and very serious imprecision (results based on only one study with low patient numbers and few events).

### Additional information

According to the Therapeutic Goods Administration, known acute harms for aprepitant include fatigue, muscle weakness, headache or dizziness, gastrointestinal symptoms, chills, hot flushes, hiccups, rash [190]. There are several known and potential interactions with other drugs including hormonal contraceptives [190].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.8 (CI 0.95% 0.06 — 10.89) Based on data from 18 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Standard care</td>
<td>Aprepitant</td>
<td>Very low Due to very serious risk of bias, very serious imprecision and serious indirectness ²</td>
<td>There were too few who died to determine whether aprepitant makes a difference ² events.</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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</tr>
<tr>
<td>Invasive mechanical ventilation&lt;br&gt;Within 5 days of commencing treatment</td>
<td>9 Critical</td>
<td>Control arm of reference</td>
<td>Aprepitant</td>
<td>Very low&lt;br&gt;Due to very serious risk of bias, very serious imprecision and serious indirectness</td>
<td>No studies were found that looked at patients requiring invasive mechanical ventilation.</td>
</tr>
<tr>
<td>Adverse events&lt;br&gt;Within 5 days of commencing treatment</td>
<td>6 Important</td>
<td>Control arm of reference</td>
<td>Aprepitant</td>
<td>Very low&lt;br&gt;Due to very serious risk of bias, very serious imprecision and serious indirectness</td>
<td>No studies were found that looked at adverse events.</td>
</tr>
<tr>
<td>Serious adverse events&lt;br&gt;Within 5 days of commencing treatment</td>
<td>6 Important</td>
<td>Control arm of reference</td>
<td>Aprepitant</td>
<td>Very low&lt;br&gt;Due to very serious risk of bias, very serious imprecision and serious indirectness</td>
<td>No studies were found that looked at serious adverse events.</td>
</tr>
<tr>
<td>Discharge from hospital&lt;br&gt;Within 5 days of commencing treatment</td>
<td>Relative risk 0.8&lt;br&gt;(CI 95% 0.06 — 10.89)&lt;br&gt;Basisd on data from 18 participants in 1 studies. (Randomized controlled)</td>
<td>Control arm of reference</td>
<td>Aprepitant</td>
<td>Very low&lt;br&gt;Due to very serious risk of bias, very serious imprecision and serious indirectness</td>
<td>There were too few who were discharged from hospital to determine whether aprepitant makes a difference (2 events).</td>
</tr>
</tbody>
</table>

2. **Risk of Bias: very serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** The outcome timeframe in studies was insufficient, and there were differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, Only data from one study, due to few events.
4. **Risk of Bias: very serious.** Selective outcome reporting, Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: serious.** The outcome timeframe in studies was insufficient, and there were differences between the population of interest and those studied. **Imprecision: very serious.** Only data from one study, Low number of patients, due to few events.
6.3.12.2 Bromhexine hydrochloride

**Evidence To Decision**

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are common side effects associated with bromhexine hydrochloride including nausea, vomiting, diarrhoea, allergy and severe, low-risk skin reactions—erythema multiforme, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis.

**Pregnant and breastfeeding women**
Benefits can be assumed to outweigh possible risks for pregnant women—limited clinical experience has not resulted in adverse effects to the fetus. Bromhexine hydrochloride is safe to use in women who are breastfeeding.

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence is low for invasive mechanical ventilation due to serious risk of bias (lack of blinding of patients and outcome assessors) and serious imprecision (wide confidence intervals). Certainty is very low for all other outcomes due to very serious risk of bias (lack of blinding of patients and outcome assessors) and very serious imprecision (low patient numbers, few events and wide confidence intervals).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is further considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the
Rationale

General adult population
There is currently limited evidence about the impact of bromhexine hydrochloride on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that bromhexine hydrochloride should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of bromhexine hydrochloride for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of bromhexine hydrochloride on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that bromhexine hydrochloride should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of bromhexine hydrochloride for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.
Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Bromhexine hydrochloride
Comparator: Standard care

Summary
There remains significant uncertainty whether bromhexine hydrochloride is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared bromhexine hydrochloride with placebo in 196 adults hospitalised with mild or moderate COVID-19 [203][204][208].

Study characteristics
Mean age of participants ranged from 50 to 60 years and the proportion of women ranged from 22 to 54%. Patients received bromhexine hydrochloride for 14 days at varying doses (8 mg three times a day [203]; 32 mg three times a day [204]; 8 mg four times a day [208]). Pregnant and breastfeeding women were ineligible.

What are the main results?
There were too few who died (nine deaths) or suffered adverse events to determine whether bromhexine hydrochloride makes a difference. No patients experienced a serious adverse event. It is unclear whether bromhexine hydrochloride increases or decreases time to clinical improvement, need for invasive mechanical ventilation, discontinuation due to adverse events, admission to ICU, discharge from hospital or viral clearance.

Our confidence in the results
Certainty of the evidence is low for invasive mechanical ventilation due to serious risk of bias (lack of blinding of patients and outcome assessors) and serious imprecision (wide confidence intervals). Certainty is very low for all other outcomes due to very serious risk of bias (lack of blinding of patients and outcome assessors) and very serious imprecision (low patient numbers, few events and wide confidence intervals).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The safety profile for bromhexine hydrochloride indicates the following adverse effects: nausea, vomiting, diarrhoea and allergy (e.g. rash, urticaria, angioedema). Bromhexine hydrochloride has been associated with a low risk of severe skin reactions including erythema multiforme, Stevens-Johnson syndrome and acute generalised exanthematous pustulosis [270].

Pregnant and breastfeeding women
Bromhexine hydrochloride is considered safe in pregnancy [270].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality End of follow-up 9 Critical</td>
<td>Relative risk 0.5 (CI 95% 0.1 — 2.47) Based on data from 196 participants in 3 studies.</td>
<td>Standard care</td>
<td>Bromhexine hydrochloride</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>There were too few who died to determine whether bromhexine hydrochloride makes a difference (9 deaths).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation Within 28 days</td>
<td>Relative risk 0.61 (CI 95% 0.22 — 1.68) Based on data from 178 participants in 2 studies.</td>
<td>Standard care</td>
<td>Bromhexine hydrochloride</td>
<td>Low Due to serious risk of bias and serious</td>
<td>There were too few who required invasive mechanical ventilation to determine whether bromhexine hydrochloride makes a difference.</td>
</tr>
</tbody>
</table>

154 per 1000
Difference: 60 fewer per 1000
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Bromhexine hydrochloride</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
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<tbody>
<tr>
<td>of commencing treatment</td>
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<tr>
<td>9 Critical</td>
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<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Based on data from 178 participants in 2 studies.</td>
<td>Bromhexine hydrochloride 1000 (CI 95% 120 fewer — 105 more)</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>Bromhexine hydrochloride makes a difference (20 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
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<tr>
<td>6 Important</td>
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<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.38 (CI 95% 0.12 — 1.16) Based on data from 118 participants in 2 studies.</td>
<td>Bromhexine hydrochloride</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>There were too few adverse events to determine whether bromhexine hydrochloride makes a difference (7 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
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<tr>
<td>6 Important</td>
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<tr>
<td>Discontinuation due to adverse events</td>
<td>End of follow-up</td>
<td>Based on data from 18 participants in 1 studies.</td>
<td>Bromhexine hydrochloride</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>No patients discontinued treatment due to adverse events.</td>
</tr>
<tr>
<td>End of follow-up</td>
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<td>6 Important</td>
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<tr>
<td>ICU admission</td>
<td>End of follow-up</td>
<td>Relative risk 0.18 (CI 95% 0.04 — 0.77) Based on data from 96 participants in 2 studies.</td>
<td>Bromhexine hydrochloride</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>There were too few who required ICU admission to determine whether bromhexine hydrochloride makes a difference (13 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
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<td>6 Important</td>
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<tr>
<td>Virological clearance (negative PCR)</td>
<td>End of follow-up</td>
<td>Relative risk 1 (CI 95% 0.79 — 1.26) Based on data from 18 participants in 1 studies.</td>
<td>Bromhexine hydrochloride</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether bromhexine hydrochloride increases or decreases virological clearance.</td>
</tr>
<tr>
<td>End of follow-up</td>
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<tr>
<td>6 Important</td>
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<tr>
<td>Discharge from hospital</td>
<td>End of follow-up</td>
<td>Relative risk 2.5 (CI 95% 0.78 — 7.97) Based on data from 18 participants in 1 studies.</td>
<td>Bromhexine hydrochloride</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether bromhexine hydrochloride increases discharge from hospital.</td>
</tr>
<tr>
<td>End of follow-up</td>
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<td>6 Important</td>
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2. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for

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Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce
6.3.12.3 Fluvoxamine

Only in research settings

Do not use fluvoxamine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Fluvoxamine should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use fluvoxamine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Evidence To Decision

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known short-term harms associated with fluvoxamine use, including headache, dizziness, nausea and vomiting. Caution should be taken when prescribing fluvoxamine to patients with a history of depression due to the potential development of symptoms such as anxiety, panic attacks and mania [244].

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
The benefits and harms associated with fluvoxamine in pregnant women and young children with COVID-19 are not well established. Fluvoxamine is not recommended for the treatment of depression in pregnant women because of known harms to the fetus [244]. Caution should be taken when prescribing fluvoxamine to children, adolescents or elderly patients.

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence is moderate for all-cause mortality due to serious imprecision (deaths only occurred in one study) and low for all other outcomes (due to reliance on a single study, few events and/or wide confidence intervals).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
For children & adolescents and pregnant & breastfeeding women, certainty is downgraded to very low due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. As there are known harms associated with fluvoxamine use in pregnant and breastfeeding women, these patients would likely not opt for treatment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.
Rationale

General adult population
There is currently limited evidence about the impact of fluvoxamine on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that fluvoxamine should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of fluvoxamine on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that fluvoxamine should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of fluvoxamine to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Fluvoxamine
Comparator: Placebo

Summary
There remains significant uncertainty whether fluvoxamine is more effective and safer than placebo in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials comparing fluvoxamine to placebo in over 1600 adult outpatients with mild COVID-19 [243][619]. The vast majority of data comes from the TOGETHER trial.

**Study characteristics**
Within the TOGETHER trial, median age of participants was 50 years and 58% were women. Pregnant women were ineligible.

**What are the main results?**
We are uncertain whether fluvoxamine increases or decreases all-cause mortality, adverse or serious adverse events, patients requiring hospitalisation or clinical deterioration. There were too few who required mechanical ventilation (one event) to determine whether fluvoxamine makes a difference.

**Our confidence in the results**
Certainty of the evidence is moderate for all-cause mortality due to serious imprecision (deaths only occurred in one study) and low for all other outcomes (due to reliance on a single study, few events and/or wide confidence intervals).

For children & adolescents and pregnant & breastfeeding women, certainty is downgraded to very low due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
According to the Therapeutic Goods Administration, known acute harms for fluvoxamine include headache, dizziness, palpitations, diarrhoea, nausea and vomiting [244]. Use of fluvoxamine to treat COVID-19 in patients with a history of depression should be carefully considered due to the possible development of symptoms such as anxiety, agitation, panic attacks and mania.

**Pregnant and breastfeeding women**
According to the Therapeutic Goods Administration, the use of fluvoxamine in pregnant women, particularly in late pregnancy, has been shown to increase the risk of persistent pulmonary hypertension in the newborn [244]. Neonates exposed to fluvoxamine during pregnancy are at risk of experiencing withdrawal symptoms that may lead to complications such as respiratory distress, cyanosis, seizures and vomiting, potentially leading to prolonged hospitalisation, requirement of respiratory support and/or tube feeding. Fluvoxamine should not be used during pregnancy unless the clinical condition of the woman requires such treatment [244].

**Children and adolescents**
Although fluvoxamine (and other SSRIs) show no detrimental effect on growth, development and maturation, it is currently not indicated in children and adolescents for other uses (as the efficacy and safety of fluvoxamine has not been satisfactorily investigated in this population) [244].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.7 (CI 95% 0.38 — 1.3) Based on data from 1,624 participants in 2 studies. ² (Randomized controlled)</td>
<td>Placebo</td>
<td>Fluvoxamine</td>
<td>Moderate Due to serious imprecision ²</td>
<td>Fluvoxamine probably has little impact on death (41 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>30 per 1000</td>
<td>21 per 1000</td>
<td>Difference: 9 fewer per 1000 (CI 95% 19 fewer — 9 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Based on data from 152 participants in 1 studies. ³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to very serious imprecision ³</td>
<td>There were too few who required mechanical ventilation to determine whether fluvoxamine makes a difference (1 event).</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------------</td>
<td>--------------------------------</td>
<td>------------</td>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>Within 15 days of commencing treatment</td>
<td>Relative risk 0.18 (CI 95% 0.02 – 1.5) Based on data from 152 participants in 1 studies.</td>
<td>Placebo</td>
<td>Fluvoxamine</td>
<td>Low Due to very serious imprecision 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>69 per 1000</td>
<td>12 per 1000</td>
<td>57 fewer per 1000 (CI 95% 68 fewer – 35 more)</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Within 15 days of commencing treatment</td>
<td>Relative risk 1.65 (CI 95% 0.64 – 4.23) Based on data from 152 participants in 1 studies.</td>
<td>Placebo</td>
<td>Fluvoxamine</td>
<td>Low Due to very serious imprecision 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>83 per 1000</td>
<td>137 per 1000</td>
<td>54 more per 1000 (CI 95% 30 fewer – 268 more)</td>
</tr>
<tr>
<td><strong>Clinical deterioration</strong></td>
<td>Within 15 days of commencing treatment</td>
<td>Relative risk 0.07 (CI 95% 0 – 1.21) Based on data from 152 participants in 1 studies.</td>
<td>Placebo</td>
<td>Fluvoxamine</td>
<td>Low Due to very serious imprecision 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>83 per 1000</td>
<td>6 per 1000</td>
<td>77 fewer per 1000 (CI 95% 83 fewer – 17 more)</td>
</tr>
<tr>
<td><strong>Hospitalisation</strong></td>
<td>End of follow-up</td>
<td>Relative risk 0.47 (CI 95% 0.08 – 2.8) Based on data from 1,624 participants in 2 studies.</td>
<td>Placebo</td>
<td>Fluvoxamine</td>
<td>Low Due to very serious imprecision 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>119 per 1000</td>
<td>56 per 1000</td>
<td>63 fewer per 1000 (CI 95% 109 fewer – 214 more)</td>
</tr>
</tbody>
</table>

2. Imprecision: serious. Deaths only occurred in one included study.
4. Imprecision: very serious. due to few events, Only data from one study.
6. Imprecision: very serious. Wide confidence intervals, Only data from one study, due to few events.
8. Imprecision: very serious. Wide confidence intervals, Only data from one study, due to few events.
6.3.12.4 Recombinant human granulocyte colony-stimulating factor (rhG-CSF)

Only in research settings

Do not use rhG-CSF for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Recombinant human granulocyte colony-stimulating factor should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use rhG-CSF to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

General adult population
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with rhG-CSF, including thrombocytopenia (common), pulmonary haemorrhage, haemoptysis, aortitis and glomerulonephritis. There have also been occasional reports of adult respiratory distress syndrome in patients receiving rhG-CSF.

Children and adolescents
Paediatricians have considerable experience with the use of rhG-CSF in children and adolescents for other indications.

Pregnant and breastfeeding women
Transplacental passage of rhG-CSF has been demonstrated, and it is not known if rhG-CSF is excreted in human milk. rhG-CSF is therefore not recommended for pregnant and breastfeeding women unless the potential benefit outweighs the potential risk to the fetus or newborn/infant.

People requiring palliative care and older people living with frailty or cognitive impairment
The benefits of rhG-CSF for this population are uncertain.

Certainty of the Evidence

General adult population
Certainty of the evidence is low for death and mechanical ventilation due to very serious imprecision (low patient
numbers, few events and reliance on a single study); low for duration of hospital stay due serious risk of bias (lack of blinding) and serious imprecision (low patient numbers and reliance on a single study); and very low for adverse and serious adverse events due to serious risk of bias and very serious imprecision (low patient numbers and reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Preference and values

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of rhG-CSF during pregnancy and breastfeeding are unknown in the context of COVID-19.

### Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered, but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

**General adult population**

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**

Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**

As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

**General adult population**

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.
Rationale

General adult population
There is currently limited evidence about the impact of rhG-CSF on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that rhG-CSF should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of rhG-CSF to treat COVID-19 in these populations should be avoided until evidence becomes available.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: rhG-CSF
Comparator: Standard care

Summary
There remains significant uncertainty whether therapy with recombinant human granulocyte colony-stimulating factor (rhG-CSF) is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared three days of subcutaneous rhG-CSF therapy (5 μg/kg) with standard care in 200 hospitalised lymphopaenic adults with no comorbidities and moderate to severe COVID-19 [304].

Study characteristics
Median age of participants was 45 years and 44% were women. Standard care comprised supplemental oxygen, non-invasive ventilation, or intravenous antibiotics when indicated. Participants were required to have a peripheral blood leukocyte count ≤ 1500 per μL and peripheral blood lymphocyte ≤ 800 per μL for inclusion. Pregnant and breastfeeding women were ineligible.

What are the main results?
For the critical outcomes of death and mechanical ventilation within 21 days of starting treatment, there were too few events (12 deaths and 16 who required ventilation) to determine whether rhG-CSF therapy makes a difference. It is unclear whether rhG-CSF therapy increases or decreases adverse or serious adverse events. rhG-CSF therapy may have little or no impact on the duration of hospital stay.

Our confidence in the results
Certainty of the evidence is low for death and mechanical ventilation due to very serious imprecision (low patient numbers, few events and reliance on a single study); low for duration of hospital stay due serious risk of bias (lack of blinding) and serious imprecision (low patient numbers and reliance on a single study); and very low for adverse and serious adverse events due to serious risk of bias and very serious imprecision (low patient numbers and reliance on a single study).
numbers and reliance on a single study).

**Additional information**

There are well-known side effects and harms associated with rhG-CSF therapy, including thrombocytopaenia (common), pulmonary haemorrhage, haemoptysis, aortitis and glomerulonephritis. There have also been occasional reports of adult respiratory distress syndrome in patients receiving rhG-CSF therapy [305].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention rhG-CSF</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong>&lt;br&gt;Within 21 days of commencing treatment</td>
<td>Relative risk 0.2 (CI 95% 0.04 — 0.89) Based on data from 200 participants in 1 studies. ¹ (Randomized controlled)</td>
<td><strong>100</strong>&lt;br&gt;per 1000</td>
<td><strong>20</strong>&lt;br&gt;per 1000</td>
<td><strong>Low</strong>&lt;br&gt;Due to very serious imprecision ²</td>
<td>There were too few who died to determine whether rhG-CSF makes a difference (12 events).</td>
</tr>
<tr>
<td><strong>Invasive mechanical ventilation</strong>&lt;br&gt;Within 21 days of commencing treatment</td>
<td>Relative risk 0.14 (CI 95% 0.03 — 0.61) Based on data from 200 participants in 1 studies. ³ (Randomized controlled)</td>
<td><strong>140</strong>&lt;br&gt;per 1000</td>
<td><strong>20</strong>&lt;br&gt;per 1000</td>
<td><strong>Low</strong>&lt;br&gt;Due to very serious imprecision ⁴</td>
<td>There were too few who required invasive mechanical ventilation to determine whether rhG-CSF makes a difference (16 events).</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong>&lt;br&gt;End of treatment</td>
<td>Relative risk 0.72 (CI 95% 0.49 — 1.05) Based on data from 200 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td><strong>Relative risk 2.02 (CI 95% 1.62 — 2.5)</strong>&lt;br&gt;Based on data from 200 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td><strong>14</strong>&lt;br&gt;(Median)</td>
<td><strong>13</strong>&lt;br&gt;(Median)</td>
<td><strong>Low</strong>&lt;br&gt;Due to serious risk of bias and very serious imprecision ⁸</td>
</tr>
<tr>
<td><strong>Adverse events</strong>&lt;br&gt;End of treatment</td>
<td>Relative risk 2.02 (CI 95% 1.62 — 2.5) Based on data from 200 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td><strong>14</strong>&lt;br&gt;(Median)</td>
<td><strong>13</strong>&lt;br&gt;(Median)</td>
<td><strong>Low</strong>&lt;br&gt;Due to serious risk of bias and serious imprecision ⁸</td>
<td>We are uncertain whether rhG-CSF increases adverse events (138 events).</td>
</tr>
<tr>
<td><strong>Duration of hospital stay</strong>&lt;br&gt;Days</td>
<td>Based on data from: 200 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td><strong>14</strong>&lt;br&gt;(Median)</td>
<td><strong>13</strong>&lt;br&gt;(Median)</td>
<td><strong>Low</strong>&lt;br&gt;Due to serious risk of bias and serious imprecision ¹⁰</td>
<td>RhG-CSF may have little impact on duration of hospital stay.</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** no serious. Inadequate/lack of blinding of participants, personnel, and outcome assessors. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Only data from one study, Low
Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Special populations with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>rhG-CSF</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary

There remains significant uncertainty whether therapy with recombinant human granulocyte colony-stimulating factor (rhG-CSF) is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?

Evidence comes from one randomised trial that compared three days of subcutaneous rhG-CSF therapy (5 μg/kg) with standard care in 200 hospitalised lymphopaenic adults with no comorbidities and moderate to severe COVID-19 [304].

Study characteristics

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What are the main results?

For the critical outcomes of death and invasive mechanical ventilation within 21 days of starting treatment, there were too few events (12 deaths and 16 who required ventilation) to determine whether rhG-CSF therapy makes a difference. It is unclear whether rhG-CSF therapy increases or decreases adverse or serious adverse events. rhG-CSF therapy may have little or no impact on the duration of hospital stay.

Our confidence in the results

Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias (lack of blinding), very serious imprecision (low patient numbers, few observed events and reliance on a single study) and serious indirectness (limited inclusion of these populations).
**Additional information**

There are well-known side effects and harms associated with rhG-CSF therapy, including thrombocytopaenia (common), pulmonary haemorrhage, haemoptysis, aortitis and glomerulonephritis. There have also been occasional reports of adult respiratory distress syndrome in patients receiving rhG-CSF therapy [305].

**Children and adolescents**

Paediatricians have considerable experience with the use of rhG-CSF in children and adolescents for other indications.

**Pregnant and breastfeeding women**

Transplacental passage of rhG-CSF has been demonstrated, and it is not known if rhG-CSF is excreted in human milk. rhG-CSF is therefore not recommended for pregnant and breastfeeding women unless the potential benefit outweighs the potential risk to the fetus or newborn/infant [305].

---

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.2 (CI 95% 0.04 — 0.89) Based on data from 200 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>Standard care</td>
<td>rhG-CSF</td>
<td>Very low Due to very serious imprecision and serious indirectness ²</td>
<td>There were too few who died to determine whether rhG-CSF makes a difference (12 events).</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Relative risk 0.14 (CI 95% 0.03 — 0.61) Based on data from 200 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Standard care</td>
<td>rhG-CSF</td>
<td>Very low Due to very serious imprecision and serious indirectness ⁴</td>
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<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.72 (CI 95% 0.49 — 1.05) Based on data from 200 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td>Standard care</td>
<td>rhG-CSF</td>
<td>Very low Due to very serious imprecision, serious risk of bias and serious indirectness ⁶</td>
<td>We are uncertain whether rhG-CSF increases or decreases serious adverse events</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 2.02 (CI 95% 1.62 — 2.5) Based on data from 200 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td>Standard care</td>
<td>rhG-CSF</td>
<td>Very low Due to very serious imprecision, serious risk of bias and serious indirectness ⁸</td>
<td>We are uncertain whether rhG-CSF increases adverse events.</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>Based on data from: 200 participants in 1</td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether rhG-CSF increases or decreases duration of hospital stay</td>
</tr>
</tbody>
</table>
6.3.13.1 Combined metabolic activators (CMA)

### Plain Language Summary

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 important</td>
<td>studies. 9 (Randomized controlled)</td>
<td>Standard care</td>
<td>rhG-CSF</td>
<td>imprecision and serious indirectness 10</td>
<td>stay.</td>
</tr>
</tbody>
</table>

1. Systematic review [177] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias:** no serious. Inadequate/lack of blinding of participants, personnel, and outcome assessors. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, Low number of patients, Few events. **Publication bias:** no serious.

2. Systematic review [177] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias:** no serious. Inadequate/lack of blinding of participants, personnel and outcome assessors. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, only data from one study, few events. **Publication bias:** no serious.

3. Systematic review [177] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Wide confidence intervals, Only data from one study. **Publication bias:** no serious.

4. Systematic review [177] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Low number of patients, Wide confidence intervals, Only data from one study. **Publication bias:** no serious.

5. Systematic review [177] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** very serious. Only data from one study, Low number of patients. **Publication bias:** no serious.

6. Systematic review [177] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the population of interest and those studied. **Imprecision:** serious. Only data from one study, Low number of patients. **Publication bias:** no serious.
Evidence To Decision

Benefits and harms

General adult population

As the safety profile for combined metabolic activators is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

Certainty of the Evidence

Very low

Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias and very serious imprecision due to low patient numbers, reliance on a single study and few events (adverse events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

Substantial variability is expected or uncertain

General adult population

We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

Variability may be expected in preferences and values for these populations given the potentially different goals of care.

Resources and other considerations

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Only in research settings

Do not use combined metabolic activators (CMA) for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Combined metabolic activators (CMA) should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use CMA to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
### Rationale

**General adult population**
There is currently limited evidence about the impact of combined metabolic activators (CMA) on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that CMA should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Important issues, or potential issues not investigated

**Equity**

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

**General adult population**
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

**General adult population**
There is currently limited evidence about the impact of combined metabolic activators (CMA) on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that CMA should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of CMA to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Combined metabolic activators</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Control</td>
</tr>
</tbody>
</table>

### Summary
There remains significant uncertainty whether combined metabolic activators (CMA) are more effective and safer...
than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared CMA with placebo in 93 non-hospitalised adults with mild or moderate COVID-19 [517].

We have found one new study comparing CMA with placebo—the phase III component of the same study by Altay et al. (Advanced Science doi: 10.1002/advs.202101222). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**
Mean age of participants was 36 years and 40% were women. Patients in the intervention group received CMAs (L-carnitine tartrate, 7.46 g/day; N-acetylcysteine, 5.1 g/day; nicotinamide riboside 2 g/day; serine 24.7 g/day) twice a day for 14 days as water-soluble powders containing the entire CMA dose. Standard care for symptomatic treatment included hydroxychloroquine. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Data were not reported for the number of patients who died or experienced serious adverse events. There were too few who experienced adverse events to determine whether CMA makes a difference (2 events). It is unclear whether CMA increases or decreases clinical recovery at day 14 or time to clinical recovery.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to serious risk of bias and very serious imprecision.

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Common side effects associated with N-acetylcysteine are nausea, vomiting and other gastrointestinal symptoms [294].

**Pregnant and breastfeeding women**
For N-acetylcysteine, benefits can be assumed to outweigh possible risks for pregnant women; limited clinical experience has not resulted in adverse effects to the fetus. N-acetylcysteine is safe to use in women who are breastfeeding [270].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Within 14 days of commencing treatment</td>
<td></td>
<td></td>
<td></td>
<td>Data for number of patients who died were not reported.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td></td>
<td></td>
<td></td>
<td>Data for number of patients experiencing one or more serious adverse events were not reported.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Adverse events | End of follow-up | Relative risk 1.6 (CI 95% 0.08 – 32.08) Based on data from 93 | | | Very low 
Due to serious risk of bias and | Too few experienced adverse events to determine whether |
### 6.3.13.2 N-acetylcysteine

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention CMA</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical recovery</td>
<td>Relative risk 1.13 (CI 95% 0.95 – 1.33) Based on data from 93 participants in 1 studies.</td>
<td>Control</td>
<td>CMA</td>
<td>very serious imprecision</td>
<td>CMAs make a difference (2 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>Hazard Ratio 2.68 (CI 95% 1.57 – 4.59) Based on data from 93 participants in 1 studies.</td>
<td>Control</td>
<td>CMA</td>
<td>very serious imprecision</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Cointerventions and compliance with intervention not reported, selective outcome reporting, Use of unvalidated and/or subjective outcome measures, Selective outcome reporting. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, Low number of patients, Only data from one study. **Publication bias:** no serious.
4. **Risk of Bias:** serious. Use of unvalidated and/or subjective outcome measures, Selective outcome reporting. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.
5. **Risk of Bias:** serious. Use of unvalidated and/or subjective outcome measures, Selective outcome reporting. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias:** no serious.
Evidence To Decision

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are common side effects and harms associated with N-acetylcysteine, including nausea, vomiting and other gastrointestinal symptoms [294].

**Pregnant and breastfeeding women**
Benefits can be assumed to outweigh possible risks for pregnant women; limited clinical experience has not resulted in adverse effects to the fetus. N-acetylcysteine is safe to use in women who are breastfeeding [270].

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence is low for mechanical ventilation, ICU admission and hospital length of stay. This judgement is based on very serious imprecision due to reliance on a single study, low patient numbers and few events. Certainty of the evidence is additionally very low for death due to serious risk of bias (incomplete data).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is further considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of N-acetylcysteine during pregnancy and breastfeeding are unknown in the context of COVID-19.
Rationale

General adult population
There is currently limited evidence about the impact of N-acetylcysteine on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that N-acetylcysteine should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of N-acetylcysteine for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of N-acetylcysteine on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that N-acetylcysteine should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of N-acetylcysteine for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
**Intervention:** N-acetylcysteine  
**Comparator:** Placebo

**Summary**
There remains significant uncertainty whether N-acetylcysteine is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared N-acetylcysteine with placebo in 135 adults with suspected (5%) or confirmed (95%) severe COVID-19 [293].

We have found two new studies comparing N-acetylcysteine with standard care (Gaynitdinova et al. Pulmonology doi: 10.18093/0869-0189-2021-31-1-21-29 and Taher et al. Pharmacol Rep doi: 10.1007/s43440-021-00296-2). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**
Median age was 59 years in the N-acetylcysteine group and 58 years in the control group; the proportion of women was 33% and 46% respectively. N-acetylcysteine was administered intravenously for each patient in two doses (totaling 1000 ml over 20 hours). Standard care included oxygen supplementation, non-invasive and invasive ventilation, and antibiotics (ceftriaxone 2 g/day and azithromycin 500 mg/day). Pregnant women were ineligible.

**What are the main results?**
There were too few events to determine whether N-acetylcysteine makes a difference to death. N-acetylcysteine may decrease the need for admission to ICU but increase the need for invasive mechanical ventilation. N-acetylcysteine may have little or no impact on ICU admission or hospital length of stay.

**Our confidence in the results**
Certainty of the evidence is low for mechanical ventilation and ICU admission, hospital length of stay and ICU length of stay. This judgement is based on very serious imprecision due to reliance on a single study, low patient numbers and few events. Certainty of the evidence is additionally very low for mortality due to serious risk of bias (incomplete data).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Common side effects associated with N-acetylcysteine are nausea, vomiting and other gastrointestinal symptoms [294].

**Pregnant and breastfeeding women**
Benefits can be assumed to outweigh possible risks for pregnant women: limited clinical experience has not resulted in adverse effects to the fetus. N-acetylcysteine is safe to use in women who are breastfeeding [270].

<table>
<thead>
<tr>
<th>Outcome and Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 1.01 (CI 95% 0.43 — 2.4)</td>
<td>Placebo</td>
<td>N-acetylcysteine</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>There were too few events to determine whether N-acetylcysteine made a difference regarding death (18 events).</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>Based on data from 135 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical</td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical</td>
<td>Relative risk 1.16 (CI 95% 0.62 — 2.18)</td>
<td>206</td>
<td>239</td>
<td>Low Due to very</td>
<td>N-acetylcysteine may make little or no</td>
</tr>
</tbody>
</table>

544 of 734
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ventilation</strong></td>
<td>End of follow-up 3</td>
<td>Based on data from 135 participants in 1 studies. 4 (Randomized controlled)</td>
<td>Placebo per 1000</td>
<td>Intervention N-acetylcysteine per 1000</td>
<td>Serious imprecision 5</td>
<td>Difference: 33 more per 1000 (CI 95% 78 fewer – 243 more)</td>
</tr>
<tr>
<td><strong>ICU admission</strong></td>
<td>End of follow-up 6</td>
<td>Relative risk 0.92 (CI 95% 0.63 – 1.33) Based on data from 135 participants in 1 studies. 5 (Randomized controlled)</td>
<td>Placebo per 1000</td>
<td>Intervention N-acetylcysteine per 1000</td>
<td>Low Due to very serious imprecision 7</td>
<td>Difference: 38 fewer per 1000 (CI 95% 174 fewer – 155 more)</td>
</tr>
<tr>
<td><strong>Hospital length of stay Days</strong></td>
<td>6 Important</td>
<td>Lower better Based on data from: 135 participants in 1 studies. 6 (Randomized controlled)</td>
<td>Placebo 10 (Median)</td>
<td>Intervention N-acetylcysteine 11 (Median)</td>
<td>Low Due to very serious imprecision 9</td>
<td>Difference: 433 fewer per 1000 (CI 95% 174 fewer – 155 more)</td>
</tr>
<tr>
<td><strong>ICU length of stay Days</strong></td>
<td>6 Important</td>
<td>Lower better Based on data from: 135 participants in 1 studies. 10 (Randomized controlled)</td>
<td>Placebo 8 (Median)</td>
<td>Intervention N-acetylcysteine 9 (Median)</td>
<td>Low Due to very serious imprecision 11</td>
<td>Difference: 243 more per 1000 (CI 95% 78 fewer – 243 more)</td>
</tr>
</tbody>
</table>

2. **Risk of Bias**: serious. Incomplete data (6 patients still in ICU at end of follow-up excluded from mortality analysis) and/or reporting error (denominator different between narrative and table result). Pre-print only. Wait for peer-reviewed publication. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Low number of patients, Only data from one study, few events, Wide confidence intervals. **Publication bias**: no serious.
3. Need for endotracheal intubation/invasive mechanical ventilation
5. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias**: no serious.
7. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias**: no serious.
9. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Only data from one study, Low number of patients, Wide confidence intervals. **Publication bias**: no serious.
11. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study, Wide confidence intervals. **Publication bias:** no serious.

### 6.3.13.3 Vitamin C

**Only in research settings**

Do not use vitamin C for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

**Vitamin C should still be considered for other evidence-based indications in people who have COVID-19.**

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use vitamin C to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

#### Evidence To Decision

**Benefits and harms**

**General adult population**

There are limited harms associated with vitamin C at the doses specified in the included studies. However, there remains significant uncertainty around benefits for patients with COVID-19.

**Uncertainty of the Evidence**

**General adult population**

Certainty of the evidence for all outcomes is very low due to very serious risk of bias, serious inconsistency and serious imprecision (studies stopped early, direction not consistent, wide confidence intervals, low patient numbers and/or observed events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the study.

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for
Rationale

**General adult population**
There is currently limited evidence about the impact of vitamin C on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that vitamin C should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of vitamin C to treat COVID-19 in these populations should be avoided until evidence becomes available.

---

### Resources and other considerations

We have no systematically collected information regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

---

### Equity

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

---

### Acceptability

**General adult population, children and adolescents, pregnant and breastfeeding women**
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

---

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

---

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

---

**Summary**

There remains significant uncertainty whether vitamin C is more effective and safer than standard care in these populations given the potentially different goals of care.

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**Resources and other considerations**

**Equity**

**Acceptability**

**Feasibility**

---

Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce
treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from four randomised trials that compared vitamin C with standard care in 364 adults with COVID-19 [338][339][340][348].

**Study characteristics**
Mean age of participants across the studies ranged from 42 to 66 years and the proportion of women ranged from 43 to 62%. Pregnant and breastfeeding women were ineligible in all trials.

**What are the main results?**
We are uncertain whether vitamin C increases or decreases risk of death, patients requiring invasive mechanical ventilation or clinical deterioration.

**Our confidence in the results**
Certainty of the evidence is very low for death within 28 days due to very serious risk of bias, serious inconsistency and serious imprecision (based on studies stopping early, direction not consistent, wide confidence intervals and few patients). Certainty is very low for death and mechanical ventilation at end of follow-up due to serious inconsistency and serious imprecision (direction not consistent, wide confidence intervals and few patients). Certainty is very low for hospitalisation and clinical deterioration due to very serious risk of bias and imprecision (studies stopped early, wide confidence intervals, few patients and single study).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Common side effects and harms associated with vitamin C are nausea, vomiting, diarrhoea, heartburn, stomach cramps, bloating, fatigue, insomnia, headache and skin flushing.

**Pregnant and breastfeeding women**
Limited information suggests that vitamin C is not associated with harm. Vitamin C may be used in women who are breastfeeding.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.72 (CI 95% 0.31 – 1.66) Based on data from 154 participants in 2 studies. 1 (Randomized controlled)</td>
<td>Standard care</td>
<td>Vitamin C</td>
<td>Very low</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>End of follow-up</td>
<td>Relative risk 0.71 (CI 95% 0.33 – 1.54) Based on data from 210 participants in 2 studies. 3 (Randomized controlled)</td>
<td>Standard care</td>
<td>Intervention</td>
<td>Very low</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>End of follow-up</td>
<td>Relative risk 0.89 (CI 95% 0.49 – 1.62) Based on data from 210 participants in 2 studies. 5 (Randomized controlled)</td>
<td>Standard care</td>
<td>Intervention</td>
<td>Very low</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Interventions</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------</td>
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<td>-------------------------------------</td>
<td>---------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Day 7 of treatment</td>
<td>Relative risk 0.98 (CI 95% 0.5 – 1.92) Based on data from 56 participants in 1 studies. 5 (Randomized controlled)</td>
<td>Standard care</td>
<td>Vitamin C</td>
<td>inconsistency and serious imprecision 6</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>6 Important</td>
<td>Relative risk 0.69 (CI 95% 0.12 – 3.98) Based on data from 98 participants in 1 studies. 7 (Randomized controlled)</td>
<td>Standard care</td>
<td>Vitamin C</td>
<td>Very low Due to very serious risk of bias and very serious imprecision 10</td>
</tr>
<tr>
<td>Clinical deterioration</td>
<td>6 Important</td>
<td>Relative risk 0.64 (CI 95% 0.17 – 2.44) Based on data from 56 participants in 1 studies. 11 (Randomized controlled)</td>
<td>Standard care</td>
<td>Vitamin C</td>
<td>Very low Due to very serious risk of bias and very serious imprecision 12</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** very serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals, Low number of patients. **Publication bias:** no serious.
4. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Low number of patients. **Publication bias:** no serious.
6. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** serious. The direction of the effect is not consistent between the included studies. **Imprecision:** serious. Low number of patients.
8. **Risk of Bias:** very serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision:** serious. Wide confidence intervals, Low number of patients. Only data from one study.
10. **Risk of Bias:** very serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** very serious. Wide confidence intervals, Low number of patients. Only data from one study.
6.3.13.4 Vitamin D analogues (calcifediol/cholecalciferol)

**Evidence To Decision**

<table>
<thead>
<tr>
<th>Benefits and harms</th>
<th>General adult population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>There are limited harms associated with calcifediol, a vitamin D analog, at the doses specified in the included study. However, there remains significant uncertainty around benefits for patients with COVID-19.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Certainty of the Evidence</th>
<th>General adult population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Certainty of the evidence for all outcomes is low due to very serious imprecision (low patient numbers and/or observed events, incomplete data and/or large loss to follow-up).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preference and values</th>
<th>General adult population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.</td>
</tr>
</tbody>
</table>

**Only in research settings**

Do not use vitamin D analogues for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Vitamin D analogues should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use vitamin D analogues to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.


**Rationale**

**General adult population**

There is currently limited evidence about the impact of vitamin D analogues on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that vitamin D analogues should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of vitamin D analogues to treat COVID-19 in these populations should be avoided until evidence becomes available.

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**Clinical Question/ PICO**

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Vitamin D analogues</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

---

**Summary**

There remains significant uncertainty whether vitamin D analogues (calcifediol/cholecalciferol) are more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials comparing vitamin D analogues with standard care or placebo in 353 adults hospitalised with COVID-19 [341][344][345].

**Study characteristics**
Mean age of participants ranged from 48 to 57 years and the proportion of women ranged from 31 to 62%. Pregnant women were ineligible.

**What are the main results?**
For the critical outcomes of death and requirement of invasive mechanical ventilation, we are unsure if vitamin D analogues make a difference. Vitamin D analogues may reduce admissions to ICU compared with standard care (211 fewer ICU admissions per 1000 patients; RR 0.20, CI 95% 0.01 to 3.50; 308 patients in 2 studies). We are uncertain whether vitamin D analogues make a difference with regards to discharge from hospital or time to discharge from hospital.

**Our confidence in the results**
Certainty of the evidence for all outcomes is low due to very serious imprecision (low patient numbers and/or observed events, incomplete data and/or large loss to follow-up).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
As a vitamin D analogue, there are limited harms associated with calcifediol at the doses specified in the study.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Vitamin D analogues</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>End of follow-up</td>
<td>Relative risk 0.58 (CI 95% 0.05 — 7.18) Based on data from 313 participants in 2 studies. (Randomized controlled)</td>
<td>56 per 1000</td>
<td>32 per 1000</td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>End of follow-up</td>
<td>Relative risk 0.47 (CI 95% 0.21 — 1.04) Based on data from 237 participants in 1 studies. (Randomized controlled)</td>
<td>144 per 1000</td>
<td>68 per 1000</td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td>ICU admission</td>
<td>End of follow-up</td>
<td>Relative risk 0.2 (CI 95% 0.01 — 3.29) Based on data from 313 participants in 2 studies. (Randomized controlled)</td>
<td>264 per 1000</td>
<td>53 per 1000</td>
<td>Low</td>
<td>Due to very serious imprecision</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td></td>
<td>Relative risk 1.09 (CI 95% 0.96 — 1.23)</td>
<td>923</td>
<td>1,000</td>
<td>Low</td>
<td>Due to very</td>
</tr>
</tbody>
</table>
### 6.3.13.5 Zinc

**Outcome**
- **Timeframe**
- **Study results and measurements**
- **Comparator**
- **Intervention**
- **Certainty of the Evidence**
- **Plain language summary**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of follow-up</td>
<td>Based on data from 76 participants in 1 studies.</td>
<td>Standard care per 1000</td>
<td>Vitamin D analogues per 1000</td>
<td>serious imprecision</td>
<td>analogues increase or decrease discharge from hospital.</td>
</tr>
<tr>
<td>Time to discharge from hospital</td>
<td>Lower better Based on data from: 237 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to very serious imprecision</td>
<td>We are uncertain whether vitamin D analogues increase or decrease time to discharge from hospital.</td>
</tr>
</tbody>
</table>

2. **Imprecision**: very serious. Wide confidence intervals, due to few events.
4. **Imprecision**: very serious. Wide confidence intervals, Low number of patients, Only data from one study.
6. **Imprecision**: very serious. Wide confidence intervals.
8. **Imprecision**: very serious. Wide confidence intervals, Low number of patients, Only data from one study.
9. **Imprecision**: very serious. Low number of patients, Only data from one study.

---

**Only in research settings**

Do not use zinc for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Zinc should still be considered for other evidence-based indications in people who have COVID-19.

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use zinc to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.**

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
### Evidence To Decision

#### Benefits and harms

**General adult population**
There are limited harms associated with zinc at the doses specified in the included studies. However, there remains significant uncertainty around benefits for patients with COVID-19.

**Small net benefit, or little difference between alternatives**

#### Certainty of the Evidence

**General adult population**
Certainty of the evidence is low for death and discharge from hospital due to very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals). Certainty is very low for hospitalisation due to serious risk of bias (issues with randomisation and blinding of participants/personnel and outcome assessors), in addition to very serious imprecision (as described above).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Low Certainty of the Evidence**

#### Preference and values

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Substantial variability is expected or uncertain**

#### Resources and other considerations

We have no systematically collected information regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Important issues, or potential issues not investigated**

#### Equity

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Important issues, or potential issues not investigated**

#### Acceptability

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**No important issues with the recommended alternative**
Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population

There is currently limited evidence about the impact of zinc on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that zinc should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of zinc to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

**Population:** Patients with COVID-19  
**Intervention:** Zinc  
**Comparator:** Standard care

Summary

There remains significant uncertainty whether zinc is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?

Evidence comes from two randomised trials. The first compared zinc with placebo in 33 adults hospitalised with COVID-19 [349] and the second compared zinc with standard care in 108 adult outpatients [348].

Removal of studies

Version 44: Due to inconsistencies in the data reported for Abd-Elsalam et al. (Biol Trace Elem Res, 27 Nov 2020) [347], we have removed this study from the analyses. The study contributed data to four outcomes (mortality, invasive mechanical ventilation, recovery and duration of hospital stay) and the removal of these data did not change the strength or direction of the recommendation.

Study characteristics

Mean age of participants in Thomas et al. was 45 years and 62% were women [348]. In Patel et al. mean age was ~62 years and 64% were women [349].

What are the main results?

We are uncertain whether zinc increases or decreases death, rate of hospitalisation or discharge from hospital, or clinical recovery.

Our confidence in the results

Certainty of the evidence is low for death and discharge from hospital due to very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals). Certainty is very low for hospitalisation due to serious risk of bias (issues with randomisation and blinding of participants/personnel and outcome assessors), in addition to very serious imprecision (as described above).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information

According to the Therapeutic Goods Administration, common side effects of zinc poisoning include hypotension, pulmonary oedema, diarrhoea, vomiting, jaundice and oliguria [350].
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Zinc</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.8 (CI 95% 0.15 — 4.18) Based on data from 141 participants in 2 studies. 1 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>We are uncertain whether zinc impacts death (5 events).</td>
</tr>
<tr>
<td><strong>Hospitalisation</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.44 (CI 95% 0.36 — 5.71) Based on data from 108 participants in 1 studies. 2 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether zinc increases or decreases hospitalisation (8 events).</td>
</tr>
<tr>
<td><strong>Discharged from hospital</strong></td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.86 (CI 95% 0.55 — 1.32) Based on data from 33 participants in 1 studies. 3 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to very serious imprecision</td>
<td>We are uncertain whether zinc increases or decreases number of patients discharged from hospital (24 events).</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Wide confidence intervals, due to [reason].
4. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, due to few events.
6. **Imprecision:** very serious. Wide confidence intervals, Only data from one study, Low number of patients.
Evidence To Decision

**Benefits and harms**

**General adult population**
Currently, there is no direct evidence to inform the potential benefits or harms of other disease-modifying treatments in patients with COVID-19.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There may be additional concerns regarding harms for these populations. For people requiring palliative care, the benefits for symptom management may be uncertain.

**Certainty of the Evidence**
We have no COVID-19 specific randomised trials for other potential disease-modifying treatments.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while others may be more willing to opt for treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations, given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of any disease-modifying treatments during pregnancy may be unknown.

The NC19CET Consumer Panel believes that informed patients may prefer to wait until there is available evidence, while other informed patients may choose to participate in clinical trials.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live...
in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**  
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**  
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

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### Acceptability

**General adult population, children and adolescents, pregnant and breastfeeding women**  
We have no systematically collected evidence regarding acceptability for other disease-modifying treatments. Substantial variability is expected as some patients would accept treatment and others not.

**People requiring palliative care and older people living with frailty or cognitive impairment**  
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

---

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

---

### Rationale

**General adult population**  
There is currently limited evidence about the impact of other disease-modifying treatments on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments.

In line with the ANZICS, ASID, AHPPC and IDSA recommendations [18][20][126][127], we therefore recommend that other disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**  
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of other disease-modifying treatments in these populations should be avoided until evidence becomes available.

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### 6.4 Disease-modifying treatments under review

We are continually monitoring new research for randomised trials that evaluate any disease-modifying treatments for COVID-19. As each new trial is published, our panels assess and make recommendations on whether the treatment should be used in the clinical care of patients. This section provides details of studies that are currently under review by our panels. Recommendations on whether these treatments should be used in the clinical care of patients will be included in a future update of the guideline.

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### 6.4.1 Tixagevimab plus cilgavimab (Evusheld)
6.5 Disease-modifying treatments not currently under review

Info Box

Many randomised trials of COVID-19 have been published that include small numbers of patients and/or report no outcomes of clinical relevance. A comprehensive list of randomised trials that do not meet our inclusion criteria, and which are not currently being reviewed by the Taskforce, can be found here.
7. Chemoprophylaxis

The primary panel for the recommendations in this section is the Disease-Modifying Treatment and Chemoprophylaxis Panel. Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. The remaining panels review recommendations when relevant to their specific population group. In addition, all our recommendations are reviewed by the Consumer Panel.

We have found one new study evaluating prophylactic ivermectin for healthcare workers and/or household contacts of COVID-19 patients (Elgazzar et al. Res Sq doi: 10.21203/rs.3.rs-100956/v3). This study is currently under review and a recommendation will be included in a future version of the guideline.

7.1 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for post-exposure prophylaxis

**Conditional recommendation**

Consider using subcutaneous casirivimab plus imdevimab as prophylaxis in seronegative or PCR-negative close household contacts of individuals with confirmed COVID-19.

The use of prophylactic casirivimab plus imdevimab probably reduces the risk of symptomatic and asymptomatic COVID-19 infection in seronegative household contacts of individuals with confirmed COVID-19 when used within 4 days of exposure. In settings for which serology testing is not readily available, consider using in unvaccinated adult household contacts who have risk factors for developing severe disease, return a negative PCR result and are considered unlikely to have had previous SARS-CoV-2 infection.

**Evidence To Decision**

**Benefits and harms**

In close household contacts of individuals with confirmed COVID-19, casirivimab plus imdevimab probably decreases the incidence of symptomatic and confirmed COVID-19 infection (symptomatic plus asymptomatic) and probably results in fewer adverse events. It is unclear if casirivimab plus imdevimab makes a difference to all-cause mortality due to few events.

Older people living with frailty or cognitive impairment
People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

People requiring palliative care
There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

Pregnant or breastfeeding women
There is uncertainty around the benefits and harms of casirivimab plus imdevimab for pregnant or breastfeeding women with COVID-19 as no details were reported in the trials for these populations.

Children or adolescents
Children aged 12 years and over were eligible for inclusion in the study on casirivimab plus imdevimab, but results were not presented separately for this subgroup and it is unclear how many children were included. As a result, there remains uncertainty around the benefits and harms of casirivimab plus imdevimab for children and adolescents at risk of COVID-19 infection.

Certainty of the evidence is moderate for symptomatic COVID-19 infection, confirmed COVID-19 infection and adverse events (due to serious imprecision based on reliance on a single study), and low for all-cause mortality and serious adverse events (due to very serious imprecision based on reliance on a single study, few events and wide confidence intervals).

Preference and values
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that since there are probable mortality benefits, most informed patients at risk of COVID-19 infection would agree with the recommendation and opt for casirivimab plus imdevimab.

Pregnant or breastfeeding patients
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations
The unavailability of casirivimab plus imdevimab, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity
We have no systematically collected evidence regarding impact on equity; however as casirivimab plus imdevimab is not currently available in Australia it is not currently accessible to patients or clinicians.

Acceptability
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both
patients and clinicians.

Rationale

In close household contacts of patients with confirmed COVID-19, casirivimab plus imdevimab probably reduces the risk of COVID-19 infection in individuals who are seronegative for SARS-CoV-2 antibodies if used within 4 days of exposure. Because of this, the Taskforce gives a conditional recommendation supporting the use of casirivimab plus imdevimab both within and outside a randomised trial.

Feasibility

On 15 October, the Therapeutic Goods Administration granted provisional approval to use casirivimab plus imdevimab in adults who have been exposed to SARS-CoV-2 and who either have a medical condition making them unlikely to respond to or be protected by vaccination or who have not been vaccinated against COVID-19. Casirivimab plus imdevimab as prophylaxis is not feasible in patients who do not meet eligibility as specified by the Australian Government Department of Health.

Implementability may be limited by the current arrangements for accessing casirivimab plus imdevimab, in terms of the total number of doses available and more general criteria (such as geographic area).

Clinical Question/ PICO

Population: Casirivimab-imdevimab prophylaxis for COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Placebo

Summary

Post-exposure prophylactic casirivimab plus imdevimab probably reduces symptomatic and asymptomatic COVID-19 infection in seronegative close household contacts of confirmed COVID-19 patients.

What is the evidence informing this recommendation?

Evidence comes from one randomised trial that compared casirivimab plus imdevimab with placebo in 1505 household contacts of confirmed COVID-19 patients [568].

Study characteristics

Median age of participants was 43 years and 55% were women. Individuals received a single subcutaneous 1200 mg dose of REGEN-COV (600 mg casirivimab plus 600 mg imdevimab) or placebo. Pregnant and breastfeeding women were ineligible. Adolescents were eligible for inclusion (12 to 17 years of age), however results were not reported separately.

What are the main results?

Results demonstrate that casirivimab plus imdevimab probably reduces incidence of symptomatic COVID-19 infection (RR 0.19 CI 95% 0.10 to 0.35; 1505 patients in 1 study) and confirmed COVID-19 infection (symptomatic plus asymptomatic; RR 0.34 CI 95% 0.23 to 0.48; 1505 patients in 1 study). In addition, results demonstrate a reduction in incidence of adverse events in individuals treated with prophylactic casirivimab plus imdevimab (RR 0.70 CI 95% 0.61 to 0.80; 2617 patients in 1 study).

We are unsure whether casirivimab plus imdevimab has an impact on mortality, serious adverse events or discontinuation due to adverse events.

Our confidence in the results

Certainty of the evidence is moderate for symptomatic COVID-19 infection, confirmed COVID-19 infection (symptomatic plus asymptomatic infection) and adverse events (due to serious imprecision based on reliance on a single study), and low for all-cause mortality and serious adverse events (due to very serious imprecision based on reliance on a single study, few events and wide confidence intervals).

For pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).
### Additional information
As of 20 August 2021, REGEN-COV (casirivimab plus imdevimab) has been granted provisional determination by the Australian Register of Therapeutic Goods allowing an application for provisional registration. Currently casirivimab plus imdevimab is not available for use within Australia.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 1 (CI 95% 0.14 – 7.06) Based on data from 2,617 participants in 1 studies.</td>
<td>Placebo</td>
<td>Casirivimab plus imdevimab</td>
<td>Low Due to very serious imprecision</td>
<td>There were too few deaths to determine if casirivimab plus imdevimab makes a difference (4 deaths).</td>
</tr>
<tr>
<td>Symptomatic COVID-19 infection</td>
<td>Relative risk 0.19 (CI 95% 0.1 – 0.35) Based on data from 1,505 participants in 1 studies.</td>
<td>Placebo</td>
<td>Casirivimab plus imdevimab</td>
<td>Moderate Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably decreases symptomatic COVID-19 (70 events).</td>
</tr>
<tr>
<td>Confirmed COVID-19 infection</td>
<td>Relative risk 0.34 (CI 95% 0.23 – 0.48) Based on data from 1,505 participants in 1 studies.</td>
<td>Placebo</td>
<td>Casirivimab plus imdevimab</td>
<td>Moderate Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably decreases confirmed COVID-19 infection (143 events).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 0.7 (CI 95% 0.61 – 0.8) Based on data from 2,617 participants in 1 studies.</td>
<td>Placebo</td>
<td>Casirivimab plus imdevimab</td>
<td>Moderate Due to serious imprecision</td>
<td>Casirivimab plus imdevimab probably decreases adverse events (644 events).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk 0.66 (CI 95% 0.3 – 1.47) Based on data from 2,617 participants in 1 studies.</td>
<td>Placebo</td>
<td>Casirivimab plus imdevimab</td>
<td>Low Due to very serious imprecision</td>
<td>Casirivimab plus imdevimab may have little impact on serious adverse events (35 events).</td>
</tr>
<tr>
<td>Discontinuation due to adverse</td>
<td>Based on data from</td>
<td>Placebo</td>
<td>Casirivimab plus imdevimab</td>
<td></td>
<td>No participants discontinued treatment due to an adverse event.</td>
</tr>
</tbody>
</table>
### 7.2 Hydroxychloroquine for pre-exposure prophylaxis

For healthcare workers with no active COVID-19, do not use hydroxychloroquine for pre-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use hydroxychloroquine for pre-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**Evidence To Decision**

**Benefits and harms**

**General adult population**

In addition to uncertainty around the benefits for people at high risk of being exposed to individuals with COVID-19, there are well-known harms, with potentially severe adverse events. Although most of the information on side effects and harms
is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

There are several known and potential interactions with other drugs. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses.

**Children and adolescents**
Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications.

**Pregnant and breastfeeding women**
Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, though further research is needed.

**People requiring palliative care and older people living with frailty or cognitive impairment**
There may be additional concerns regarding harms in these populations.

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence is low for laboratory-confirmed diagnosis, moderate for adverse events and confirmed or probable infection (due to included studies terminating early), low for serious adverse events and symptoms compatible with COVID-19 (due to studies being terminated early and few events), and very low for discontinuation due to adverse events.

**Children and adolescents, pregnant women, people requiring palliative care and older people living with frailty or cognitive impairment**
Certainty of the evidence was downgraded further for all outcomes due to indirectness, as these special populations were not included in the trials.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

**General adult population**
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

**Equity**

**General adult population**
We have no systematically collected direct evidence regarding impact on equity. There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for...
enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
Since these populations are particularly at risk from COVID-19, we encourage trials that include these populations (with appropriate baseline measurement of frailty and cognitive impairment). Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, hydroxychloroquine is likely to be acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability of the recommendation is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of hydroxychloroquine for pre-exposure prophylaxis on the prevention of COVID-19 in healthcare workers. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that hydroxychloroquine for pre-exposure prophylaxis should only be used to prevent COVID-19 infection in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of once-weekly hydroxychloroquine for pre-exposure prophylaxis for the prevention of COVID-19 infection in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

| Population: | Healthcare workers (with no active or prior COVID-19) |
| Intervention: | Pre-exposure hydroxychloroquine |
| Comparator: | Placebo |

Summary

Pre-exposure prophylactic hydroxychloroquine may be no more effective at preventing COVID-19 infection in high-risk healthcare workers than placebo and may result in more adverse events.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared hydroxychloroquine as pre-exposure prophylaxis with placebo in 1884 high-risk healthcare workers with no active or prior COVID-19 [355][356][627].
We have found two new studies comparing hydroxychloroquine as pre-exposure prophylaxis with placebo among healthcare workers at high risk (Syed et al. medRxiv doi: 10.1101/2021.05.17.21257012 and Naggie et al. medRxiv doi: 10.1101/2021.08.19.21262275). These studies are currently under review and will be incorporated in a future version of the guideline.

Study characteristics
Two studies reported comparatively low doses of hydroxychloroquine: in Rajasingham et al. participants were given a loading dose of 400 mg (two 200 mg tablets) of hydroxychloroquine twice separated by 6-8 hours, followed by 400 mg (two 200 mg tablets) either once or twice-weekly for 12 weeks [356]. Participants in Grau-Pujol et al. were given 400 mg hydroxychloroquine daily for four days, followed by 400 mg once weekly for one month [?]. In the study by Abella et al. participants received 600 mg of hydroxychloroquine daily for eight weeks [355].

Median age ranged from 31 to 42 years in the hydroxychloroquine arms and from 34 to 40 years in the placebo arms. The proportion of women ranged from 53% to 83% in the hydroxychloroquine arms and 49% to 73% in the placebo arms. One study explicitly excluded pregnant women [?], one study did not specify whether pregnant or breastfeeding women were eligible [355], and no pregnant women enrolled in the third study, although 30 women reported breastfeeding at baseline [356].

What are the main results?
Pre-exposure prophylactic hydroxychloroquine probably increases incidence of adverse events (108 more events per 1000 healthcare workers (RR 1.45 CI 95% 1.14 to 1.84; 1801 participants in 3 studies)). Pre-exposure prophylactic hydroxychloroquine may make little or no difference to the number of people who contract laboratory-confirmed COVID-19, experience symptoms compatible with COVID-19, develop confirmed or probable infection, experience serious adverse events or who discontinue treatment due to adverse events.

Our confidence in the results
Certainty of the evidence is low for laboratory-confirmed diagnosis, moderate for adverse events and confirmed or probable infection (due to included studies terminating early), low for serious adverse events and symptoms compatible with COVID-19 (due to studies being terminated early and few events), and very low for discontinuation due to adverse events.

Additional information
According to the Therapeutic Goods Administration, known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [52]. There are several known and potential interactions with other drugs [52]. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses. In pregnancy, it is only recommended when benefits outweigh harms [52].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Placebo</th>
<th>Intervention Pre-exp HCQ</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory-confirmed diagnosis End of treatment</td>
<td>Relative risk 0.87 (CI 95% 0.4 — 1.88) Based on data from 1,877 participants in 3 studies. [Randomized controlled]</td>
<td>16 per 1000 Difference: 2 fewer per 1000 (CI 95% 10 fewer — 14 more)</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>Hydroxychloroquine pre-exposure prophylaxis may have little impact on laboratory-confirmed diagnosis in healthcare workers (26 events).</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality End of treatment</td>
<td>Based on data from 1,608 participants in 2 studies.</td>
<td>9</td>
<td></td>
<td>There were no deaths.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse</td>
<td>Relative risk 0.78</td>
<td>11</td>
<td></td>
<td>Hydroxychloroquine pre-</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
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<tr>
<td>events</td>
<td>End of treatment</td>
<td>(CI 95% 0.31 — 2.01) Based on data from 1,752 participants in 2 studies. 4 (Randomized controlled)</td>
<td>Placebo per 1000</td>
<td>Pre-exp HCQ per 1000</td>
<td>Due to serious risk of bias and serious imprecision 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Difference:</strong> 2 fewer per 1000 (CI 95% 8 fewer — 11 more)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Adverse events</strong></td>
<td>Relative risk 1.45 (CI 95% 1.14 — 1.84) Based on data from 1,801 participants in 3 studies. 5 (Randomized controlled)</td>
<td>Placebo per 1000</td>
<td>Pre-exp HCQ per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Difference:</strong> 108 more per 1000 (CI 95% 34 more — 202 more)</td>
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<td></td>
<td></td>
<td><strong>Symptoms compatible with COVID-19</strong></td>
<td>Relative risk 0.75 (CI 95% 0.5 — 1.11) Based on data from 1,483 participants in 1 studies. 8 (Randomized controlled)</td>
<td>Placebo per 1000</td>
<td>Pre-exp HCQ per 1000</td>
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<tr>
<td></td>
<td>12 weeks</td>
<td><strong>Difference:</strong> 19 fewer per 1000 (CI 95% 39 fewer — 8 more)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Confirmed or probable infection</strong></td>
<td>Relative risk 0.87 (CI 95% 0.6 — 1.27) Based on data from 1,483 participants in 1 studies. 10 (Randomized controlled)</td>
<td>Placebo per 1000</td>
<td>Pre-exp HCQ per 1000</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td><strong>Difference:</strong> 10 fewer per 1000 (CI 95% 32 fewer — 21 more)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Discontinuation due to adverse events</strong></td>
<td>Relative risk 0.95 (CI 95% 0.2 — 4.54) Based on data from 125 participants in 1 studies. 12 (Randomized controlled)</td>
<td>Placebo per 1000</td>
<td>Pre-exp HCQ per 1000</td>
</tr>
<tr>
<td></td>
<td>8 weeks</td>
<td><strong>Difference:</strong> 69 fewer per 1000 (CI 95% 19 more — 185 more)</td>
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</tr>
</tbody>
</table>


2. **Risk of Bias:** serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** serious. due to few events.


5. **Risk of Bias:** serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. due to few events.

7. Risk of Bias: serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


11. Risk of Bias: serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.


13. Risk of Bias: serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Imprecision: very serious. Only data from one study, due to few events, Low number of patients.

7.3 Hydroxychloroquine for post-exposure prophylaxis

Not recommended

For people exposed to individuals with SARS-CoV-2 infection, do not use hydroxychloroquine for post-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use hydroxychloroquine for post-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

General adult population
In addition to uncertainty around the benefits for people exposed to individuals with COVID-19, there are well-known harms, with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

There are several known and potential interactions with other drugs. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses.

Children and adolescents
Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications.

Pregnant and breastfeeding women
Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, though further research is needed.

**People requiring palliative care and older people living with frailty or cognitive impairment**
There may be additional concerns regarding harms in these populations.

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**Certainty of the Evidence**

**General adult population**
Certainty of the evidence for the primary outcome of laboratory-confirmed diagnosis is moderate. Certainty is high for adverse events and low for all other outcomes, due either to serious risk of bias and serious imprecision (symptoms compatible with COVID-19, confirmed or probable infection and discontinuation due to adverse events) or very serious imprecision (all-cause mortality and serious adverse events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
Certainty of the evidence was downgraded further for all outcomes due to indirectness, as it is unclear whether these special populations were included in the trials.

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**Preference and values**

The Consumer Panel believes that as there is evidence of harm but no evidence of benefit, informed individuals would not choose to use hydroxychloroquine for prophylaxis.

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

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**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

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**Equity**

**General adult population**
We have no systematically collected direct evidence regarding impact on equity. There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
These populations are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability**

**General adult population, children and adolescents, pregnant and breastfeeding women**
Although we have no systematically collected evidence regarding acceptability, hydroxychloroquine is likely to be acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**

Implementability of the recommendation is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

**General adult population**
There is currently limited evidence about the impact of prophylactic hydroxychloroquine on the prevention of infection in people exposed to COVID-19. The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects. We, therefore, recommend that hydroxychloroquine chemoprophylaxis should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, the use of hydroxychloroquine as post-exposure prophylaxis in these populations should be avoided until evidence becomes available.

**Clinical Question/ PICO**

| Population: | People exposed to COVID-19 |
| Intervention: | Hydroxychloroquine post-exposure prophylaxis |
| Comparator: | Placebo |

**Summary**

Based on the available evidence, post-exposure prophylactic hydroxychloroquine is probably no more effective at preventing COVID-19 infection than placebo, and results in more adverse events.

**What is the evidence informing this recommendation?**

Evidence informing this recommendation comes from two randomised trials that compared post-exposure prophylaxis using hydroxychloroquine to placebo in 3135 asymptomatic people [357][359]. All study participants were exposed to a person with a confirmed COVID-19 infection and were asymptomatic when treatment started.

We have found two new studies comparing post-exposure prophylactic hydroxychloroquine with placebo—one in direct household contacts of patients with COVID-19 (Barnabas et al. Ann Intern Med doi: 10.7326/M20-6519) and the other in health personnel exposed to patients infected by SARS-COV-2 (Rojas-Serrano et al. medRxiv doi: 10.1101/2021.05.14.21257059). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.
**Study characteristics**
In the first trial of 821 people, median age was 40 years and 52% were women [357]. In the second trial of 2314 people, mean age was 49 years and 73% were women [359].

**Our confidence in the results**
Certainty of the evidence is moderate for laboratory-confirmed diagnosis and adverse events (due to imprecision). Certainty is low for all other outcomes either due to serious inconsistency and serious risk of bias (symptoms compatible with COVID-19, confirmed or probable infection and discontinuation due to adverse events) or very serious imprecision (all-cause mortality and serious adverse events).

**Additional information**
According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [133]. There are several known and potential interactions with other drugs [133]. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses. In pregnancy, it is only recommended when benefits outweigh harms [133].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory-confirmed diagnosis</strong></td>
<td>14 days after commencing treatment</td>
<td>Relative risk 0.96 (CI 95% 0.71 – 1.3) Based on data from 3,135 participants in 2 studies.</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>Moderate</td>
<td>Hydroxychloroquine post-exposure prophylaxis probably has no effect on the number of laboratory-confirmed diagnoses.</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td>52 per 1000</td>
<td>50 per 1000</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Difference: 2 fewer per 1000 (CI 95% 15 fewer – 16 more)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms compatible with COVID-19</strong></td>
<td>14 days after commencing treatment</td>
<td>Relative risk 0.98 (CI 95% 0.82 – 1.18) Based on data from 3,135 participants in 2 studies.</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>Low</td>
<td>Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of symptoms compatible with COVID-19.</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td></td>
<td>128 per 1000</td>
<td>125 per 1000</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Difference: 3 fewer per 1000 (CI 95% 23 fewer – 23 more)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Confirmed or probable infection</strong></td>
<td>14 days after commencing treatment</td>
<td>Relative risk 0.83 (CI 95% 0.58 – 1.18) Based on data from 821 participants in 1 studies.</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>Low</td>
<td>Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of patients with confirmed or probable infection.</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td></td>
<td>143 per 1000</td>
<td>119 per 1000</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Difference: 24 fewer per 1000 (CI 95% 60 fewer – 26 more)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>End of treatment</td>
<td>Relative risk 0.68 (CI 95% 0.22 – 2.07) Based on data from 3,318 participants in 2 studies.</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>Low</td>
<td>We are uncertain whether hydroxychloroquine post-exposure prophylaxis improves or worsens all-cause mortality (13 events).</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td></td>
<td>5 per 1000</td>
<td>3 per 1000</td>
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<tr>
<td></td>
<td></td>
<td>Difference: 2 fewer per 1000 (CI 95% 4 fewer – 5 more)</td>
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</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Placebo</td>
<td>Intervention Hydroxychloroquine post-exposure prophylaxis</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
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</tr>
<tr>
<td>Serious adverse events End of treatment</td>
<td>Relative risk 0.89 (CI 95% 0.44 – 1.81) Based on data from 2,497 participants in 1 studies.</td>
<td>13 per 1000</td>
<td>12 per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases or decreases serious adverse events (31 events).</td>
<td></td>
</tr>
<tr>
<td>Adverse events End of treatment</td>
<td>Relative risk 4.76 (CI 95% 1.19 – 19.1) Based on data from 3,197 participants in 2 studies.</td>
<td>82 per 1000</td>
<td>390 per 1000</td>
<td>Moderate Due to serious risk of bias</td>
<td>Hydroxychloroquine post-exposure prophylaxis probably increases the number of adverse events.</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse events End of treatment</td>
<td>Relative risk 4.1 (CI 95% 0.52 – 32.23) Based on data from 3,346 participants in 2 studies.</td>
<td>5 per 1000</td>
<td>20 per 1000</td>
<td>Very low Due to serious risk of bias and very serious imprecision</td>
<td>We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases discontinuation due to adverse events (33 events).</td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision:** serious. Wide confidence intervals.
4. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Wide confidence intervals.
6. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** serious. Wide confidence intervals.
8. **Imprecision:** very serious. Only 13 events.
10. **Imprecision:** very serious. Only 31 events.
12. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
14. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
of blinding of outcome assessors, resulting in potential for detection bias. Imprecision: very serious. Only 33 events.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Special populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Summary

Based on the available evidence, post-exposure prophylactic hydroxychloroquine is probably no more effective at preventing COVID-19 infection than placebo, and results in more adverse events.

What is the evidence informing this recommendation?

Evidence informing this recommendation comes from two randomised trials that compared post-exposure prophylaxis using hydroxychloroquine to placebo in 3135 asymptomatic people [357][359]. All study participants were exposed to a person with a confirmed COVID-19 infection and were asymptomatic when treatment started.

We have found one new study comparing post-exposure prophylactic hydroxychloroquine with placebo in direct household contacts of patients with COVID-19 (Barnabas et al. Ann Intern Med doi: 10.7326/M20-6519). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics

In the first trial of 821 people, median age was 40 years and 52% were women [357]. In the second trial of 2314 people, mean age was 49 years and 73% were women [359].

Our confidence in the results

Certainty of the evidence is moderate for laboratory-confirmed diagnosis and adverse events (due to imprecision). Certainty is low for all other outcomes either due to serious inconsistency and serious risk of bias (symptoms compatible with COVID-19, confirmed or probable infection and discontinuation due to adverse events) or very serious imprecision (all-cause mortality and serious adverse events).

Additional information

According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [133]. There are several known and potential interactions with other drugs [133]. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses. In pregnancy, it is only recommended when benefits outweigh harms [133].

Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, with no increase in fetal malformations [138][139]. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine [138][139][140]. While this evidence is reassuring, further research is needed.

Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications. To date, no specific information on its benefits or harms for children and adolescents has been collected on the use of hydroxychloroquine as post-exposure prophylaxis in this population.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
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<th>Comparator Placebo</th>
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<td>Hydroxychloroquine post-exposure prophylaxis may have no</td>
</tr>
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<td>-----------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Timeframe</strong></td>
<td><strong>Study results and measurements</strong></td>
<td><strong>Comparator</strong></td>
<td><strong>Intervention</strong></td>
<td><strong>Certainty of the Evidence (Quality of evidence)</strong></td>
</tr>
<tr>
<td>14 days after commencing treatment</td>
<td>9 Critical</td>
<td>3,135 participants in 2 studies. ¹ (Randomized controlled)</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>² Indirectness</td>
</tr>
<tr>
<td>Symptoms compatible with COVID-19</td>
<td>6 Important</td>
<td>Relative risk 0.98 (CI 95% 0.82 – 1.18) Based on data from 3,135 participants in 2 studies. ² (Randomized controlled)</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>² Indirectness</td>
</tr>
<tr>
<td>Confirmed or probable infection</td>
<td>6 Important</td>
<td>Relative risk 0.83 (CI 95% 0.58 – 1.18) Based on data from 821 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>⁵ Indirectness</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6 Important</td>
<td>Relative risk 0.68 (CI 95% 0.22 – 2.07) Based on data from 3,318 participants in 2 studies. ⁷ (Randomized controlled)</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>⁷ Indirectness</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>6 Important</td>
<td>Relative risk 0.89 (CI 95% 0.44 – 1.81) Based on data from 2,497 participants in 1 studies. ⁹ (Randomized controlled)</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>⁹ Indirectness</td>
</tr>
<tr>
<td>Adverse events</td>
<td>6 Important</td>
<td>Relative risk 4.76 (CI 95% 1.19 – 19.1) Based on data from 3,197 participants in 2 studies. ¹¹ (Randomized controlled)</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>¹¹ Indirectness</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>6 Important</td>
<td>Relative risk 4.1 (CI 95% 0.52 – 32.23) Based on data from 5 per 1000</td>
<td>Placebo</td>
<td>Hydroxychloroquine post-exposure prophylaxis</td>
<td>¹² Indirectness</td>
</tr>
</tbody>
</table>
7.4 Tixagevimab plus cilgavimab (Evusheld) for pre-exposure prophylaxis

7.5 Tixagevimab plus cilgavimab (Evusheld) for post-exposure prophylaxis
8. Respiratory support in adults

Current evidence suggests that about 19% of patients with COVID-19 experience hypoxic respiratory failure, 14% of whom will develop severe disease requiring oxygen therapy and 5% requiring mechanical ventilation within an ICU setting [360]. The majority of early guidelines generally base recommendations on indirect evidence from studies involving SARS, MERS and influenza, although it is presently unclear if patients with COVID-19 would benefit from alternative strategies to optimise the effective administration of respiratory support.

Panels responsible for the recommendations in this section:

<table>
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<tr>
<th>Recommendations</th>
<th>Primary Panel</th>
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<td>HFNO and NIV</td>
<td>Hospital and Acute Care Panel</td>
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<tr>
<td>Respiratory management of the deteriorating patient,</td>
<td>Critical Care Panel</td>
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<td>video-laryngoscopy,</td>
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<td>neuromuscular blockers, PEEP,</td>
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<td>prone positioning, recruitment</td>
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<td>manoeuvres and ECMO</td>
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<tr>
<td>Respiratory support for pregnant and postpartum women</td>
<td>Pregnancy and Perinatal Care Panel</td>
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</table>

Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published.

The remaining panels review recommendations when relevant to their specific population group. In addition, all our recommendations are reviewed by the Consumer Panel.

8.1 Respiratory management

Consensus recommendation

Guiding principles of care

For patients with COVID-19 receiving respiratory support, use single and negative pressure rooms wherever possible. If none are available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients. Ensure contact, droplet and airborne precautions are in place. Healthcare workers should be fully vaccinated and wearing fit-tested N95 masks.

The additional relative risk of infection to healthcare workers associated with specific oxygen therapies and respiratory support is uncertain but is thought to add minimal additional risk in an environment where transmission of infection with COVID-19 is already high.
Info Box

When caring for patients with COVID-19, clinicians need to determine a target range of oxygen saturation to titrate oxygen therapy. Advisable target ranges of oxygen saturation are:

- 92–96% in most patients
- 88–92% in patients at risk of hypercapnia

All awake patients receiving respiratory support should be educated on proning (see section 8.7) and should be encouraged/assisted to prone for as long as is practicable.

Conventional oxygen therapy can be delivered by:

- Nasal prongs at 1–4 L/min (FiO2 approx. 0.24-0.36) to maintain oxygen saturation within the target range.
- Mask at 6–10 L/min (FiO2 approx. 0.35-0.60) to maintain oxygen saturation within the target range.
- Non-rebreather mask 15L/min (FiO2 approx. 1.00) to maintain oxygen saturation within the target range.
- High-flow nasal oxygen (HFNO) therapy with flow rates up to 60L/min with an oxygen/air blender supplying oxygen at FiO2. 0.21-1.00 to maintain oxygen saturation within the target range. It delivers high flow oxygen that is humidified and heated, via large diameter nasal cannula.

Non-invasive ventilation can be delivered by:

- Continuous positive airway pressure (CPAP), a mode of non-invasive ventilation which applies continuous positive airway pressure (with or without entrained oxygen). It can aid in alveolar recruitment and optimise oxygen delivery. CPAP is generally used for hypoxaemic respiratory failure.
- Bilevel positive pressure support (e.g. BiPAP), another mode of non-invasive ventilation which provides a higher level of pressure during the inspiratory phase to enhance ventilation, while a lower level of positive pressure is delivered during the expiratory phase (known as positive end-expiratory pressure (PEEP)). Supplemental oxygen can also be delivered through the device. Bilevel positive pressure support is generally used when there is hypercapnia with or without hypoxaemia.

Conditional recommendation

For patients with COVID-19 who have hypoxaemic respiratory failure and are unable to maintain oxygen saturations within target range despite oxygen delivery by nasal prongs or mask, consider using CPAP.

The evidence suggests that continuous positive airway pressure (CPAP) therapy is preferred for patients with persistent hypoxaemia associated with COVID-19 (defined as requiring an FiO2 ≥ 0.4 to maintain oxygen saturation in their target range). Adjust continuous positive airway pressure as required, most patients require pressures of 10 to 12 cmH2O. Excessive pressures may increase the risk of pneumothorax. Titrate oxygen to maintain oxygen saturation in the target range. There is currently insufficient direct evidence available to support the use of bilevel positive pressure support in the setting of COVID-19.

If CPAP is not available or not tolerated, consider HFNO as an alternative using the same safety parameters.

Patients receiving CPAP (and/or HFNO) for COVID-19, monitor closely at all times and liaise with ICU in case of deterioration. Do not delay endotracheal intubation and invasive mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies.

Clinical Question/ PICO

<p>| Population: | Patients with COVID-19 patients |
| Intervention: | Continuous positive airway pressure |
| Comparator: | Conventional oxygen therapy |</p>
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality or tracheal intubation [composite] Within 30 days</td>
<td>Relative risk 0.82 (CI 95% 0.69 — 0.98) Based on data from 733 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>Conventional oxygen therapy</td>
<td>CPAP</td>
<td>Moderate Due to serious imprecision ²</td>
<td>CPAP probably decreases death or tracheal intubation [composite] (295 events).</td>
</tr>
<tr>
<td>Tracheal intubation Within 30 days</td>
<td>Relative risk 0.81 (CI 95% 0.67 — 0.98) Based on data from 733 participants in 1 studies. ³ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Moderate Due to serious imprecision ⁴</td>
<td>CPAP probably decreases tracheal intubation (273 events).</td>
</tr>
<tr>
<td>All-cause mortality Within 30 days</td>
<td>Relative risk 0.87 (CI 95% 0.64 — 1.18) Based on data from 737 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to very serious imprecision ⁶</td>
<td>CPAP may decrease all-cause mortality slightly (132 events).</td>
</tr>
<tr>
<td>Admission to critical care</td>
<td>Relative risk 0.88 (CI 95% 0.78 — 1) Based on data from 733 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Moderate Due to serious imprecision ⁸</td>
<td>CPAP probably decreases admission to critical care (424 events).</td>
</tr>
<tr>
<td>Critical care length of stay Mean</td>
<td>Lower better Based on data from: 882 participants in 1 studies. ⁹ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to very serious imprecision ¹⁰</td>
<td>CPAP may have little impact on critical care length of stay.</td>
</tr>
<tr>
<td>Hospital length of stay Mean</td>
<td>Lower better Based on data from: 882 participants in 1 studies. ¹¹ (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to very serious imprecision ¹²</td>
<td>CPAP may have little impact on hospital length of stay.</td>
</tr>
</tbody>
</table>

2. **Imprecision: serious.** Only data from one study, Wide confidence intervals.


4. **Imprecision: serious.** Only data from one study.

5. Systematic review [579] with included studies: Recovery-RS. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.

7. Systematic review [579] with included studies: Recovery-RS. **Baseline/comparator:** Control arm of reference used for intervention.

8. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.


10. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.


12. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.

### Clinical Question/ PICO

**Population:** Patients with COVID-19 patients  
**Intervention:** High-flow nasal oxygen therapy  
**Comparator:** Conventional oxygen therapy

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator standard oxygen therapy</th>
<th>Intervention HFNO</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
</table>
| All-cause mortality or tracheal intubation [composite]  
Within 30 days | Relative risk 1  
(CI 95% 0.85 — 1.17)  
Based on data from 770 participants in 1 studies.  
1 (Randomized controlled) | 444 per 1000 | 444 per 1000  
Difference: 0 fewer per 1000  
(CI 95% 67 fewer — 75 more) | Moderate  
Due to serious imprecision | HFNO probably has little impact on all-cause mortality or tracheal intubation [composite]  
(342 events). |
| Tracheal intubation  
Within 30 days | Relative risk 0.99  
(CI 95% 0.84 — 1.18)  
Based on data from 770 participants in 1 studies.  
3 (Randomized controlled) | 413 per 1000 | 409 per 1000  
Difference: 4 fewer per 1000  
(CI 95% 66 fewer — 74 more) | Moderate  
Due to serious imprecision | HFNO probably has little impact on tracheal intubation (317 events). |
| All-cause mortality  
Within 30 days | Relative risk 0.98  
(CI 95% 0.73 — 1.31)  
Based on data from 774 participants in 1 studies.  
5 (Randomized controlled) | 192 per 1000 | 188 per 1000  
Difference: 4 fewer per 1000  
(CI 95% 52 fewer — 60 more) | Low  
Due to very serious imprecision | HFNO may have little impact on all-cause mortality (147 events). |
<p>| Admission to | Relative risk 0.99 | 615 | 609 | Moderate | HFNO probably has little... |</p>
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator standard oxygen therapy</th>
<th>Intervention HFNO</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>critical care</td>
<td>6 Important</td>
<td>(CI 95% 0.89 — 1.11) Based on data from 770 participants in 1 studies.</td>
<td>per 1000</td>
<td>6 fewer per 1000 ( CI 95% 68 fewer — 68 more )</td>
<td>Due to serious imprecision 8</td>
<td>impact on admission to critical care (472 events).</td>
</tr>
<tr>
<td>Critical care length of stay Mean</td>
<td>6 Important</td>
<td>Lower better Based on data from: 882 participants in 1 studies.</td>
<td>9.6 (Mean)</td>
<td>MD 0.9 higher ( CI 95% 1.03 lower — 2.83 higher )</td>
<td>Low</td>
<td>HFNO may have little impact on critical care length of stay.</td>
</tr>
<tr>
<td>Hospital length of stay Mean</td>
<td>6 Important</td>
<td>Lower better Based on data from: 882 participants in 1 studies.</td>
<td>17.3 (Mean)</td>
<td>MD 1 higher ( CI 95% 1.51 lower — 3.51 higher )</td>
<td>Low</td>
<td>HFNO may have little impact on hospital length of stay.</td>
</tr>
</tbody>
</table>

1. Systematic review [579] with included studies: Recovery-RS. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision:** serious. Only data from one study.
4. **Imprecision:** serious. Only data from one study.
5. Systematic review [579] with included studies: Recovery-RS. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision:** very serious. Only data from one study, Wide confidence intervals.
7. Systematic review [579] with included studies: Recovery-RS. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision:** serious. Only data from one study.
10. **Imprecision:** very serious. Wide confidence intervals, Only data from one study.
12. **Imprecision:** very serious. Only data from one study, Wide confidence intervals.

**Clinical Question/ PICO**

**Population:** Patients with hypoxaemia associated with COVID-19

**Intervention:** Non-invasive ventilation (helmet or face mask)

**Comparator:** High-flow nasal oxygen (HFNO) or supplementary oxygen therapy (SOT)

**Summary**

No evidence has been identified in patients with COVID-19. Evidence informing this recommendation comes from a
network meta-analysis of 25 randomised trials (3804 participants) in patients with acute hypoxaemic respiratory failure [370]. Mean age ranged from 30 to 75 years, mean PaO2:FiO2 ratio was predominantly below 200 (14 trials), and more than half of the trials (14 trials) allowed inclusion of immunocompromised patients. Community-acquired pneumonia was the most common cause of acute hypoxaemic respiratory failure in 16 trials.

The results reported helmet NIV as among the most effective but we are uncertain if helmet NIV compared to supplemental oxygen therapy, HFNO and face mask NIV increases or decreases all-cause mortality up to 90 days and endotracheal intubation up to 30 days. This is followed by face mask NIV compared to supplemental oxygen therapy which probably decreases all-cause mortality and endotracheal intubation and HFNO compared to supplemental oxygen therapy for endotracheal intubation. We are uncertain if face mask NIV compared to HFNO is different for all-cause mortality and endotracheal intubation. We are uncertain if HFNO compared to supplemental oxygen therapy is different for all-cause mortality and endotracheal intubation.

The certainty of the evidence in the table below is as reported by Ferreyro [370]. In the context of this recommendation, the certainty of the evidence should be downgraded further due to indirectness as none of the patients had COVID-19.

**Summary Of Treatments**

| Comparator | Helmet NIV v SOT (0.24–0.63) | Helmet NIV v HFNO (0.26–0.80) | Helmet NIV v Face mask NIV (0.29–0.76) | HFNO v SOT (0.26–0.80) | HFNO v Face mask NIV (0.19–0.61) | Face mask NIV v SOT (0.26–0.80) | Face mask NIV v HFNO (0.18–0.66) | Face mask NIV v Face mask NIV (0.19–0.61) | High-Mod certainty | Most effective |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | Most effective |
| Among the most effective or safest | Face mask NIV v SOT 0.83 (0.68 – 0.99) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v HFNO 0.76 (0.55-0.99) | Face mask NIV v HFNO 0.95 (0.69 – 1.37) | Face mask NIV v HFNO 1.01 (0.74-1.38) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v HFNO 0.76 (0.55-0.99) | Face mask NIV v Face mask NIV 0.87 (0.62 – 1.15) | Effective |
| Among the effective | Face mask NIV v HFNO 0.95 (0.69 – 1.37) | Face mask NIV v HFNO 1.01 (0.74-1.38) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v HFNO 0.76 (0.55-0.99) | Face mask NIV v HFNO 0.76 (0.55-0.99) | Face mask NIV v Face mask NIV 0.87 (0.62 – 1.15) | Harmful |
| Not convincingly different | Face mask NIV v HFNO 0.95 (0.69 – 1.37) | Face mask NIV v HFNO 1.01 (0.74-1.38) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v HFNO 0.76 (0.55-0.99) | Face mask NIV v HFNO 0.76 (0.55-0.99) | Face mask NIV v Face mask NIV 0.87 (0.62 – 1.15) | No difference |
| Among the harmful | Face mask NIV v HFNO 0.95 (0.69 – 1.37) | Face mask NIV v HFNO 1.01 (0.74-1.38) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v SOT 0.76 (0.62-0.90) | Face mask NIV v HFNO 0.76 (0.55-0.99) | Face mask NIV v HFNO 0.76 (0.55-0.99) | Face mask NIV v Face mask NIV 0.87 (0.62 – 1.15) | No difference |
| Trials (participants) | 22 (3,633) | 26 (4,067) | 22 (3,633) | 26 (4,067) | 22 (3,633) | 26 (4,067) | 22 (3,633) | 26 (4,067) | No difference |

**Note:** Estimates are network risk ratios and 95% credible intervals
Clinical Question/ PICO

**Population:** Patients with hypoxaemia associated with COVID-19

**Intervention:** Non-invasive ventilation (helmet or face mask)

**Comparator:** High-flow nasal oxygen (HFNO) or supplementary oxygen therapy (SOT)

Summary

See the Summary in the NIV recommendation for consider using in negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator HFNO or SOT</th>
<th>Intervention Helmet or face mask NIV</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>See summary</td>
<td>Based on data from 3,804 participants in 25 studies. (Randomized controlled)</td>
<td>See summary for findings on all-cause mortality and endotracheal intubation.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.2 Respiratory management of the deteriorating patient

**Consensus recommendation**

Do not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies.

Patients can deteriorate rapidly 5 to 10 days after onset of symptoms.

The net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and an advance care directive or plan if available, and consideration of the patient’s expected short- and long-term responses to more invasive forms of treatment.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

**Benefits and harms**

Benefits and harms should be considered on a case-by-case basis as the net clinical benefit is likely to vary for each patient. Frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms. Benefits can include a decrease in self-inflicted lung injury and rapid decline. Harms relevant to transmission should also be considered, as there may be different risks of transmission associated with different settings, for example ICU compared to the emergency department.
8.3 Videolaryngoscopy
Conditional recommendation

In adults with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Time to intubation varies depending on the experience of the operator and the setting. Another important consideration is the potential risk of contamination to the operator due to the infectious nature of COVID-19. In a simulation study using a manikin, the distance between the operator and patient’s mouth increased when using video compared to direct laryngoscopy, thus potentially benefitting operators in the case of COVID-19.

Certainty of the Evidence

For the two critical outcomes—distance between patient and operator, and time to successful intubation—certainty of the evidence is very low due to serious risk of bias, inconsistency, indirectness and imprecision.

Preference and values

We have no systematically collected information regarding patients’ preferences and values. Although there is uncertainty regarding the time to successful intubation, we are reasonably confident that patients would find videolaryngoscopy an acceptable intervention compared to direct laryngoscopy.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the recommendation for this treatment for COVID-19. The Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. The main costs associated with videolaryngoscopy are attributed to the initial equipment outlay, maintenance and operator training. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

Equity

There is a risk of creating inequity as people who live in rural and remote areas may have limited access to videolaryngoscopy and experienced operators. Due to costs and maintenance, there will be variation in the type of clinical settings likely to have access to the appropriate equipment—larger, specialised centres in urban areas are more likely to provide access than those in smaller more remote centres.

The panel noted that rural and remote hospitals do not routinely have access to videolaryngoscopy. The outcome of time to successful intubation is dependent on operator expertise and would likely take longer in non-specialist centres. However, the panel felt that most people intubating would be trained in videolaryngoscopy, although experience would vary. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.
Acceptability

Videolaryngoscopy is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility

Feasibility is affected by the initial equipment costs, maintenance and operator training. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

Rationale

Videolaryngoscopy allows for increased distance between operator and patient.

Clinical Question/ PICO

| Population: | Patients requiring emergency intubation |
| Intervention: | Videolaryngoscopy |
| Comparator: | Direct laryngoscopy |

Summary

Evidence informing this recommendation comes from a systematic review of video versus direct laryngoscopy for the emergency intubation of adults in the inpatient setting [375]. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation [380].

Effectiveness and adverse events

| Study design | Randomised trials |
| Population | Critically ill patients requiring emergency intubation in emergency departments or intensive care units. No studies available in patients with COVID-19. |
| Intervention | Videolaryngoscopy |
| Comparator | Direct laryngoscopy |
| Synthesis method | Meta-analysis |

Results

We included six of the eight randomised trials (1023 patients) in the Rombey review [373][374][376][377][378][379]. (Two were excluded because patients were intubated before hospital admission.) We included an additional randomised trial of 163 patients that was published after the Rombey review [372]. This study did not change the overall results for the outcomes, but did improve the precision of the estimate for inadvertent oesophageal intubation.

There was no difference between video and direct laryngoscopy with respect to successful intubation at first attempt or time to successful intubation. In the four randomised trials that reported inadvertent oesophageal intubation, the use of videolaryngoscopy was associated with fewer of these adverse events, however the number was small (27 events).

Operator distance (Hall 2020)

| Study design | Crossover study |
| Population | 25 doctors of mixed experience performing tracheal intubation on a high-fidelity manikin. |
| Intervention | Videolaryngoscopy |
| Comparator | Direct laryngoscopy |

Results

Videolaryngoscopy may extend the mouth-to-mouth distance from laryngoscopist to patient compared to direct laryngoscopy, and places the laryngoscopist's face above the direct line of sight to the pharynx.

Certainty of the evidence is low to very low due to indirectness (not based on COVID-19 patients or exclusively patients with ARDS), risk of bias, lack of precision in some outcomes and small number of adverse events.
### Outcome Timeframe

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-pass intubation success</td>
<td>Relative risk 1.05 (CI 95% 0.94 — 1.17) Based on data from 1,186 participants in 7 studies.</td>
<td>Direct laryngoscopy</td>
<td>Videolaryngoscopy</td>
<td>Very low Due to serious risk of bias, inconsistency and indirectness</td>
<td>We are uncertain whether videolaryngoscopy increases or decreases first-pass intubation success.</td>
</tr>
<tr>
<td>Oesophageal intubation</td>
<td>Relative risk 0.4 (CI 95% 0.17 — 0.93) Based on data from 795 participants in 4 studies.</td>
<td>Videolaryngoscopy</td>
<td>Videolaryngoscopy</td>
<td>Low Due to serious risk of bias and indirectness</td>
<td>Videolaryngoscopy may decrease oesophageal intubation.</td>
</tr>
<tr>
<td>Operator distance in cm</td>
<td>Measured by: distance analysed from videorecording High better Based on data from: 25 participants in 1 studies.</td>
<td>Videolaryngoscopy</td>
<td>Videolaryngoscopy</td>
<td>Very low Due to serious risk of bias, indirectness and imprecision</td>
<td>Videolaryngoscopy may increase the operator distance.</td>
</tr>
<tr>
<td>Time to successful intubation</td>
<td>Based on data from: 988 participants in 6 studies.</td>
<td>Videolaryngoscopy</td>
<td>Videolaryngoscopy</td>
<td>Very low Due to serious risk of bias, indirectness and imprecision</td>
<td>We are uncertain whether videolaryngoscopy increases or decreases time to successful intubation.</td>
</tr>
</tbody>
</table>

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2. **Risk of Bias: serious.** Personnel blinding was not possible for this outcome, resulting in potential for performance bias. Outcome assessor blinding was also not possible, resulting in potential for detection bias. **Inconsistency: serious.** There was clinical heterogeneity across the included studies in relation to setting (ED vs ICU), operator experience and devices used. Subgroup analyses in Rombe et al 2018 reported that effect sizes were not decisively altered by sensitivity or subgroup analyses. **Indirectness: serious.** The included studies were in non COVID-19 populations, with mixed presentations of respiratory and other critically ill patients. Differences between the population of interest and those studied. **Imprecision: no serious.** **Publication bias: no serious.** Rombe 2018 visually evaluated the funnel plot for publication bias, with distribution for this outcome relatively symmetrical.


4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, and inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.. **Inconsistency: no serious.** **Indirectness: serious.** The included studies were in non COVID-19 populations, with mixed presentations of respiratory and other critically ill patients. **Imprecision: no serious.** **Publication bias: no serious.** Rombe 2018 visually evaluated the funnel plot for publication bias, with distribution for this outcome relatively symmetrical.

5. The 'mouth-to-mouth' distance between operator and manikin as measured by video analysis.

6. Primary study[380]. **Baseline/comparator:** Control arm of reference used for intervention[380].

7. **Risk of Bias: serious.** Blinding of personnel not possible, resulting in potential for performance bias, unclear sequence
Neuromuscular blockers (NMBAs) are a pharmaceutical intervention that may facilitate protective lung ventilation in patients who are mechanically ventilated with moderate to severe acute respiratory distress syndrome (ARDS). NMBAs may reduce patient-ventilator dyssynchrony and facilitate improved oxygenation by various mechanisms, including reducing the inspiratory muscle effort and the work of breathing, and reducing ventilator-induced lung injury.

Clinical Question/ PICO

**Population:** Mechanically ventilated adults with COVID-19 and persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation or persistently high plateau pressures  
**Intervention:** Continuous infusion of NMA  
**Comparator:** No continuous infusion of NMA

Summary

Evidence informing this recommendation comes from five randomised trials involving 1461 adults with acute respiratory distress syndrome. Currently, there is no evidence in patients with COVID-19. The five trials compared continuous infusions of neuromuscular blocking agents with cisatracurium for up to 48 hours to no continuous infusions of NMBAs [382][383][384][385][386].

For all critical outcomes, it is uncertain whether infusion of neuromuscular blockers makes a difference. The ROSE trial, which had a different sedation strategy to the other trials and implemented a higher PEEP strategy, is the largest (1006 participants) and most recent trial, and may be the most reflective of current practice [383]. There were no differences for the mortality outcomes, but the trial found a small increase in muscle weakness at 28 days in the neuromuscular blocker group.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-day mortality</td>
<td></td>
<td>Relative risk 0.81 (CI 95% 0.62 — 1.06) Based on data from 1,461 participants in 5 studies. 3 (Randomized controlled)</td>
<td>No NMBA</td>
<td>Intervention</td>
<td>Very low Due to serious inconsistency, indirectness and imprecision 4</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (612 events).</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td>441 per 1000</td>
<td>357 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 84 fewer per 1000 (CI 95% 168 fewer — 26 more)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ICU mortality</td>
<td>6 Important</td>
<td>Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 participants in 4 studies. 5 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious indirectness and imprecision 6</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (171 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>438 per 1000</td>
<td>315 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 123 fewer per 1000 (CI 95% 188 fewer — 39 fewer)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ICU weakness at day 28</td>
<td>9 Critical</td>
<td>Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 participants in 4 studies. 7 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and indirectness, and very serious indirectness 8</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (91 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>230 per 1000</td>
<td>283 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 53 more per 1000 (CI 95% 44 fewer — 202 more)</td>
<td></td>
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</tr>
<tr>
<td>Barotrauma</td>
<td>6 Important</td>
<td>Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 participants in 4 studies. 9 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, indirectness and indirectness 10</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen barotrauma (81 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>74 per 1000</td>
<td>41 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 33 fewer per 1000 (CI 95% 48 fewer — 11 fewer)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation duration</td>
<td>Days</td>
<td>Measured by: Days Based on data from: 92 participants in 2 studies. 11 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, inconsistency and indirectness, and very serious indirectness 12</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease mechanical ventilation duration.</td>
</tr>
<tr>
<td></td>
<td>6 Important</td>
<td></td>
<td>18 (Median)</td>
<td>20 (Median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 2 higher</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator-free days at day 28</td>
<td>6 Important</td>
<td>Measured by: Days Based on data from: 1,462 participants in 5 studies. 13 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, indirectness and indirectness, and very serious indirectness 14</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen ventilator-free days at day 28.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9.6 (Median)</td>
<td>9.9 (Median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: 0.3 higher</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MRC score at day 28</td>
<td></td>
<td>Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias and indirectness, and</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49.8 muscle strength (Median)</td>
<td>45.9 muscle strength (Median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>---------</td>
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<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>6 Important</td>
<td>better</td>
<td>Based on data from 1,346 participants in 2 studies. (Randomized controlled) Follow up: 28 days.</td>
<td>Difference:</td>
<td>MD 4.1 lower</td>
<td>very serious inconsistency</td>
<td>day 28.</td>
</tr>
</tbody>
</table>

1. **Baseline/comparator**: Control arm of reference used for intervention.
2. **Inconsistency**: serious. The magnitude of statistical heterogeneity was high, with $I^2$:25.0%. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials.. **Indirectness**: serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. Only one study (largest study) used a high PEEP strategy.. **Imprecision**: serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials.. **Publication bias**: no serious.
3. **Baseline/comparator**: Control arm of reference used for intervention.
4. **Inconsistency**: serious. The magnitude of statistical heterogeneity was high, with $I^2$:25.6%. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials.. **Indirectness**: serious. Differences between the population of interest and those studied: no studies in patients with COVID-19.. **Imprecision**: serious. substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials.. **Publication bias**: no serious.
5. **Baseline/comparator**: Control arm of reference used for intervention.
6. **Inconsistency**: no serious. **Indirectness**: very serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. The largest trial, with the most applicable strategy reflecting current clinical practice, did not report on on this outcome.. **Imprecision**: serious. The largest trial did not report on this outcome.. **Publication bias**: no serious.
7. **Baseline/comparator**: Control arm of reference used for intervention.
8. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.. **Inconsistency**: no serious. **Indirectness**: very serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. The largest trial, with the most applicable strategy reflecting current clinical practice, only included a very small subset of patients for this outcome.. **Imprecision**: serious. Low number of patients.. **Publication bias**: no serious.
9. **Baseline/comparator**: Control arm of reference used for intervention.
10. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.. **Inconsistency**: serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials.. **Indirectness**: serious. Differences between the population of interest and those studied: no studies in COVID-19 patients.. **Imprecision**: no serious. **Publication bias**: no serious.
11. **Baseline/comparator**: Control arm of reference used for intervention.
12. **Risk of Bias**: serious. **Inconsistency**: no serious. **Indirectness**: serious. Differences between the population of interest and those studied: no studies in patients with COVID-19.. **Imprecision**: very serious. Low number of patients, Wide confidence intervals. **Publication bias**: no serious.
13. **Baseline/comparator**: Control arm of reference used for intervention.
14. **Risk of Bias**: serious. **Inconsistency**: no serious. **Indirectness**: serious. Differences between the population of interest and those studied.. **Imprecision**: serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials.. **Publication bias**: no serious.
15. **Baseline/comparator**: Control arm of reference used for intervention.
16. **Risk of Bias**: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance
Evidence To Decision

**Bias. Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2:91 %. Clinical heterogeneity.. **Indirectness: serious.** Differences between the population of interest and those studied: No studies in COVID-19 patients.. **Imprecision: serious.** Publication bias: no serious.

**Conditional recommendation against**

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

*However, if protective lung ventilation cannot be achieved, consider using NMBAs for up to 48 hours. If indicated, consider cisatracurium as first-line agent, if cisatracurium is not available alternatives include atracurium or vecuronium by infusion.*

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**Evidence To Decision**

**Benefits and harms**

Small net benefit, or little difference between alternatives

There is no substantial net benefit to using neuromuscular blockers. Prolonged use of NMBAs could have negative effects on intubated patients, such as muscle weakness and difficulty weaning from mechanical ventilation.

**Certainty of the Evidence**

Very low

Outcomes identified as most critical were 90-day mortality and muscle weakness at 28 days. No studies were identified that included patients with COVID-19. Certainty of the evidence for all outcomes is very low, mostly due to serious inconsistency, indirectness and imprecision. There were substantial methodological inconsistencies between the trials.

**Preference and values**

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. Since there is uncertainty regarding the critical outcome of muscle weakness, some patients might consider NMBAs unacceptable. The inability to move or communicate while being treated with neuromuscular blockers is likely to be an additional consideration for patients.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the recommendation for this treatment for COVID-19. The Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. There are potential resource considerations due to supply issues for some neuromuscular blockers (e.g. cisatracurium).

**Equity**

Important issues, or potential issues not investigated

There is a risk of creating inequity as some populations may have limited access to neuromuscular blockers, particularly if there is a shortage.
Acceptability

Neuromuscular blockers may be less acceptable because of possible harms—patients and clinicians may consider the benefits are not worth the risk. In addition to the risk of muscle weakness, patients and their families may deem it unacceptable to be paralysed and non-responsive.

Feasibility

Feasibility may be affected by potential supply issues for some neuromuscular blockers (e.g. cisatracurium).

Rationale

Routine use of continuous infusions of neuromuscular blockers could have negative effects on intubated patients, such as muscle weakness and difficulty weaning from mechanical ventilation.

Clinical Question/ PICO

**Population:** Mechanically ventilated adults with COVID-19 and persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation or persistently high plateau pressures

**Intervention:** Continuous infusion of NMBA

**Comparator:** No continuous infusion of NMBA

Summary

Evidence informing this recommendation comes from five randomised trials involving 1461 adults with acute respiratory distress syndrome. Currently, there is no evidence in patients with COVID-19. The five trials compared continuous infusions of neuromuscular blocking agents with cisatracurium for up to 48 hours to no continuous infusions of NMBA [382][383][384][385][386].

For all critical outcomes, it is uncertain whether infusion of neuromuscular blockers makes a difference. The ROSE trial, which had a different sedation strategy to the other trials and implemented a higher PEEP strategy, is the largest (1006 participants) and most recent trial, and may be the most reflective of current practice [383]. There were no differences for the mortality outcomes, but the trial found a small increase in muscle weakness at 28 days in the neuromuscular blocker group.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator No NMBA</th>
<th>Intervention NMBA</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>Relative risk 0.78 (CI 95% 0.58 – 1.06) Based on data from 1,461 participants in 5 studies. (Randomized controlled)</td>
<td>372 per 1000</td>
<td>290 per 1000</td>
<td>Very low Due to serious inconsistency, indirectness and imprecision</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (513 events).</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>Relative risk 0.81 (CI 95% 0.62 – 1.06) Based on data from 1,461 participants in 5 studies. (Randomized controlled)</td>
<td>441 per 1000</td>
<td>357 per 1000</td>
<td>Very low Due to serious inconsistency, indirectness and imprecision</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (612 events).</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
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<td>------------------------</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 participants in 4 studies. (Randomized controlled)</td>
<td>438 per 1000</td>
<td>315 per 1000</td>
<td>Very low Due to serious imprecision and very serious indirectness</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (171 events).</td>
</tr>
<tr>
<td>ICU weakness at day 28</td>
<td>Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 participants in 4 studies. (Randomized controlled)</td>
<td>230 per 1000</td>
<td>283 per 1000</td>
<td>Very low Due to serious risk of bias and imprecision, and very serious indirectness</td>
<td>We are uncertain whether neuromuscular blockers increase or worsen ICU weakness at day 28 (91 events).</td>
</tr>
<tr>
<td>Barotrauma</td>
<td>Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 participants in 4 studies. (Randomized controlled)</td>
<td>74 per 1000</td>
<td>41 per 1000</td>
<td>Very low Due to serious risk of bias, indirectness and indirectness</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen barotrauma (81 events).</td>
</tr>
<tr>
<td>Mechanical ventilation duration Days</td>
<td>Measured by: Days Based on data from: 92 participants in 2 studies. (Randomized controlled)</td>
<td>18 (Median)</td>
<td>20 (Median)</td>
<td>Very low Due to serious risk of bias, inconsistency and indirectness, and very serious imprecision</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease mechanical ventilation duration.</td>
</tr>
<tr>
<td>Ventilator-free days at day 28</td>
<td>Measured by: Days Based on data from: 1,462 participants in 5 studies. (Randomized controlled)</td>
<td>9.6 (Median)</td>
<td>9.9 (Median)</td>
<td>Very low Due to serious risk of bias, indirectness and indirectness</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen ventilator-free days at day 28.</td>
</tr>
<tr>
<td>MRC score at day 28</td>
<td>Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High better Based on data from: 1,346 participants in 2 studies. (Randomized controlled) Follow up: 28 days.</td>
<td>49.8 (Median)</td>
<td>45.9 (Median)</td>
<td>Very low Due to serious risk of bias and indirectness, and very serious inconsistency</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.</td>
</tr>
</tbody>
</table>

2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:50 %. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials. **Indirectness: serious.** Differences between the population

593 of 734
of interest and those studied: no studies in patients with COVID-19. Only one study (largest study) used a high PEEP strategy. **Imprecision: serious.** Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. **Publication bias: no serious.**


4. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with $I^2:56\%$. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials. **Indirectness: serious.** Differences between the population of interest and those studied: no studies in patients with COVID-19. **Imprecision: serious,** substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. **Publication bias: no serious.**


6. **Inconsistency: no serious.** **Indirectness: very serious.** Differences between the population of interest and those studied: no studies in patients with COVID-19. The largest trial, with the most applicable strategy reflecting current clinical practice, did not report on this outcome. **Imprecision: serious.** The largest trial did not report on this outcome. **Publication bias: no serious.**


8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious.** **Indirectness: very serious.** Differences between the population of interest and those studied: no studies in COVID-19 patients. The largest trial, with the most applicable strategy reflecting current clinical practice, only included a very small subset of patients for this outcome. **Imprecision: serious.** Low number of patients. **Publication bias: no serious.**


10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: serious.** Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. **Indirectness: serious.** Differences between the population of interest and those studied: no studies in COVID-19 patients. **Imprecision: no serious.** **Publication bias: no serious.**


12. **Risk of Bias: serious.** **Inconsistency: no serious.** **Indirectness: serious.** Differences between the population of interest and those studied: no studies in patients with COVID-19. **Imprecision: very serious.** Low number of patients, Wide confidence intervals. **Publication bias: no serious.**


14. **Risk of Bias: serious.** **Inconsistency: no serious.** **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. **Publication bias: no serious.**


16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with $I^2:91\%$. Clinical heterogeneity. **Indirectness: serious.** Differences between the population of interest and those studied: No studies in COVID-19 patients. **Imprecision: serious.** **Publication bias: no serious.**

**8.5 Positive end-expiratory pressure**
Evidence To Decision

Benefits and harms
While there is no current evidence for using a higher PEEP strategy in patients with COVID-19 and moderate to severe ARDS, a higher PEEP strategy is recommended for ventilated patients with moderate to severe ARDS of other aetiologies. A higher PEEP strategy may be associated potential harms, e.g. pneumothorax.

Certainty of the Evidence
No studies were identified in COVID-19 patients that address the question of lower versus higher PEEP strategy.

Preference and values
We have no systematically collected information regarding patients' preferences and values at this point.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, some informed patients would agree with the recommendation and consider this treatment. The Panel recognises that some informed patients may choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit.

Equity
There are likely no important equity issues.

Acceptability
We are uncertain if a higher PEEP ventilation strategy would be acceptable to both patients and healthcare providers.

Feasibility
There are likely no important feasibility issues.

Rationale
While there is no current evidence for using a higher PEEP strategy in patients with COVID-19 and moderate to severe ARDS, a higher PEEP strategy is recommended for ventilated patients with moderate to severe ARDS of other aetiologies.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
8.6 Prone positioning

8.6.1 Prone positioning for adults

**Info Box**

Positioning the patient in a face-down (prone) position may help to open up (recruit) collapsed alveoli and improve oxygen levels in the blood.

**Consensus recommendation**

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

*Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.*

*Net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.*

*Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker.*

This is a **low priority** recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**Evidence To Decision**

**Benefits and harms**

While there is no current evidence for using prone positioning in patients with COVID-19, it is recommended for ventilated patients with moderate to severe ARDS of other aetiologies. In these patients it is known to have a survival benefit, but may increase the risk of harms from complications such as pressure injury, endotracheal tube obstruction or accidental extubation.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Net clinical benefit for each patient should be considered on a case-by-case basis. For example, older people living with frailty may be at particular risk of harm from proning. The symptom benefits of proning in palliative patients remain unclear.
Preference and values
We have no systematically collected information regarding patients’ preferences and values at this point.

People requiring palliative care and older people living with frailty or cognitive impairment
Consider the preferences and values of the patient and whether they have an advanced care directive or plan. Decisions around proceeding to more invasive forms of ventilation should be discussed with the patient or their medical treatment decision-maker.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, most informed patients/carers would agree with the recommendation for this treatment. The Panel recognises that some informed patients/carers may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Proning is associated with significant cost since additional staff are needed to move and monitor those in prone position. Healthcare workers must be effectively trained to facilitate safe practice.

Equity
There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability
We have no systematically collected evidence regarding acceptability. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

Feasibility
Prone positioning of mechanically ventilated patients is likely feasible if performed by trained personnel in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

People requiring palliative care and older people living with frailty or cognitive impairment
It may not be feasible to prone patients in this population as they may be at particular risk of harm from proning.

Adaptation
The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [360]. Wording has been adapted for clarity and applicability to the Australian context.
Conditional recommendation

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning for at least 3 hours per day as tolerated. When positioning a patient in prone, ensure proning is used with caution and accompanied by close monitoring of the patient. Use of prone positioning should not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised less invasive respiratory therapies.

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, prone positioning for as long as tolerated (ideally 8 hours or more) is likely to increase benefits.

Vulnerable people who are treated outside the ICU, for example people who are older and living with frailty, cognitive impairment or unable to communicate, may especially be at increased risk of harm from proning. Despite the potential risks of awake proning associated with frailty, there may be benefits for this group. The net clinical benefit for each individual patient should be considered on a case-by-case basis.

Currently, the evidence indicates that prone positioning probably decreases treatment failure and the need for intubation, with no increase in harms. Prone positioning should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Prone positioning is recommended in mechanically ventilated patients with moderate to severe ARDS of other aetiologies. In these patients prone positioning improves the rates of treatment failure and reduces the need for intubation within 28 to 30 days. The randomised controlled trials have indicated no increase in harms, but possible pressure injury should be monitored.

People requiring palliative care and older people living with frailty or cognitive impairment

Net clinical benefit for each individual patient should be considered on a case-by-case basis. For example, older people living with frailty who are treated outside the ICU and patients who are unable to communicate may be at particular risk of harm from proning.

Certainty of the Evidence

The certainty of the evidence is low. Outcomes ranged from moderate to low, with important outcomes such as admission to ICU, all-cause mortality, adverse events, including pressure sores. Outcomes were downgraded because of methodological limitations of included studies and serious imprecision due to few events and participants in included studies.

Preference and values

We have no systematically collected information regarding patients’ preferences and values at this point. However, patients in one small prospective cohort study who received proning rated their comfort levels as acceptable, good or excellent.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, most informed patients/carers would agree with the recommendation for this treatment. The Panel recognises that some informed patients/carers may choose not to proceed with this treatment based on reasons unrelated to COVID-19.
Rationale
Prone positioning is used in people with severe hypoxaemic respiratory failure in the context of ARDS. In ventilated people with ARDS, prone positioning improves oxygenation and clinical outcomes. Prone positioning is thought to work by improving tidal ventilation, especially to dependent parts of the lung, enhancing ventilation and perfusion matching as well as favourably distributing the pleural pressures throughout the lung thus minimising further damage.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Proning is associated with significant cost as additional staff are needed to move and monitor those in prone position. Healthcare workers must be trained to facilitate safe practice.

Equity
Staff carrying out prone positioning need to move and monitor those who are in the prone position, which may be resource intensive. This may result in potential inequity as some healthcare facilities may not be able to offer prone positioning.

Acceptability
We have no systematically collected evidence regarding acceptability of prone positioning. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

Feasibility
Prone positioning is likely feasible if performed by trained personnel in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events.

People requiring palliative care and older people living with frailty or cognitive impairment
It may not be feasible to prone patients in this population as older people living with frailty and patients who are unable to communicate may be at particular risk of harm from proning. Feasibility may vary depending on setting and may be less feasible when patients are treated outside the ICU.

Rationale
Prone positioning is used in people with severe hypoxaemic respiratory failure in the context of ARDS. In ventilated people with ARDS, prone positioning improves oxygenation and clinical outcomes. Prone positioning is thought to work by improving tidal ventilation, especially to dependent parts of the lung, enhancing ventilation and perfusion matching as well as favourably distributing the pleural pressures throughout the lung thus minimising further damage.

Clinical Question/ PICO
Population: Patients with COVID-19 on supplementary oxygen who are not yet intubated
Intervention: Prone positioning
Comparator: No prone positioning

Summary
Evidence for this recommendation comes from two randomised trials of 1196 adults with acute hypoxaemic respiratory failure requiring respiratory support with high-flow nasal cannula or non-invasive ventilation. The trials compared the use of prone positioning (either 16 hours per day or as long and as frequently as possible) with standard care where prone positioning was not encouraged [561][562].
Patients' age ranged from 18–74 years (mean 61 years) and two-thirds were men. Many patients had co-existing illness, with around a third with diabetes mellitus or obesity.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 1.08 (CI 95% 0.51 – 2.31) Based on data from 1,196 participants in 2 studies.</td>
<td>Not proning</td>
<td>Proning</td>
<td>Moderate Due to serious imprecision</td>
<td>Proning probably has little impact on all-cause mortality.</td>
</tr>
<tr>
<td>30 days</td>
<td></td>
<td>227 per 1000</td>
<td>245 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheal intubation</td>
<td>Relative risk 0.83 (CI 95% 0.71 – 0.96) Based on data from 1,196 participants in 2 studies.</td>
<td>Not proning</td>
<td>Proning</td>
<td>Moderate Due to serious risk of bias</td>
<td>Proning probably decreases the need for tracheal intubation.</td>
</tr>
<tr>
<td>28–30 days</td>
<td></td>
<td>396 per 1000</td>
<td>329 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>Relative risk 1.08 (CI 95% 0.82 – 1.44) Based on data from 75 participants in 1 studies.</td>
<td>Not proning</td>
<td>Proning</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>We are uncertain whether proning impacts admission to ICU.</td>
</tr>
<tr>
<td>28 days</td>
<td></td>
<td>692 per 1000</td>
<td>747 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure sores</td>
<td>Relative risk 0.5 (CI 95% 0.16 – 1.56) Based on data from 1,196 participants in 2 studies.</td>
<td>Not proning</td>
<td>Proning</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>Proning may have little or no difference on pressure sores.</td>
</tr>
<tr>
<td>28–30 days</td>
<td></td>
<td>32 per 1000</td>
<td>16 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 0.9 (CI 95% 0.47 – 1.72) Based on data from 1,196 participants in 2 studies.</td>
<td>Not proning</td>
<td>Proning</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>Proning may have little or no difference on adverse events.</td>
</tr>
<tr>
<td>28 - 30 days</td>
<td></td>
<td>94 per 1000</td>
<td>85 per 1000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8.6.2 Prone positioning for pregnant and postpartum women

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Not proning</th>
<th>Intervention Proning</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

2. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals. **Publication bias:** no serious.
4. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study. **Publication bias:** no serious.
6. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals. **Publication bias:** no serious.
8. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals. **Publication bias:** no serious.
10. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals. **Publication bias:** no serious.

**Consensus recommendation**

For mechanically ventilated pregnant women with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

*Current reports suggest prone ventilation in adult patients is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff, and that minimises the risk of adverse events, e.g. accidental extubation.*

*Proning of a pregnant woman should avoid abdominal compression and ensure a woman’s hips and chest are supported. In the absence of specialised equipment, proning can be performed using pillows and blankets.*

*Proning can be challenging in late gestation and delivery of the baby may be warranted.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*
Evidence To Decision

Benefits and harms
The benefit of prone positioning in pregnant women with COVID-19 is unknown, but it may improve lung mechanics and gas exchange. However, it can be associated with harms such as hypoperfusion, compartment syndrome, pressure ulcers, airway swelling and peripheral arterial compression.

Certainty of the Evidence
No studies were identified in COVID-19 patients that address the interventions or outcomes of interest.

Preference and values
We have no systematically collected information regarding the preferences and values of pregnant and breastfeeding women with COVID-19 at this point.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, most informed pregnant or postpartum women in this group of COVID-19 patients would agree with the recommendation and consider this treatment. The Panel recognises that some pregnant or postpartum women may choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (irrespective of prone positioning) requires greater resources than for women without COVID-19. Pruning is associated with significant cost since additional staff are needed to move and monitor those in prone position. Healthcare workers must be effectively trained to facilitate safe practice.

Equity
There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability
We have no systematically collected evidence regarding acceptability. Acceptability of prone positioning is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

Feasibility
Prone positioning may be less feasible later in pregnancy. Prone positioning of mechanically ventilated patients is likely feasible if performed by trained personnel in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.
For pregnant and postpartum women with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a pregnant woman in prone, care should be taken to support the gravid uterus to reduce aorta-caval compression. Women who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation. Birth of the baby should be considered when it may enhance maternal resuscitation or be beneficial to the fetus.

Current reports suggest prone ventilation in adult patients is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

Proning of a pregnant woman should avoid abdominal compression and ensure a woman’s hips and chest are supported. In the absence of specialised equipment, it can be performed using pillows and blankets.

Proning can be challenging in late gestation and delivery of the baby may be warranted.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

The benefit of prone positioning in pregnant women with COVID-19 is unknown, but it may improve lung mechanics and gas exchange. However, it can be associated with harms such as hypoperfusion, compartment syndrome, pressure ulcers, airway swelling and peripheral arterial compression.

Certainty of the Evidence

No studies were identified in COVID-19 patients that address the interventions or outcomes of interest.

Preference and values

We have no systematically collected information regarding the preferences and values of pregnant and breastfeeding women with COVID-19 at this point.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, some informed pregnant or postpartum women in this group of COVID-19 patients would agree with the recommendation and consider this treatment. The Panel recognises that some pregnant or postpartum women may choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (irrespective of prone positioning) requires greater resources than for women without COVID-19. Proning is associated with significant cost since additional staff are needed to move and monitor those in prone position. Healthcare workers must be effectively trained to facilitate safe practice.
Equity
There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability
We have no systematically collected evidence regarding acceptability. Acceptability of prone positioning is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

Feasibility
Prone positioning may be less feasible later in pregnancy. Prone positioning of mechanically ventilated patients is likely feasible if performed by trained personnel in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g., accidental extubation.

8.6.3 Prone positioning and CPR

Consensus recommendation
For patients with COVID-19 in prone position requiring cardiopulmonary resuscitation (CPR), where safe and feasible, return the patient to supine position and commence resuscitation.

If returning the patient to supine position is not safe and feasible, commence CPR in prone position. Once it is safe and feasible, return the patient to supine position and continue the resuscitation process.

When caring for patients with COVID-19, consider the options available for providing cardiopulmonary resuscitation (CPR) when instituting prone positioning.

It is reasonable to provide CPR in the prone position when supine CPR cannot be feasibly or safely implemented, and the airway is secured.

Returning the patient to supine position should only be performed when there are suitable resources to minimise risk of harm to staff and patients, e.g., accidental extubation, venous or arterial line dislodgement.

Provision of CPR for patients in prone position should be performed where there are hospital guidelines, and training in provision of prone CPR has been undertaken.

Decisions to commence CPR should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker in advance of need.

Consideration should also be given to whether prone positioning has contributed to the need for CPR, for example by including abdominal compression and obstruction to venous return.

8.7 Recruitment manoeuvres
Evidence To Decision

Info Box

Patients receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an 'open lung approach' to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure (incremental PEEP, stepwise or staircase); and high driving pressures.

Consensus recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider using recruitment manoeuvres.

If recruitment manoeuvres are used, do not use staircase or stepwise (incremental PEEP) recruitment manoeuvres.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Benefits and harms

Recruitment manoeuvres may benefit mechanically ventilated patients with COVID-19 by opening collapsed lung units during mechanical ventilation. However, they may also be associated with harms, such as increased risk of barotrauma and transient hypotension.

Certainty of the Evidence

No studies were identified in COVID-19 patients that compare recruitment manoeuvres to no recruitment manoeuvres or variations on recruitment manoeuvres.

Preference and values

We have no systematically collected information regarding patients' preferences and values at this point.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, most informed patients would agree with the recommendation for this treatment. The Panel recognises that some informed patients may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. However, patients receiving recruitment manoeuvres may require more intensive monitoring.
8.8 Extracorporeal membrane oxygenation

Info Box

Extracorporeal membrane oxygenation (ECMO) is a form of life support that removes blood from the body via large cannulae, oxygenates and removes carbon dioxide from the blood external to the patient, and then returns the blood to the body.

Venovenous (VV) ECMO provides oxygenation support for the lungs only, while venoarterial (VA) ECMO supports the heart and lungs.

8.8.1 ECMO for adults

Conditional recommendation

Consider early referral to an ECMO centre for patients developing refractory respiratory failure in mechanically ventilated adults with COVID-19 (despite optimising ventilation, including proning and neuromuscular blockers).

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected patients with COVID-19 and severe ARDS.

Net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
### Evidence To Decision

#### Benefits and harms

ECMO is only used as a form of life support in patients who are severely ill—it may increase oxygenation and reduce ventilator-induced lung injuries, which may assist to increase recovery and decrease mortality. However, ECMO may be associated with risk of serious side effects, such as major bleeding, disseminated intravascular coagulation and injuries from cannulation. ECMO is only used in carefully selected patients who are at decreased risk of harms from receiving ECMO and may benefit the most from the potential survival benefits of ECMO.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Net clinical benefit for each patient should be considered on a case-by-case basis. For example, older people living with frailty may be at particular risk of harm from more invasive forms of therapy, and the symptom benefits in palliative patients remain unclear.

#### Certainty of the Evidence

Two non-comparative observational studies were identified in COVID-19 patients receiving ECMO.

#### Preference and values

We have no systematically collected information regarding patients' preferences and values at this point. However, the serious risk of side effects may be unacceptable for some patients and their families.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Consider the preferences and values of the patient and whether they have an advanced care directive or plan. Decisions around proceeding to more invasive forms of therapy should be discussed with the patient or their medical treatment decision-maker.

The Consumer Panel believes that in line with the limited available evidence, some informed patients/carers may prefer to wait until the available evidence is clearer, while others may agree to have more invasive treatment initiated if this is consistent with their goals of care. The Panel recognises that some patients/carers may still choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

#### Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

#### Equity

Due to the resource-intensive nature of ECMO there may be issues with inequity as only certain centres will have the ability to offer ECMO or ECMO retrieval. ECMO will only be considered in selected patients who are likely to have access to appropriate centres.

#### Acceptability

There may be important issues with acceptability. The intervention could be considered less acceptable due to its possible harms and some may not consider its benefits worth the risk.
Feasibility
Due to the resource-intensive nature of ECMO there are likely to be feasibility issues. ECMO is likely to only be feasible in a limited number of centres.

Adaptation
The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [360]. Wording has been adapted for clarity and applicability to the Australian context.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>ECMO</td>
</tr>
<tr>
<td>Comparator:</td>
<td>No ECMO</td>
</tr>
</tbody>
</table>

Summary
We are uncertain if extracorporeal membrane oxygenation (ECMO) is more effective than no ECMO in patients who are critically ill with COVID-19. ECMO may be associated with risk of serious side effects.

Systematic reviews of ECMO for acute respiratory failure in non-COVID-19 patients suggest there may be a benefit, but that ECMO may also be associated with significant harms. Data comparing ECMO to no ECMO in patients with COVID-19 are still lacking.

What is the evidence informing this recommendation?
Evidence comes from two non-comparative observational studies in critically ill patients with COVID-19 receiving ECMO. One study included 1035 patients [388] and the other included 83 patients [389].

Study characteristics
The Extracorporeal Life Support Organization (ELSO) Registry included 1035 patients (median age of 49 years) from 213 hospitals in 36 countries [388]. The proportion of women was 26%, of whom 22 were pregnant. Ninety-four percent of patients received venous ECMO. Before initiation of ECMO, 72% of patients received neuromuscular blockers, 60% were placed in prone position and 99% were ventilated. Before ventilation, 59% of patients received non-invasive ventilation and 35% high-flow nasal oxygen therapy. Patients received pharmacological therapies for COVID-19, including chloroquine or hydroxychloroquine (52%), glucocorticoids (41%), anticytokine (28%), lopinavir–ritonavir (11%), remdesivir (8%) and intravenous immunoglobulin (3%).

In the retrospective cohort of 83 patients from five ICUs in France, median age was 49 years and the proportion of women was 27% [389]. Ninety-seven percent of patients received venovenous ECMO. Before initiation of ECMO, 96% of patients received neuromuscular blockers and 94% were placed in prone position. Patients received pharmacological therapies for COVID-19, including lopinavir-ritonavir (23%), hydroxychloroquine (19%), high-dose corticosteroids (14%), tocilizumab (10%) and remdesivir (10%).

What are the main results?
In the ELSO registry study, at 90 days following initiation of ECMO, 37% of patients had died in hospital, 30% were discharged home or to an acute rehabilitation centre, 17% were discharged to another hospital, 10% were discharged to a long-term acute care centre or unspecified location, and 6% either remained in ICU or hospital.

A subgroup analysis found that the risk of in-hospital mortality increased with age. Acute kidney injury, chronic respiratory insufficiency, an immunocompromised state, or a pre-ECMO cardiac arrest were also associated with an increased risk of in-hospital mortality. Conversely, higher PaO2:FiO2 was associated with lower mortality. Renal replacement therapy was used in 44% of patients. Complications other than renal replacement therapy were reported in 55% of patients.

The retrospective cohort of five ICUs in France reported that at 90 days 36% of patients had died, 56% were discharged from ICU, 6% were in ICU but no longer receiving ECMO and 1% were still receiving ECMO. Renal replacement therapy was used in 46% of patients. The most common ECMO-related complications were massive haemorrhage (42% of patients) and ECMO-circuit changes (27%). Other complications were also observed.

Our confidence in the results
Certainty of the evidence is very low due to reliance on non-comparative observational data.

Additional information
While the ELSO registry included data from many countries, it may not be generalisable to the Australian setting. Mortality rates in Australia have been lower than most other countries and Australia's health system has been operating within its capacity, unlike in other parts of the world where resource considerations may have contributed to adverse outcomes.

Of note, patients received therapies for COVID-19 that are not currently recommended by our guideline, with 19 to 54% of patients receiving chloroquine or hydroxychloroquine and 11 to 23% receiving lopinavir-ritonavir. Our guideline recommends corticosteroids in patients requiring oxygen, which includes all patients receiving ECMO—only 14 to 41% of patients in these studies received steroids.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 90 days</td>
<td>Based on data from: 1,118 participants in 2 studies. (Observational (non-randomized))</td>
<td>Please see summary</td>
<td>Please see summary</td>
<td>Very low Due to very serious risk of bias and very serious indirectness. 2</td>
<td>We are uncertain whether ECMO increases or decreases mortality at 90 days.</td>
</tr>
<tr>
<td>90 days</td>
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<tr>
<td>Critical</td>
<td></td>
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</tr>
</tbody>
</table>

1. 90 days after initiation of ECMO
2. **Risk of Bias: very serious.** Non-comparative observational studies. **Indirectness: very serious.** Population may not be generalisable to Australia and direct comparisons not available.

### 8.8.2 ECMO for pregnant and postpartum women

**Consensus recommendation**

Consider referral to an ECMO centre for venovenous ECMO in mechanically ventilated pregnant women with COVID-19 and refractory respiratory failure (despite optimising ventilation, including proning). Delivery of the baby prior to ECMO to enhance maternal resuscitation should be considered on a case-by-case basis.

**Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected pregnant women with COVID-19 and severe ARDS.**

**The decision on whether to use ECMO should be taken in consultation with the woman’s family, as well as obstetric and intensive care specialists. Key considerations include gestational age, fetal viability, fetal well-being and the risks and benefits to mother and baby.**

**Early referral to an ECMO centre is preferred.**

**As pregnant and postpartum women may have haemostatic alterations, anticoagulation regimens may need to be modified appropriately.**

**This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.**
Evidence To Decision

**Benefits and harms**

The benefit of ECMO in pregnant women with COVID-19 is unclear. ECMO is only used as a form of life support in selected patients who are severely ill; it aims to increase oxygenation and reduce ventilator-induced lung injuries. However, it may be associated with risk of serious side effects, such as major bleeding and injuries from cannulation. The need for anticoagulation and risk of bleeding concomitant to the use of ECMO needs to be considered carefully in pregnant women, given that this therapy may not be effectively administrated without anticoagulation and it increases the risk of bleeding in pregnant women.

**Certainty of the Evidence**

No studies were identified in COVID-19 patients that compare ECMO to no ECMO.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values at this point. However, the serious risk of side effects may be unacceptable for some patients and their families.

The Consumer Panel believes that in line with the limited available evidence, some informed patients/carers may prefer to wait until the available evidence is clearer, while others may agree to have more invasive treatment initiated if this is consistent with their goals of care. The Panel recognises that some patients/carers may still choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

**Equity**

Due to the resource-intensive nature of ECMO there may be issues with inequity as only certain centres will have the ability to offer ECMO and it will only be considered in selected patients who are likely to have access to these centres.

**Acceptability**

There may be important issues with acceptability. The intervention could be considered less acceptable due to its possible harms and some may not consider its benefits worth the risk.

**Feasibility**

Due to the resource-intensive nature of ECMO there are likely to be feasibility issues. ECMO is likely to only be feasible in a limited number of centres.

Rationale

ECMO is only used as a form of life support in those who are severely ill with refractory respiratory failure (despite optimising ventilation, including proning) and aims to increase oxygenation and reduce ventilator-induced lung injuries. It is recommended as a therapy for selected patients with severe ARDS of other aetiologies.
9. Respiratory support in neonates, children and adolescents

The primary panel for the recommendations in this section is the Paediatric and Adolescent Care Panel. Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. The remaining panels review recommendations when relevant to their specific population group. In addition, all our recommendations are reviewed by the Consumer Panel.

9.1 Requiring non-invasive respiratory support

9.1.1 High-flow nasal oxygen and non-invasive ventilation

Info Box

**High-flow nasal oxygen** (HFNO) therapy is a form of respiratory support where warmed, humidified oxygen is delivered at high-flow rates.

**Non-invasive ventilation** (NIV) refers to any type of positive pressure support delivered without an endotracheal tube during spontaneous breathing. Supplemental oxygen can also be delivered through the device.

HFNO or NIV should be considered when low-flow oxygen is unable to maintain target peripheral oxygen saturation and/or to treat respiratory distress. Target peripheral oxygen saturations may vary in neonates, children and adolescents with co-morbid conditions, such as preterm birth, cyanotic congenital heart disease or chronic lung disease.

Practical Info

**High-flow nasal oxygen**

The concentration of oxygen can be titrated (using a blender) between 21% and 100%. Flow rates can be given up to 60 L/min in adults. In children, flow rates are typically 2 L/kg/min (maximum 50 L/min), except in neonates ≤ 4 kg where flow rates of 4 to 8 L/min are typically used.

Consensus recommendation

Consider using high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) therapy for neonates, children and adolescents with hypoxaemia or respiratory distress associated with COVID-19 and not responding to low-flow oxygen. Use it with caution and pay strict attention to staff safety, including the use of appropriate PPE.

The preferred location for high-flow nasal oxygen is a negative pressure room or a single room with the door closed. If these locations are not immediately available then HFNO or NIV should not be withheld if indicated. However, it should be recognised that this therapy may pose an aerosol risk to staff and other patients, and appropriate precautions should be used.

In children and adolescents with COVID-19 for whom HFNO or NIV is appropriate for an alternate clinical presentation (e.g. concomitant bronchiolitis or severe asthma), ensure airborne and other infection control precautions are also optimised.

Consider early transfer in the deteriorating neonate, child or adolescent to a specialised paediatric or neonatal critical care unit.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

**Benefits and harms**

Evidence from non-COVID neonates with acute hypoxaemic respiratory failure shows a reduction in endotracheal intubation and chronic lung disease. NIV/HFNO may be helpful for children with severe bronchiolitis or asthma and may reduce the need for intubation. Since NIV/HFNO is a known aerosol-generating procedure, with possible increased risk
of aerosolisation with poor mask fit \cite{18}, harms associated with a potential risk of transmission to healthcare workers need to be considered and the procedure used with caution, with strict attention paid to staff safety. Benefits and harms need to be considered in the context of the relevant alternate clinical presentation.

**Certainty of the Evidence**

No studies were identified in neonates, children and adolescents with COVID-19 that address the interventions, comparators and outcomes of interest.

**Preference and values**

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree with the recommendation that infection control precautions are optimised to minimise the risk of infection for others.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. NIV/HFNO requires less staffing and equipment than mechanical ventilation via an endotracheal tube. There are likely to be resource issues associated with different settings. There are limited negative pressure rooms in private and some public hospitals, although some hospitals have converted rooms into negative pressure rooms.

There are additional resource considerations for hospital spaces where caution needs to be applied and strict attention paid to staff safety. In single rooms or shared ward spaces with cohorting of neonates, children and adolescents with confirmed COVID-19, there are additional resource considerations for use of PPE and performing NIV/HFNO safely.

**Equity**

There may be equity issues due to the availability of negative pressure rooms and hospital spaces that are able to perform NIV/HFNO safely. NIV/HFNO can be provided in hospital settings outside an intensive care unit.

**Acceptability**

We have no systematically collected information regarding acceptability. NIV/HFNO is generally a well-accepted practice by neonates, children and adolescents, their families and healthcare providers in non-COVID-19 conditions.

**Feasibility**

There may be feasibility issues due to the availability of negative pressure rooms and hospital spaces that are able to perform NIV/HFNO safely.
9.1.2 Prone positioning (non-invasive)

For neonates, children and adolescents with COVID-19 and respiratory symptoms who are receiving non-invasive respiratory support, consider prone positioning if patient co-operation is possible. When positioning a patient prone, ensure it is used with caution and close monitoring of the patient.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms
While there is no current evidence for using prone positioning in neonates, children and adolescents with COVID-19, it is recommended for ventilated, children and adolescents with moderate to severe ARDS due to non-COVID causes, and is frequently used in neonates requiring mechanical ventilation. In these patients it may have a survival benefit but may also increase the risk of harms from complications, such as pressure injury, endotracheal tube obstruction or accidental extubation. Younger children who are awake and not receiving mechanical ventilation are less likely to comply with prolonged periods of prone positioning.

Certainty of the Evidence
No studies were identified in neonates, children and adolescents with COVID-19 that address the interventions or outcomes of interest.

Preference and values
We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. Children with milder respiratory disease and not receiving sedation may not comply with prone positioning.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Prone positioning is not associated with significant cost for infants and small children who require minimal nursing care to position. In larger children and adolescents, additional staff are needed to move and monitor in prone position, which will increase costs. Healthcare workers must be trained to facilitate safe practice in larger children and adolescents.

Equity
There is the potential for inequity as some healthcare facilities may not have sufficient staff or training to offer prone
Acceptability

We have no systematically collected evidence regarding acceptability. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

Feasibility

Prone positioning of mechanically ventilated neonates, children and adolescents is feasible if performed by trained personnel in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [360]. Wording has been adapted for clarity and applicability to the Australian context.

9.1.3 Respiratory management of the deteriorating child

Consider endotracheal intubation and mechanical ventilation in neonates, children and adolescents with COVID-19 who are deteriorating despite optimised, non-invasive respiratory support.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Benefits and harms should be considered on a case-by-case basis before undertaking invasive respiratory support, especially in children with a pre-existing life-limiting illness. There are well-known benefits of invasive ventilation, including improved oxygenation and reduced mortality in ARDS due to causes other than COVID-19. Harms relevant to SARS-CoV-2 transmission should be considered as with all children with respiratory failure—there may be complications related to invasive mechanical ventilation. There may also be accentuated risks of COVID-19 transmission to other patients or staff in critical care settings.

Certainty of the Evidence

No studies in neonates, children and adolescents with COVID-19 were identified that address the interventions, comparators and outcomes of interest.
Preference and values

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. However, there are likely to be resource issues associated with different settings.

Equity

We recognise that access to staff trained in paediatric critical care is not equitable, and is concentrated in tertiary metropolitan hospitals or retrieval services. Some children may therefore not have immediate access to a clinician with skills and experience intubating a critically ill child.

Acceptability

Although we have no systematically collected evidence regarding acceptability, we do not expect acceptability issues in neonates, children and adolescents.

Feasibility

Access to staff trained in paediatric critical care in rural and remote areas may impact on feasibility for intubation.

Rationale

Evidence for management of severe COVID-19 in children is limited. However, there are no data to suggest modifications to standard respiratory care are necessary.

9.2 Requiring invasive mechanical ventilation

9.2.1 Prone positioning (mechanical ventilation)

**Consensus recommendation**

For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning if there are no contraindications.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Evidence To Decision

**Benefits and harms**

While there is no current evidence for using prone positioning in neonates, children and adolescents with COVID-19, it is recommended for ventilated children and adolescents with moderate to severe ARDS due to non-COVID causes, and is frequently used in neonates requiring mechanical ventilation. In these patients it may have a survival benefit but may also increase the risk of harms from complications such as pressure injury, endotracheal tube obstruction or accidental extubation. Younger children are less likely to comply with prolonged periods of prone positioning.

**Certainty of the Evidence**

No studies were identified in neonates, children or adolescents with COVID-19 that address the interventions or outcomes of interest.

**Preference and values**

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Prone positioning is not associated with significant cost for infants and small children since they require minimal nursing care to position. In larger children and adolescents, additional staff are needed to move and monitor in prone position, which will increase costs. Healthcare workers must be trained to facilitate safe practice in larger children and adolescents.

**Equity**

There is the potential for inequity as some healthcare facilities may not have sufficient staff or training to offer prone positioning.

**Acceptability**

We have no systematically collected evidence regarding acceptability. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

**Feasibility**

Prone positioning of mechanically ventilated children and adolescents is feasible if performed by trained personnel in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.
Rationale
Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19 in adults. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

9.2.2 Positive end-expiratory pressure (PEEP)

Consensus recommendation
For mechanically ventilated neonates, children and adolescents with COVID-19 and moderate to severe ARDS with atelectasis, consider using a higher PEEP strategy over a lower PEEP strategy. The absolute PEEP values that constitute a high and low PEEP strategy will depend on age and patient size.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms
While there is no current evidence for using a higher PEEP strategy in neonates, children and adolescents with COVID-19 and moderate to severe ARDS, higher PEEP levels are recommended for ventilated neonates, children and adolescents with moderate to severe ARDS of other aetiologies. A high PEEP level may be associated with potential harms, including increased work of breathing, hypotension and air leaks.

Certainty of the Evidence
No studies were identified in neonates, children or adolescents with COVID-19 that address the question of lower versus higher PEEP strategy.

Preference and values
We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, some informed patients, parents, carers, families and guardians would agree with the recommendation and consider this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit.
9.2.3 Recruitment manoeuvres

Info Box

Neonates, children and adolescents receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an 'open lung approach' to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure, or the use of escalating mean airway pressure during high-frequency oscillatory ventilation (incremental PEEP, stepwise or staircase); and high driving pressures.

Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxic respiratory failure characterised by severe atelectasis unresponsive to other ventilation strategies, consider using recruitment manoeuvres.

In neonates and infants, staircase or stepwise incremental recruitment manoeuvres should only be performed using mean airway pressure in a high-frequency oscillatory ventilation mode. Staircase or stepwise (incremental PEEP) recruitment manoeuvres should not be performed during conventional ventilation.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Recruitment manoeuvres may benefit mechanically ventilated children and adolescents with severe hypoxaemia due to COVID-19 by opening collapsed lung units and improving oxygenation and lung mechanics during mechanical ventilation. However, they may also be associated with harms, such as the increased risk of volutrauma/barotrauma and hypotension.
**9.2.4 Neuromuscular blockers**

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Certainty of the Evidence</strong></td>
<td>No studies were identified in neonates, children or adolescents with COVID-19 that compare recruitment manoeuvres to no recruitment manoeuvres or variations on recruitment manoeuvres.</td>
</tr>
<tr>
<td><strong>Preference and values</strong></td>
<td>We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. The Consumer Panel believes that in line with expert consensus and the available evidence, some informed patients, parents, carers, families and guardians would agree with the recommendation and consider this treatment. The Panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19. The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.</td>
</tr>
<tr>
<td><strong>Resources and other considerations</strong></td>
<td>We have no systematically collected evidence regarding cost-benefit. However, neonates, children and adolescents receiving recruitment manoeuvres may require more intensive monitoring.</td>
</tr>
<tr>
<td><strong>Equity</strong></td>
<td>Due to the potential to cause transient cardiovascular instability, and the requirement for intensive monitoring, recruitment manoeuvres in neonates, children and adolescents will usually only be performed in a dedicated paediatric critical care setting by an experienced clinician familiar with the intervention.</td>
</tr>
<tr>
<td><strong>Acceptability</strong></td>
<td>We are uncertain if recruitment manoeuvres would be acceptable to neonates, children, adolescents and their families, and healthcare providers.</td>
</tr>
<tr>
<td><strong>Feasibility</strong></td>
<td>There are likely no important feasibility issues.</td>
</tr>
</tbody>
</table>

**Important issues, or potential issues not investigated**

**Substantial variability is expected or uncertain**
For intubated neonates, children and adolescents with COVID-19, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

However, if effective lung-protective ventilation cannot be achieved, consider targeted intermittent use of NMBAs. If indicated, the choice of NMBA should be guided by the age group and regional practice.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

There is no substantial net benefit to using neuromuscular blockers. Prolonged use of NMBAs could have negative effects on intubated neonates, children and adolescents, such as muscle weakness, oedema and difficulty weaning from mechanical ventilation.

Certainty of the Evidence

Outcomes identified as most critical were 90-day mortality and muscle weakness at 28 days. No studies were identified that included neonates, children or adolescents with COVID-19. Certainty of the evidence for all outcomes is very low, mostly due to serious inconsistency, indirectness and imprecision. There were substantial methodological inconsistencies between the trials involving adults with COVID-19.

Preference and values

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families and guardians. Since there is uncertainty regarding the critical outcome of muscle weakness, some might consider NMBAs unacceptable. The inability to move or communicate while being treated with neuromuscular blockers is likely to be an additional consideration for children and adolescents.

The Consumer Panel believes that in line with the available evidence, informed patients, parents, carers, families and guardians would agree with the recommendation; however, some informed patients, parents, carers, families and guardians may consider this treatment as a short-term intervention. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to have this treatment based on reasons unrelated to COVID-19.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. There are potential resource considerations due to supply issues for some neuromuscular blockers.

Equity

There is a risk of creating inequity as some facilities may have limited access to neuromuscular blockers suitable for neonates, children and adolescents.
Acceptability
As the indication for NMBAs in severe or critical COVID-19 disease is to improve critical care delivery, generally NMBAs will be acceptable to neonates, children, adolescents and their families. The potential harms and effects of NMBAs may be less acceptable to some children, adolescents and their families, especially being paralysed and non-responsive. Clinicians should weigh the risks and benefits in decision making.

Feasibility
Feasibility may be affected by potential supply issues for some neuromuscular blockers.

Rationale
Routine use of continuous infusions of neuromuscular blockers could have negative effects on intubated neonates, children and adolescents, such as muscle weakness, oedema and difficulty weaning from mechanical ventilation.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Mechanically ventilated children and adolescents with COVID-19 and persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation or persistently high plateau pressures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Continuous infusion of NMBA</td>
</tr>
<tr>
<td>Comparator:</td>
<td>No continuous infusion of NMBA</td>
</tr>
</tbody>
</table>

Summary
Evidence informing this recommendation comes from five randomised trials involving 1461 adults with acute respiratory distress syndrome. Currently, there is no evidence in patients with COVID-19. The five trials compared continuous infusions of neuromuscular blocking agents with cisatracurium for up to 48 hours to no continuous infusions of NMBAs [382][383][384][385][386].

For all critical outcomes, it is uncertain whether infusion of neuromuscular blockers makes a difference. The ROSE trial, which had a different sedation strategy to the other trials and implemented a higher PEEP strategy, is the largest (1006 participants) and most recent trial, and may be the most reflective of current practice [383]. There were no differences for the mortality outcomes, but the trial found a small increase in muscle weakness at 28 days in the neuromuscular blocker group.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator No NMBA</th>
<th>Intervention NMBA</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>Relative risk 0.78 (CI 95% 0.58 – 1.06) Based on data from 1,461 participants in 5 studies. ¹ (Randomized controlled)</td>
<td>372 per 1000</td>
<td>290 per 1000</td>
<td>Very low Due to serious inconsistency, indirectness and imprecision ²</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (513 events).</td>
</tr>
<tr>
<td></td>
<td>Difference: 82 fewer per 1000 (CI 95% 156 fewer – 22 more )</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>90-day mortality</td>
<td>Relative risk 0.81 (CI 95% 0.62 – 1.06) Based on data from 1,461 participants in 5 studies. ³ (Randomized controlled)</td>
<td>441 per 1000</td>
<td>357 per 1000</td>
<td>Very low Due to serious inconsistency, indirectness and imprecision ⁴</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (612 events).</td>
</tr>
<tr>
<td></td>
<td>Difference: 84 fewer per 1000 (CI 95% 168)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
</tr>
<tr>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>6 Important</td>
<td>Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 participants in 4 studies.</td>
<td>No NMBA</td>
<td>NMBA</td>
<td>Very low Due to serious imprecision and very serious indirectness</td>
</tr>
<tr>
<td>ICU weakness at day 28</td>
<td>9 Critical</td>
<td>Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 participants in 4 studies.</td>
<td>No NMBA</td>
<td>NMBA</td>
<td>Very low Due to serious risk of bias and very serious indirectness</td>
</tr>
<tr>
<td>Barotrauma</td>
<td>6 Important</td>
<td>Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 participants in 4 studies.</td>
<td>No NMBA</td>
<td>NMBA</td>
<td>Very low Due to serious risk of bias, indirectness and inconsistency</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Days</td>
<td>Measured by: Days Based on data from: 92 participants in 2 studies.</td>
<td>No NMBA</td>
<td>NMBA</td>
<td>Very low Due to serious risk of bias, indirectness and inconsistency</td>
</tr>
<tr>
<td>Ventilator-free days at day 28</td>
<td>6 Important</td>
<td>Measured by: Days Based on data from: 1,462 participants in 5 studies.</td>
<td>No NMBA</td>
<td>NMBA</td>
<td>Very low Due to serious risk of bias, indirectness and inconsistency</td>
</tr>
<tr>
<td>MRC score at day 28</td>
<td>6 Important</td>
<td>Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High better Based on data from: 1,346 participants in 2 studies.</td>
<td>No NMBA</td>
<td>NMBA</td>
<td>Very low Due to serious risk of bias and very serious inconsistency</td>
</tr>
</tbody>
</table>

2. **Inconsistency:** **comparator:** The magnitude of statistical heterogeneity was high, with I²:50 %. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials. **Indirectness:** **serious.** Differences between the population of interest and those studied: no studies in patients with COVID-19. Only one study (largest study) used a high PEEP strategy. **Imprecision:** **serious.** Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. **Publication bias:** no serious.


4. **Inconsistency:** **serious.** The magnitude of statistical heterogeneity was high, with I²:56 %. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials. **Indirectness:** **serious.** Differences between the population of interest and those studied: no studies in patients with COVID-19. **Imprecision:** **serious.** Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials.

**Publication bias:** no serious.


6. **Inconsistency:** no serious. **Indirectness:** very serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. The largest trial, with the most applicable strategy reflecting current clinical practice, did not report on this outcome. **Imprecision:** serious. The largest trial did not report on this outcome. **Publication bias:** no serious.


8. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** very serious. Differences between the population of interest and those studied: no studies in COVID-19 patients. The largest trial, with the most applicable strategy reflecting current clinical practice, only included a very small subset of patients for this outcome. **Imprecision:** serious. Low number of patients. **Publication bias:** no serious.


10. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. **Indirectness:** serious. Differences between the population of interest and those studied: no studies in COVID-19 patients. **Imprecision:** no serious. **Publication bias:** no serious.


12. **Risk of Bias:** serious. Inconsistency: no serious. **Indirectness:** serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. **Imprecision:** very serious. Low number of patients, wide confidence intervals. **Publication bias:** no serious.


14. **Risk of Bias:** serious. Inconsistency: no serious. **Indirectness:** serious. Differences between the population of interest and those studied: **Imprecision:** serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. **Publication bias:** no serious.


16. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** very serious. The magnitude of statistical heterogeneity was high, with I²:91 %. Clinical heterogeneity. **Indirectness:** serious. Differences between the population of interest and those studied: No studies in COVID-19 patients. **Imprecision:** serious. **Publication bias:** no serious.
9.2.5 High-frequency oscillatory ventilation (HFOV)

Info Box

High-frequency oscillatory ventilation (HFOV) is a specialised mode of respiratory support via an endotracheal tube that delivers very small tidal volumes at a rate much faster than normal breathing rates (> 2 Hz). It is used as a rescue therapy in neonates and children for severe respiratory failure when conventional mechanical ventilation is not effective. In neonates with severe respiratory failure, HFOV reduces need for ECMO. HFOV requires specialist equipment, and nursing and medical expertise.

Consensus recommendation

Do not routinely use HFOV as a first line mode of mechanical ventilation in neonates, children and adolescents with severe COVID-19. HFOV should be limited to a rescue therapy in neonates and children not responding to conventional mechanical ventilation in a specialist centre with experience with HFOV.

HFOV delivers gas at very high flow rates. This may increase the aerosol-generating potential compared to other forms of respiratory support used in intensive care. This may limit the suitability of HFOV in patients with COVID-19 unless strict attention to staff safety and infection control measures can be applied.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

While there is no current evidence for using HFOV in neonates, children or adolescents with COVID-19, it is recommended as a rescue therapy for ventilated neonates, children and adolescents with moderate to severe respiratory failure, including ARDS of other aetiologies. In these patients, it may have a survival benefit but may also increase the risk of harms from complications, such as cardiac compromise, barotrauma, endotracheal tube obstruction or accidental extubation. Infection prevention and staff safety should also be considered.

Certainty of the Evidence

No studies were identified in neonates, children or adolescents with COVID-19 that address the interventions or outcomes of interest.

Preference and values

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus, informed patients, parents, carers, families and guardians would agree to initiate this more invasive treatment if consistent with their goals of care. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.
**Rationale**

While there is no current evidence for using HFOV in neonates, children or adolescents with COVID-19 and severe respiratory failure, HFOV is used for ventilated neonates, children and adolescents with severe respiratory failure of other aetiologies, such as rescue therapy when conventional ventilation is not effective.

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### 9.2.6 Videolaryngoscopy

**Conditional recommendation**

In neonates, children and adolescents with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

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### Evidence To Decision

**Benefits and harms**

Laryngoscopy is a specialist medical procedure. Time to intubation varies depending on the experience of the operator and the setting, irrespective of the method of laryngoscopy. In non-COVID-19 neonates and children, videolaryngoscopy may reduce intubation failure rates. Another important consideration is the potential risk of contamination to the operator due to the infectious nature of COVID-19. In a simulation study using a manikin, the distance between the operator and patient’s mouth increased when using video compared to direct laryngoscopy, thus potentially benefitting operators in the case of COVID-19.
Certainty of the Evidence
For the two critical outcomes—distance between patient and operator, and time to successful intubation—certainty of the evidence is very low due to serious risk of bias, inconsistency, indirectness and imprecision.

Preference and values
We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families and guardians. Although there is uncertainty regarding the time to successful intubation, we are reasonably confident that they would find videolaryngoscopy an acceptable intervention compared to direct laryngoscopy.

The Consumer Panel believes that in line with the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment, if available and the operator is trained in its use. The panel also believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. The main costs associated with videolaryngoscopy are attributed to the initial equipment outlay, maintenance and operator training. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

Equity
There is a risk of creating inequity as people who live in rural and remote areas may have limited access to videolaryngoscopy and experienced operators. Due to costs and maintenance, there will be variation in the type of clinical settings likely to have access to the appropriate equipment—larger, specialised centres in urban areas are more likely to provide access than those in smaller more remote centres.

The panels noted that rural and remote hospitals may not routinely have access to videolaryngoscopy. The outcome of time to successful intubation is dependent on operator expertise and would likely take longer in non-specialist centres. However, the panel felt that most people intubating would be trained in videolaryngoscopy, although experience would vary. The panels clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

The Paediatric Panel noted that intubation of infants and young children is a specialist procedure. Clinicians experienced in intubating adults may not be trained to perform intubation in infants and young children. This may reduce equity outside of dedicated paediatric centres.

Acceptability
Videolaryngoscopy is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility
Feasibility is affected by the initial equipment costs, maintenance and operator training. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

Rationale
Videolaryngoscopy allows for increased distance between operator and patient, and may reduce the risk of aerosol
Clinical Question/ PICO

Population: Neonates, children and adolescents requiring emergency intubation
Intervention: Videolaryngoscopy
Comparator: Direct laryngoscopy

Summary

Evidence informing this recommendation comes from a systematic review of video versus direct laryngoscopy for the emergency intubation of adults in the inpatient setting [375]. A simulation study is also included that evaluated the distance between a dummy’s mouth and physician’s face during intubation [380].

Effectiveness and adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Synthesis method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised trials</td>
<td>Critically ill patients requiring emergency intubation in emergency departments or intensive care units. No studies available in patients with COVID-19.</td>
<td>Videolaryngoscopy</td>
<td>Direct laryngoscopy</td>
<td>Meta-analysis</td>
</tr>
</tbody>
</table>

Results

We included six of the eight randomised trials (1023 patients) in the Rombey review [373][374][376][377][378][379]. (Two were excluded because patients were intubated before hospital admission.) We included an additional randomised trial of 163 patients that was published after the Rombey review [372]. This study did not change the overall results for the outcomes, but did improve the precision of the estimate for inadvertent oesophageal intubation.

There was no difference between video and direct laryngoscopy with respect to successful intubation at first attempt or time to successful intubation. In the four randomised trials that reported inadvertent oesophageal intubation, the use of videolaryngoscopy was associated with fewer of these adverse events, however the number was small (27 events).

Operator distance (Hall 2020)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crossover study</td>
<td>25 doctors of mixed experience performing tracheal intubation on a high-fidelity manikin.</td>
<td>Videolaryngoscopy</td>
<td>Direct laryngoscopy</td>
<td>Videolaryngoscopy may extend the mouth-to-mouth distance from laryngoscopist to patient compared to direct laryngoscopy, and places the laryngoscopist’s face above the direct line of sight to the pharynx.</td>
</tr>
</tbody>
</table>

Certainty of the evidence is low to very low due to indirectness (not based on COVID-19 patients or exclusively patients with ARDS), risk of bias, lack of precision in some outcomes and small number of adverse events.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-pass intubation success</td>
<td>Relative risk 1.05 (CI 95% 0.94 — 1.17) Based on data from 1,186 participants in 7 studies.</td>
<td>716 per 1000</td>
<td>752 per 1000</td>
<td>Very low Due to serious risk of bias, inconsistency and indirectness</td>
<td>We are uncertain whether videolaryngoscopy increases or decreases first-pass intubation success.</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Plain language summary</td>
</tr>
<tr>
<td>------------------------------</td>
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<td>-------------------------------------------------------------------------------------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>Oesophageal intubation</td>
<td></td>
<td>Relative risk 0.4 (CI 95% 0.17 – 0.93) Based on data from 795 participants in 4 studies. 3 (Randomized controlled)</td>
<td>Direct laryngoscopy</td>
<td>50 per 1000</td>
<td>Very low Due to serious risk of bias and indirectness</td>
<td>Videolaryngoscopy may decrease oesophageal intubation.</td>
</tr>
<tr>
<td>Operator distance in cm</td>
<td>8 Critical</td>
<td>Measured by: distance analysed from videorecording High better Based on data from: 25 participants in 1 studies. 6 (Randomized controlled)</td>
<td>Videolaryngoscopy</td>
<td>16.4 centimetres (Mean)</td>
<td>Very low Due to serious risk of bias, indirectness and imprecision</td>
<td>Videolaryngoscopy may increase the operator distance.</td>
</tr>
<tr>
<td>Time to successful intubation</td>
<td>7 Critical</td>
<td>Based on data from: 988 participants in 6 studies. 8 (Randomized controlled)</td>
<td>Direct laryngoscopy</td>
<td>Difference: 20 per 1000 30 fewer per 1000 (CI 95% 41 fewer – 3 fewer)</td>
<td>Very low Due to serious risk of bias, indirectness and imprecision</td>
<td>We are uncertain whether videolaryngoscopy increases or decreases time to successful intubation.</td>
</tr>
</tbody>
</table>

2. Risk of Bias: serious. Personnel blinding was not possible for this outcome, resulting in potential for performance bias. Outcome assessor blinding was also not possible, resulting in potential for detection bias. Inconsistency: serious. There was clinical heterogeneity across the included studies in relation to setting (ED vs ICU), operator experience and devices used. Subgroup analyses in Rombey et al 2018 reported that effect sizes were not decisively altered by sensitivity or subgroup analyses. Indirectness: serious. The included studies were in non COVID-19 populations, with mixed presentations of respiratory and other critically ill patients. Differences between the population of interest and those studied. Imprecision: no serious. Publication bias: no serious. Rombey 2018 visually evaluated the funnel plot for publication bias, with distribution for this outcome relatively symmetrical. 3. Systematic review [371] with included studies: Silverberg 2015, Lascarrou 2017, Gao 2018, Janz 2016. Baseline/comparator: Control arm of reference used for intervention.
4. Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, and inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Inconsistency: no serious. Indirectness: serious. The included studies were in non COVID-19 populations, with mixed presentations of respiratory and other critically ill patients. Imprecision: no serious. Publication bias: no serious. Rombey 2018 visually evaluated the funnel plot for publication bias, with distribution for this outcome relatively symmetrical. 5. The ‘mouth-to-mouth’ distance between operator and manikin as measured by video analysis.
6. Primary study[380]. Baseline/comparator: Control arm of reference used for intervention[380].
9.2.7 Extracorporeal membrane oxygenation (ECMO)

**Consensus recommendation**

Consider early referral to an ECMO centre for venovenous or venoarterial ECMO in mechanically ventilated neonates, children and adolescents with COVID-19 with refractory respiratory or cardiovascular failure despite optimising other critical care interventions.

*Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected neonates, children and adolescents with severe or critical COVID-19 and no contraindications for ECMO, such as severe, irreversible organ dysfunction.*

*The decision on whether to use ECMO should be taken in consultation with the child’s family. Key considerations include pre-existing conditions and the suitability of anticoagulation.*

*Early referral to an ECMO centre is preferred.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

**Evidence To Decision**

**Benefits and harms**

ECMO is only used as a form of life support in selected neonates, children and adolescents who are severely ill; it aims to increase oxygenation and reduce ventilator-induced lung injuries. However, it may be associated with risk of serious side effects, such as neurological injury, major bleeding, disseminated intravascular coagulation and injuries from cannulation.

**Certainty of the Evidence**

No studies were identified involving neonates, children and adolescents with COVID-19 that compare ECMO to no ECMO.

**Preference and values**

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families and guardians. However, the serious risk of side effects may be unacceptable for some children and adolescents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, some informed patients,
parents, carers, families and guardians would agree with the recommendation and consider this treatment, while others may not wish to have more invasive treatment initiated if this is consistent with their goals of care. The panel recognises that some patients, parents, carers, families and guardians may choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

**Equity**

Paediatric ECMO is only available at some tertiary centres in Australia. Some neonates, children and adolescents live in states and territories where ECMO is not available.

**Acceptability**

There may be important issues with acceptability. ECMO could be considered less acceptable due to its possible harms and some may not consider its benefits are worth the risk.

**Feasibility**

There are likely to be feasibility issues due to the resource-intensive nature of ECMO. ECMO is likely to only be feasible in a limited number of centres.

**Rationale**

ECMO is only used as a form of life support in those who are severely ill with refractory respiratory failure (despite optimising ventilation, including proning) and aims to increase oxygenation and reduce ventilator-induced lung injuries. It is recommended as a therapy for selected patients with severe ARDS of other aetiologies.
10. Venous thromboembolism (VTE) prophylaxis

Patients with COVID-19 are at a higher risk of clotting conditions (e.g. pulmonary emboli, deep vein thrombosis) compared with patients without COVID-19. It is important to establish if patients with COVID-19 require enhanced clotting prevention methods to prevent clotting conditions.

Standard prophylactic methods exist to prevent clotting conditions in hospital in-patients (herein referred to as usual-care thromboprophylaxis). Recent research has explored the efficacy of methods used to treat clotting conditions (herein referred to as treatment-level thromboprophylaxis) for preventing clotting conditions in patients with COVID-19. The following recommendations have been extrapolated from the evidence comparing these two methods.

Research question: Does providing patients with COVID-19 with treatment-level thromboprophylaxis while in hospital result in fewer clots and lower mortality compared with usual-care thromboprophylaxis, while avoiding life-threatening complications such as major bleeding? Furthermore, does the effect differ for patients with severe/critical COVID-19 (e.g. ICU admitted, mechanically ventilated) compared with non-severe/non-critical COVID-19 (e.g. ward-based, not mechanically ventilated)?

The comparisons and outcomes referred to within the research question were developed in consultation with members of our expert panels and, specifically, experts in the field of thromboprophylaxis. The primary panel for the recommendations for adults is the Hospital and Acute Care Panel. The primary panel for the recommendations for pregnant and postpartum women is the Pregnancy and Perinatal Care Panel.

The recommendations outlined below were reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability and applicability to the clinical and patient populations they are most relevant to.

10.1 VTE prophylaxis for adults

Evidence from six studies inform the following recommendations on the use of treatment-level thromboprophylaxis or usual-care thromboprophylaxis for preventing clotting conditions in patients hospitalised with COVID-19.

The use of treatment-level thromboprophylaxis can reduce the risk of non-critically ill patients with COVID-19 developing major clots without an associated risk of major bleeding. However, this reduction in risk was not seen for critically-ill patients. These findings are only based on a small number of studies with a moderate risk of bias, due to a lack of blinding and unclear reporting of deviations from intended interventions.

In summary the existing evidence suggests that treatment-level thromboprophylaxis should not be used in place of usual-care thromboprophylaxis for preventing clotting conditions in patients hospitalised with COVID-19.

**Conditional recommendation**

Use prophylactic doses of anticoagulants, preferably low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily), in adults with moderate, severe or critical COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding. Where the estimated glomerular filtration rate (eGFR) (see below) is less than 30 mL/min/1.73m², unfractionated heparin or clearance-adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily).

For body weights outside 50–90 kg or heights outside 150–180 cm, calculate the body surface area (BSA) and multiply the eGFR by BSA/1.73.

The Taskforce notes that in critical illness, creatinine-based estimation of kidney function can be unreliable.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.
Evidence To Decision

Benefits and harms

There is little to no difference in benefits for patients with COVID-19 and there may be important harms. The benefits as well as harms associated with the use of LMW heparin and other anticoagulants are well-known in other patient groups.

Certainty of the Evidence

In patients with severe or critical COVID-19, comparing standard/intermediate-dose anticoagulants with therapeutic-dose anticoagulants, the certainty of the evidence is low (due to serious imprecision and risk of bias) or very low (due to serious risk of bias and very serious imprecision) for all outcomes except for hospital survival, which is moderate (due to serious risk of bias). For standard-dose compared with intermediate-dose anticoagulants, certainty of the evidence is moderate (due to serious imprecision) for all outcomes. In non-critically ill hospitalised patients with COVID-19, comparing standard/intermediate-dose anticoagulants with therapeutic-dose anticoagulants, the certainty of the evidence is low (due to serious imprecision and risk of bias) for all outcomes.

Preference and values

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients may prefer to wait while other patients may be more willing to take risks.

The Consumer Panel believes that, due to the known risk of thrombosis in hospitalised individuals with COVID-19, most informed patients would agree with the recommendation for prophylactic anticoagulation unless contraindicated.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

Equity

We have no systematically collected evidence regarding equity.

Acceptability

Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

Feasibility

There are no identified feasibility issues.

Rationale

The panel believes that the benefits of pharmacologic prophylaxis among medically ill patients outweigh potential harm, such as bleeding caused by this prophylaxis. The panel believes that this will also apply to patients with COVID-19 and therefore recommend pharmacologic prophylaxis.
Clinical Question/ PICO
Population: Patients with severe COVID-19
Intervention: Therapeutic-dose thromboprophylaxis
Comparator: Prophylactic-dose thromboprophylaxis

Summary
Evidence indicates that using therapeutic dosages instead of prophylactic dosages of anticoagulants probably has little or no difference on critical outcomes in patients with severe or critical COVID-19.

What is the evidence informing this recommendation?
Evidence comes from four randomised trials in patients with severe or critical COVID-19. One study of 1098 patients was an open-label, adaptive, multiplatform study that included data from three trials (REMAP-CAP, ACTIV-4a, ATTACC) that compared prophylactic-dose (or standard) anticoagulants with therapeutic-dose anticoagulants [536]. An additional 20-patient trial also compared prophylactic-dose with therapeutic-dose anticoagulants [410]. A third study (INSPIRATION Trial) included 562 patients that compared prophylactic-dose with intermediate-dose (or therapeutic) anticoagulants [418] and has published 90-day results separately [419]. Finally, a study of 176 patients compared intermediate-dose (or therapeutic) anticoagulants to standard-dose (or prophylactic) anticoagulants [523].

Study characteristics
Mean or median age of participants ranged from 55 to 65 years. The proportion of women ranged from 10% to 46%.

What are the main results?
Evidence indicates that therapeutic-dose anticoagulants probably have little or no additional effect when compared with prophylactic-dose anticoagulants on critical outcomes in patients with severe or critical COVID-19.

Our confidence in the results
Comparing prophylactic-dose anticoagulants with therapeutic-dose anticoagulants for patients with severe or critical COVID-19 involved examination of inadequate quality evidence. The certainty we have in the evidence is moderate (due to serious risk of bias) or low (due to serious risk of bias and inconsistency). Thus, our confidence that the results reflect true differences in effect is low.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Prophylactic dose</th>
<th>Intervent Therapeutic dose</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality 1</td>
<td>28-30 days</td>
<td>Relative risk 1.03 (CI 95% 0.91 – 1.17) Based on data from 1,853 participants in 4 studies. 2 (Randomized controlled)</td>
<td>340 per 1000</td>
<td>350 per 1000</td>
<td>Moderate Due to serious risk of bias 3</td>
<td>Therapeutic dose anticoagulants probably have little impact on death (673 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow up: 28-30 days.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotting events 4</td>
<td>7 Critical</td>
<td>Relative risk 0.81 (CI 95% 0.51 – 1.28) Based on data from 1,824 participants in 3 studies. 2 (Randomized controlled)</td>
<td>77 per 1000</td>
<td>62 per 1000</td>
<td>Low Due to serious risk of bias and serious inconsistency 6</td>
<td>Therapeutic dose anticoagulants may have little impact on new clotting events (132 events).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>8 Critical</td>
<td>Relative risk 1.6 (CI 95% 0.9 – 2.84) Based on data from 1,846 participants in 4 studies. 2 (Randomized controlled)</td>
<td>19 per 1000</td>
<td>30 per 1000</td>
<td>Moderate Due to serious risk of bias 8</td>
<td>Therapeutic dose anticoagulants probably has little impact on new major bleeding (48 events).</td>
</tr>
</tbody>
</table>
Evidence indicates that using therapeutic dosages instead of prophylactic dosages of anticoagulants probably has little or no difference on most critical outcomes in patients with non-critical COVID-19.

### Clinical Question/ PICO

**Population:** Patients with non-critical COVID-19  
**Intervention:** Therapeutic-dose thromboprophylaxis  
**Comparator:** Prophylactic-dose thromboprophylaxis

### Summary

Evidence comes from three randomised trials in patients with non-critical COVID-19. One study of 2221 patients was an open-label, adaptive, multiplatform study that included data from three trials (REMAP-CAP, ACTIV-4a, ATTACC) comparing prophylactic-dose anticoagulants with therapeutic-dose anticoagulants [537]. Two further studies—the RAPID trial of 465 patients [587] and the ACTION trial of 614 patients [526]—also compared prophylactic-dose with therapeutic-dose anticoagulants.

### What is the evidence informing this recommendation?

Evidence comes from three randomised trials in patients with non-critical COVID-19. One study of 2221 patients was an open-label, adaptive, multiplatform study that included data from three trials (REMAP-CAP, ACTIV-4a, ATTACC) comparing prophylactic-dose anticoagulants with therapeutic-dose anticoagulants [537]. Two further studies—the RAPID trial of 465 patients [587] and the ACTION trial of 614 patients [526]—also compared prophylactic-dose with therapeutic-dose anticoagulants.

### Study characteristics

Mean or median age of participants ranged from 56 to 60 years. The proportion of women ranged from 38% to 46%.

### What are the main results?

One study of 2221 people with COVID-19 found a small effect favouring prophylactic dosages on organ-support free days [537]. Three studies of 3306 patients with COVID-19 found a small effect favouring therapeutic dosages on clotting events.

### Our confidence in the results

Comparing prophylactic-dose anticoagulants with therapeutic-dose anticoagulants for patients with non-critical COVID-19 involved examination of inadequate quality evidence. The certainty we have in the evidence is very low (due to serious risk of bias, imprecision and inconsistency) to moderate (due to serious risk of bias). Thus, our confidence that the results reflect true differences in effect is low.
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Prophylactic-dose thromboprophy laxis</th>
<th>Intervention Therapeutic-dose thromboprophy laxis</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.8 (CI 95% 0.4 – 1.61) Based on data from 3,306 participants in 3 studies.</td>
<td>127 per 1000</td>
<td>102 per 1000</td>
<td>Very low Due to serious imprecision and very serious inconsistency</td>
<td>We are uncertain whether therapeutic dose anticoagulants increases or decreases death (252 events).</td>
</tr>
<tr>
<td>Clotting event 3</td>
<td>Relative risk 0.62 (CI 95% 0.41 – 0.92) Based on data from 3,306 participants in 3 studies.</td>
<td>60 per 1000</td>
<td>37 per 1000</td>
<td>Moderate Due to serious risk of bias</td>
<td>Therapeutic dose anticoagulants probably decreases thrombotic events (98 events).</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Relative risk 1.79 (CI 95% 0.87 – 3.67) Based on data from 3,307 participants in 3 studies.</td>
<td>17 per 1000</td>
<td>30 per 1000</td>
<td>Low Due to serious risk of bias and serious inconsistency</td>
<td>Therapeutic dose anticoagulants may have little impact on major bleeding (51 events).</td>
</tr>
<tr>
<td>Organ support not required 8</td>
<td>Relative risk 1.05 (CI 95% 1 – 1.09) Based on data from 2,221 participants in 1 studies.</td>
<td>765 per 1000</td>
<td>803 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Therapeutic dose anticoagulants probably improves organ support not being required (1721 events).</td>
</tr>
</tbody>
</table>

1. Primary study[525], [526], [537]. Baseline/comparator: Control arm of reference used for intervention.
2. Inconsistency: very serious. Point estimates vary widely. The magnitude of statistical heterogeneity was high, with I² 90%. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. The direction of the effect is not consistent between the included studies. Indirectness: no serious. Imprecision: serious. Wide confidence intervals. Publication bias: no serious.
3. Composite clotting events (e.g. PE, MI, DVT, arterial clot)
4. Primary study[537], [526], [525]. Baseline/comparator: Control arm of reference used for intervention.
6. Primary study[537], [526], [525]. Baseline/comparator: Control arm of reference used for intervention.
8. Number of people surviving to 21/7 w/o organ support
9. Primary study[537]. Baseline/comparator: Control arm of reference used for intervention.
Conditional recommendation against

Do not routinely offer therapeutic anticoagulant dosing in adults with moderate, severe or critical COVID-19. There is no additional indication for therapeutic dosing for anticoagulants in adults with severe or critical COVID-19 beyond current standard best practice.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is little to no difference in benefits for patients with COVID-19 and there may be important harms. The benefits as well as harms associated with the use of LMW heparin and other anticoagulants are well-known in other patient groups.

Certainty of the Evidence

Very low

In patients with severe or critical COVID-19, comparing standard/intermediate-dose anticoagulants with therapeutic-dose anticoagulants, the certainty of the evidence is low (due to serious imprecision and risk of bias) or very low (due to serious risk of bias and very serious imprecision) for all outcomes except for hospital survival, which is moderate (due to serious risk of bias). For standard-dose compared with intermediate-dose anticoagulants, certainty of the evidence is moderate (due to serious imprecision) for all outcomes. In non-critically ill hospitalised patients with COVID-19, comparing standard/intermediate-dose anticoagulants with therapeutic-dose anticoagulants, the certainty of the evidence is low (due to serious imprecision and risk of bias) for all outcomes.

Preference and values

We expect few to want the intervention

We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is no evidence of benefit but there may be potential harm and that most patients would not want increased-dose anticoagulation.

The Consumer Panel believes that as there is no clear benefit in the use of therapeutic anticoagulation in hospitalised patients with severe or critical COVID-19, most informed patients would agree with this recommendation and not opt for treatment.

Resources and other considerations

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding equity.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.
Feasibility

We have no systematically collected evidence regarding feasibility.

Clinical Question/ PICO

Population: Patients with severe COVID-19
Intervention: Therapeutic-dose thromboprophylaxis
Comparator: Prophylactic-dose thromboprophylaxis

Summary

Evidence indicates that using therapeutic dosages instead of prophylactic dosages of anticoagulants probably has little or no difference on critical outcomes in patients with severe or critical COVID-19.

What is the evidence informing this recommendation?

Evidence comes from four randomised trials in patients with severe or critical COVID-19. One study of 1098 patients was an open-label, adaptive, multiplatform study that included data from three trials (REMAP-CAP, ACTIV-4a, ATTACC) that compared prophylactic-dose (or standard) anticoagulants with therapeutic-dose anticoagulants [536]. An additional 20-patient trial also compared prophylactic-dose with therapeutic-dose anticoagulants [410]. A third study (INSPIRATION Trial) included 562 patients that compared prophylactic-dose with intermediate-dose (or therapeutic) anticoagulants [418] and has published 90-day results separately [419]. Finally, a study of 176 patients compared intermediate-dose (or therapeutic) anticoagulants to standard-dose (or prophylactic) anticoagulants [523].

Study characteristics

Mean or median age of participants ranged from 55 to 65 years. The proportion of women ranged from 10% to 46%.

What are the main results?

Evidence indicates that therapeutic-dose anticoagulants probably have little or no additional effect when compared with prophylactic-dose anticoagulants on critical outcomes in patients with severe or critical COVID-19.

Our confidence in the results

Comparing prophylactic-dose anticoagulants with therapeutic-dose anticoagulants for patients with severe or critical COVID-19 involved examination of inadequate quality evidence. The certainty we have in the evidence is moderate (due to serious risk of bias) or low (due to serious risk of bias and inconsistency). Thus, our confidence that the results reflect true differences in effect is low.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator Prophylactic dose</th>
<th>Intervention Therapeutic dose</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality 1</td>
<td>Relative risk 1.03 (CI 95% 0.91 – 1.17)</td>
<td>340 per 1000</td>
<td>350 per 1000</td>
<td>Moderate Due to serious risk of bias 3</td>
<td>Therapeutic dose anticoagulants probably have little impact on death (673 events).</td>
</tr>
<tr>
<td>28-30 days</td>
<td>Based on data from 1,853 participants in 4 studies. 2 (Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Critical</td>
<td>Follow up: 28-30 days.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotting events 4</td>
<td>Relative risk 0.81 (CI 95% 0.51 – 1.28)</td>
<td>77 per 1000</td>
<td>62 per 1000</td>
<td>Low Due to serious risk of bias and serious inconsistency 6</td>
<td>Therapeutic dose anticoagulants may have little impact on new clotting events (132 events).</td>
</tr>
<tr>
<td>28-30 days</td>
<td>Based on data from 1,824 participants in 3 studies. 3 (Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Question/ PICO

**Population:** Patients with non-critical COVID-19

**Intervention:** Therapeutic-dose thromboprophylaxis

**Comparator:** Prophylactic-dose thromboprophylaxis

**Summary**

Evidence indicates that using therapeutic dosages instead of prophylactic dosages of anticoagulants probably has little or no difference on most critical outcomes in patients with non-critical COVID-19.

**What is the evidence informing this recommendation?**

Evidence comes from three randomised trials in patients with non-critical COVID-19. One study of 2221 patients was an open-label, adaptive, multiplatform study that included data from three trials (REMAP-CAP, ACTIV-4a, ATTACC) comparing prophylactic-dose anticoagulants with therapeutic-dose anticoagulants [537]. Two further studies—the RAPID trial of 465 patients [587] and the ACTION trial of 614 patients [526]—also compared prophylactic-dose with therapeutic-dose anticoagulants.

**Study characteristics**

Mean or median age of participants ranged from 56 to 60 years. The proportion of women ranged from 38% to 46%.

**What are the main results?**

One study of 2221 people with COVID-19 found a small effect favouring prophylactic dosages on organ-support free days [537]. Three studies of 3306 patients with COVID-19 found a small effect favouring therapeutic dosages on clotting events.

**Our confidence in the results**

Comparing prophylactic-dose anticoagulants with therapeutic-dose anticoagulants for patients with non-critical COVID-19 involved examination of inadequate quality evidence. The certainty we have in the evidence is very low (due to serious risk of bias, imprecision and inconsistency) to moderate (due to serious risk of bias). Thus, our confidence that the results reflect true differences in effect is low.
<table>
<thead>
<tr>
<th>Outcome/Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Prophylactic- dose thromboprophylaxis</th>
<th>Intervention Therapeutic- dose thromboprophylaxis</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality 9 Critical</td>
<td>Relative risk 0.8 (CI 95% 0.4 – 1.61) Based on data from 3,306 participants in 3 studies.</td>
<td>127 per 1000</td>
<td>102 per 1000</td>
<td>Very low Due to serious imprecision and very serious inconsistency</td>
<td>We are uncertain whether therapeutic dose anticoagulants increases or decreases death (252 events).</td>
</tr>
<tr>
<td>Clotting event 8 Critical</td>
<td>Relative risk 0.62 (CI 95% 0.41 – 0.92) Based on data from 3,306 participants in 3 studies.</td>
<td>60 per 1000</td>
<td>37 per 1000</td>
<td>Moderate Due to serious risk of bias</td>
<td>Therapeutic dose anticoagulants probably decreases thrombotic events (98 events).</td>
</tr>
<tr>
<td>Major bleeding 9 Critical</td>
<td>Relative risk 1.79 (CI 95% 0.87 – 3.67) Based on data from 3,307 participants in 3 studies.</td>
<td>17 per 1000</td>
<td>30 per 1000</td>
<td>Low Due to serious risk of bias and serious inconsistency</td>
<td>Therapeutic dose anticoagulants may have little impact on major bleeding (51 events).</td>
</tr>
<tr>
<td>Organ support not required 7 Critical 21 days</td>
<td>Relative risk 1.05 (CI 95% 1 – 1.09) Based on data from 2,221 participants in 1 studies.</td>
<td>765 per 1000</td>
<td>803 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Therapeutic dose anticoagulants probably improves organ support not being required (1721 events).</td>
</tr>
</tbody>
</table>

1. Primary study[525],[526],[537]. Baseline/comparator: Control arm of reference used for intervention.
2. Inconsistency: very serious. Point estimates vary widely. The magnitude of statistical heterogeneity was high, with I^2:90%. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. The direction of the effect is not consistent between the included studies. Indirectness: no serious. Imprecision: serious. Wide confidence intervals. Publication bias: no serious.
3. Composite clotting events (e.g. PE, MI, DVT, arterial clot).
4. Primary study[537],[526],[525]. Baseline/comparator: Control arm of reference used for intervention.
6. Primary study[537],[526],[525]. Baseline/comparator: Control arm of reference used for intervention.
8. Number of people surviving to 21/7 w/o organ support
9. Primary study[537]. Baseline/comparator: Control arm of reference used for intervention.
10.2 VTE prophylaxis for pregnant and postpartum women

Info Box

Pregnant women in general are at an increased risk of venous thromboembolism (VTE). Hospitalised pregnant women with an acute infective illness (such as COVID-19) are at even greater risk of VTE. However, the exact duration of increased risk of VTE in association with COVID-19 infection is not yet established.

All pregnant and postpartum women should undergo a documented assessment of risk factors for VTE on admission to hospital, if COVID-19 is diagnosed, if COVID-19 severity changes and postpartum.

The use of pharmacological prophylaxis in women should be accompanied by other measures to prevent VTE, such as anti-embolism stockings and sequential compression devices.

Consensus recommendation

For pregnant or postpartum women who are admitted to hospital (for any indication) and who have COVID-19, use prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding or imminent birth.

Prophylactic anticoagulants should be continued for at least 14 days after discharge or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

- Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function.
- For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.
- There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19. However, acute infective illnesses such as COVID-19 are known to increase the risk of VTE.

Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19.

Preference and values

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for those without COVID-19.
Rationale

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19. However, acute infective illnesses (such as COVID-19) are known to increase the risk of VTE.

Consensus recommendation

For pregnant women with severe or critical COVID-19, or where there are additional risk factors for VTE, consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 10^9/L.

Prophylactic anticoagulants should be continued for at least four weeks after discharge or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

- **Dosing is dependent on pre-pregnancy body weight and current renal function.** For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.
- **There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.**
- **Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.**
- **In some situations, continuation of LMWH throughout the rest of pregnancy and postpartum may be required.** Involvement of specialist obstetricians, obstetric medicine physicians, haematologists or other physicians with expertise in VTE in pregnant women would be warranted.

This is a **low priority recommendation** and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

**Benefits and harms**

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19. However, acute infective illnesses such as COVID-19 are known to increase the risk of VTE.

**Certainty of the Evidence**

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19.
Rationale

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19, however, acute infectious illnesses (such as COVID-19) are known to increase the risk of VTE.

Consensus recommendation

For pregnant or postpartum women who are self-isolating at home with mild COVID-19 and where additional risk factors for VTE are present, consider using prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding or imminent birth. Prophylactic anticoagulants should be continued for at least 14 days or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

For pregnant or postpartum women who are self-isolating at home with mild COVID-19 and who have no additional risk factors for VTE, routine pharmacological prophylaxis is not recommended.

- Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function. For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.
- There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.
- Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
### Evidence To Decision

#### Benefits and harms

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19. However, acute infective illnesses such as COVID-19 are known to increase the risk of VTE.

#### Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19.

#### Preference and values

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

#### Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for those without COVID-19.

#### Equity

There are likely no important equity issues.

#### Acceptability

There is no systematically collected information regarding the acceptability of VTE prophylaxis in women with COVID-19 at this point. However, since prophylaxis with anticoagulants is commonly used in women with risk factors for VTE, it is likely to be acceptable to all stakeholders.

#### Feasibility

There are likely no important feasibility issues.

### Rationale

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19, however, acute infective illnesses (such as COVID-19) are known to increase the risk of VTE.
Consensus recommendation

For postpartum women who have had COVID-19 during pregnancy, consider using at least 14 days of prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding. Increased duration of six weeks should be considered if severe or critical COVID-19 and/or additional risk factors for VTE are present.

- Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function. For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.
- There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.
- Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19. However, acute infective illnesses such as COVID-19 are known to increase the risk of VTE.

Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19.

Preference and values

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for those without COVID-19.

Equity

There are likely no important equity issues.

Acceptability

There is no systematically collected information regarding the acceptability of VTE prophylaxis in women with COVID-19 at this point. However, since prophylaxis with anticoagulants is commonly used in women with risk factors for VTE, it is likely to be acceptable to all stakeholders.

Feasibility

There are likely no important feasibility issues.
**Rationale**

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19, however, acute infective illnesses (such as COVID-19) are known to increase the risk of VTE.

**10.3 VTE prophylaxis for children and adolescents**

**Consensus recommendation**

For children and adolescents admitted to hospital with COVID-19, refer to local thromboprophylaxis protocols and seek expert advice.

*Trials of thromboprophylaxis in children and adolescents are underway and this recommendation will be updated once new evidence is available.*

- There is insufficient evidence in children and adolescents to recommend a modified thromboprophylaxis regimen.
- Consider known risk factors for initiating thromboprophylaxis in children and adolescents.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

**Evidence To Decision**

**Benefits and harms**

Prophylactic anticoagulants are used in children and adolescents who are at risk of VTE. The benefit of a modified thromboprophylaxis regimen for children and adolescents with COVID-19 is unclear. There are well-known benefits of this strategy on selected children with risk factors for VTE. There are well-known harms of thromboprophylaxis such as major bleeding.

**Certainty of the Evidence**

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in children and adolescents with COVID-19.

**Preference and values**

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. However, we expect the intervention would be generally acceptable as it is regularly used in other procedures.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit.

**Equity**

It is unlikely that the use of thromboprophylaxis will create equity issues as it is common practice.
### Rationale

Given the available evidence, it is unclear whether children and adolescents will benefit from a modified thromboprophylaxis regimen when hospitalised with COVID-19. Thromboprophylaxis is indicated for children and adolescents with well-known risk factors.

<table>
<thead>
<tr>
<th>Acceptability</th>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboprophylaxis is generally a well-accepted intervention, and there are no important issues regarding acceptability.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no major feasibility issues as the recommendation reflects usual practice.</td>
<td></td>
</tr>
</tbody>
</table>

Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce

### 11.1 ACEIs/ARBs in patients with COVID-19

**Benefits and harms**

Stopping ACEI/ARB medication could lead to acute heart failure or unstable blood pressure. There is currently no randomised trial evidence specific to patients with COVID-19 and the use of ACEIs/ARBs.

**Certainty of the Evidence**

While there are no randomised trials of ACEIs/ARBs in patients with COVID-19, there are observational studies that seek to determine if there is an association between ACEIs/ARBs and diagnosis of COVID-19 or mortality for patients with a diagnosis of COVID-19.

**Preference and values**

We have no systematically collected information regarding patients' preferences and values. The panel believes that, while there is uncertainty about the benefit to harm ratio regarding the use of ACEIs/ARBs in patients with COVID-19, there are likely harms associated with stopping ACEIs/ARBs. The panel believes that most patients would prefer to continue their current medication although some may want to discuss benefits and risks of discontinuing treatment.

The Consumer Panel has considered issues around pre-existing conditions and treatments, and believes that in line with available evidence, informed patients would wish to continue with their current prescribed treatment for their pre-existing conditions.

**Resources and other considerations**

We have no systematically collected information regarding cost-benefit. Continued use of ACEIs/ARBs as per usual care is unlikely to have an impact on availability of these drugs.

**Equity**

There are no identified equity issues.
ACEIs/ARBs for people with hypertension, where indicated, are considered usual care. There is currently no evidence to indicate that it is necessary to deviate from usual care. Stopping these medications abruptly can lead to acute heart failure or unstable blood pressure.

Adaptation

This recommendation is adapted from published recommendations from numerous Australian and international guidelines and position statements. Wording has been adapted for clarity and applicability to the Australian context.

Acceptability

Continued concomitant ACEI/ARB medication is likely to be acceptable to both patients and clinicians.

Feasibility

There are likely no important feasibility issues as the recommendation reflects usual care.

Rationale

ACEIs/ARBs for people with hypertension, where indicated, are considered usual care. There is currently no evidence to indicate that it is necessary to deviate from usual care. Stopping these medications abruptly can lead to acute heart failure or unstable blood pressure.

Adaptation

This recommendation is adapted from published recommendations from numerous Australian and international guidelines and position statements. Wording has been adapted for clarity and applicability to the Australian context.

Clinical Question/ PICO

| Population: | People with COVID-19 who are taking ACEIs/ARBs |
| Intervention: | Continued use of concomitant ACEIs/ARBs |
| Comparator: | Stopping concomitant ACEIs/ARBs |

Summary

At present no randomised trials have investigated the benefits of continuing or stopping ACEIs/ARBs in patients with COVID-19. There is, however, unanimous international consensus that ACEI or ARB medications should be continued in patients with COVID-19.

Systematic reviews of observational studies provide further support for the continuation of ACEIs/ARBs in patients with COVID-19. These reviews conclude that continued use of ACEIs/ARBs is unlikely to be associated with an increased risk of disease severity or death in patients with COVID-19. The conclusions are based on very low certainty evidence due to serious risk of bias, imprecision and inconsistency in findings between studies.

Despite the very low certainty evidence that continued use of concomitant ACEIs/ARBs increases or decreases death or disease severity in patients with COVID-19, there is high certainty evidence of harm if ACEIs/ARBs are stopped abruptly in patients who are already receiving them. Stopping these medications could lead to acute heart failure or unstable blood pressure. For this reason the recommendation is designated as ‘Strong’ in favour of continuation.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Stopping concomitant ACEIs/ARBs</th>
<th>Intervention Continued use of concomitant ACEIs/ARBs</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>9 Critical</td>
<td>Odds Ratio 0.86 (CI 95% 0.63 – 1.16) Based on data from 7,492 participants in 12 studies.</td>
<td>287 per 1000</td>
<td>262 per 1000</td>
<td>Very low Due to serious risk of bias, inconsistency and imprecision.</td>
<td>We are uncertain whether continued use of concomitant ACEIs/ARBs increases or decreases death in patients with COVID-19.</td>
</tr>
</tbody>
</table>

| Risk of severe or lethal COVID-19 | Odds Ratio 1 (CI 95% 0.84 – 1.18) Based on data from | 309 per 1000 | 309 per 1000 | Very low Due to serious | We are uncertain whether continued use of concomitant ACEIs/ARBs increases or decreases death in patients with COVID-19. |
### 11.2 ACEIs in postpartum women

#### Consensus recommendation

In postpartum women with COVID-19 who have hypertension requiring treatment with ACE inhibitors, there is currently no evidence to deviate from usual care. These medications should be initiated or continued unless otherwise contraindicated.

**ACE inhibitors are contraindicated in the antenatal period due to risk of fetal and neonatal harm.**

This is a **low priority recommendation** and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

#### Evidence To Decision

**Benefits and harms**

ACE inhibitors, such as enalapril, captopril and quinapril, are used for the management of postpartum hypertension and are considered compatible with breastfeeding [438]. Their use is contraindicated during pregnancy as they have been associated with fetal death and neonatal renal failure. There is currently no evidence to indicate that ACE inhibitors should not be used postpartum in a woman with confirmed COVID-19.
Certainty of the Evidence
No studies were identified that address the use of ACE inhibitors for postpartum women with COVID-19.

Preference and values
We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

The Consumer Panel has considered issues around pre-existing conditions and treatments, and believes that in line with available evidence, informed patients would wish to have treatment initiated, or to continue with prescribed treatment for their condition.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (irrespective of postpartum hypertension) requires greater resources than for women without COVID-19.

Equity
There are no identified equity issues as the recommendation reflects usual care.

Acceptability
Although we have no systematically collected evidence regarding acceptability, this recommendation is likely to be acceptable to both patients and clinicians.

Feasibility
There are likely no important feasibility issues as the recommendation reflects usual care.

11.3 Steroids for people with asthma or COPD with COVID-19

Consensus recommendation
Use inhaled or oral steroids for the management of people with co-existing asthma or chronic obstructive pulmonary disease (COPD) and COVID-19 as you would normally for viral exacerbation of asthma or COPD. Do not use a nebuliser.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms
Stopping long-term inhaled or oral corticosteroids suddenly can lead to exacerbation of symptoms of asthma and COPD or risk of relative adrenal insufficiency. There is currently no evidence specific to patients with COVID-19 and asthma or...
Rationale
Oral steroids and continuation of inhaled steroids reduce harms in patients experiencing exacerbations of asthma or COPD and are considered usual care. There is currently no evidence to indicate that it is necessary to deviate from usual care.

Adaptation
The recommendation is adapted from published recommendations from three clinical guidelines: Australian Asthma Handbook [439], NICE [NG168] [440] and NICE [NG 166] [441]. Wording has been adapted for clarity and applicability to the Australian context.
Clinical Question/ PICO

**Population:** People with asthma or COPD and COVID-19  
**Intervention:** Corticosteroids  
**Comparator:** Standard care

**Summary**

For patients with severe asthma, the Australian Asthma Handbook recommends that clinicians “administer or prescribe systemic (oral) corticosteroids to manage severe flare-ups or acute asthma as indicated, following recommendations based on age-group” but to be cautious using corticosteroids when acute viral infection is suspected or confirmed (e.g. avoid use for mild flare-ups) [439]. This recommendation is in concordance with NICE NG166, which recommends that patients who develop symptoms and signs of an asthma exacerbation should follow their personalised asthma action plan and start a course of oral corticosteroids if clinically indicated [441].

For patients with asthma who are receiving inhaled steroids, the Australian Asthma Handbook also advises patients "to continue taking inhaled corticosteroids during the COVID-19 pandemic". It reminds clinicians to “warn patients that stopping their preventer increases the risk of severe asthma flare-ups, including those triggered by viral respiratory infections”. This recommendation is in concordance with NICE NG166, which recommends that patients continue using oral or inhaled steroids and to avoid stopping oral or inhaled steroids.

For patients with COPD, NICE NG168 recommends that patients who are having an exacerbation for COPD start a course of oral corticosteroids and/or antibiotics if oral corticosteroids and/or antibiotics are clinically indicated [440]. Oral corticosteroids are not recommended for symptoms of COVID-19 alone (e.g. fever, dry cough or myalgia).

The recommendations take into consideration potential harms with starting oral corticosteroids (particularly at high doses for a prolonged period) and harms associated with withholding corticosteroids suddenly.

According to the Therapeutic Goods Administration, starting oral corticosteroids (prednisolone or dexamethasone) can lead to disturbed endocrine function, ophthalmological conditions and adrenal suppression [442][443].

Abrupt withdrawal of corticosteroids can lead to acute adrenal insufficiency or exacerbation of symptoms of asthma or COPD.

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<tr>
<td>See summary</td>
<td></td>
<td>Standard care</td>
<td>Coticosteroids</td>
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</table>

11.4 Oestrogen-containing therapies
Consider stopping oral menopausal hormone therapy (MHT), also known as hormone replacement therapy (HRT), in women with mild or moderate COVID-19.

Before restarting oral MHT, review the indication for this. If MHT is continued, consider using a transdermal preparation.

Decisions around stopping hormone therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patients individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

**Benefits and harms**

Although there is no evidence to suggest VTE risk is elevated in women with COVID-19 who are taking oral MHT, both the use of oral MHT and COVID-19 (severe or critical) are associated with an increased risk of VTE—the risk of VTE in mild or moderate COVID-19 is unknown.

**Certainty of the Evidence**

No studies were identified that address the use of MHT in women with mild or moderate COVID-19.

**Preference and values**

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients would agree with the recommendation. The panel recognises that some informed patients may choose not to proceed with this recommendation based on reasons unrelated to COVID-19.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Use of oral or transdermal MHT as per usual care is unlikely to have an impact on availability of these drugs.

**Equity**

There are no identified equity issues.

**Acceptability**

The treatment is likely to be acceptable to both patients and clinicians.

**Feasibility**

There are likely no important feasibility issues.
Rationale

Although there is no evidence to suggest VTE risk is elevated in women with COVID-19 who are taking oral MHT, both the use of oral MHT and COVID-19 (severe or critical) are associated with an increased risk of VTE—the risk of VTE in mild or moderate COVID-19 is unknown. Transdermal MHT is not associated with increased VTE risk.

Consensus recommendation

Stop oral menopausal hormone therapy (MHT) in women with severe or critical COVID-19.

Before restarting oral MHT, review the indication for this and consider transitioning to a transdermal preparation.

Decisions around stopping hormone therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patient's individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Both COVID-19 (severe or critical) and oral MHT are associated with an increased risk of VTE. While we do not have evidence of a further increased risk of thromboembolic events for women who have COVID-19 and are taking oral MHT, this risk is theoretically possible.

The duration of elevated VTE risk after acute COVID-19 infection is uncertain. Current Taskforce guidelines recommend that VTE prophylaxis be given to all patients with severe or critical COVID-19. While there is a lack of direct evidence that the prophylactic anticoagulant doses prescribed in our VTE recommendations completely alleviate the risk of VTE in women taking oral MHT, it is likely that these doses are effective.

Certainty of the Evidence

No studies were identified that address the risk of VTE associated with the use of MHT in women with severe or critical COVID-19.

Preference and values

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients would agree with the recommendation. The panel recognises that some informed patients may choose not to proceed with this recommendation based on reasons unrelated to COVID-19.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Use of oral or transdermal MHT as per usual care is unlikely to have an impact on availability of these drugs.

Equity

There are no identified equity issues.
Rationale

Both COVID-19 (severe or critical) and oral MHT are associated with an increased risk of VTE. While we do not have evidence of a further increased risk of thromboembolic events for women who have COVID-19 and are taking oral MHT, this risk is theoretically possible.

The duration of elevated VTE risk after acute COVID-19 infection is uncertain. Current Taskforce guidelines recommend that VTE prophylaxis be given to all patients with severe or critical COVID-19. While there is a lack of direct evidence that the prophylactic anticoagulant doses prescribed in our VTE recommendations completely alleviate the risk of VTE in women taking oral MHT, it is likely that these doses are effective.

Evidence To Decision

**Benefits and harms**

Both COVID-19 (severe or critical) and oestrogen-containing contraception are associated with an increased risk of venous thromboembolism (VTE). While the use of oestrogen-containing contraception is associated with an increased risk of VTE, this risk is assessed when prescribing oestrogen-containing contraceptives. Furthermore, it is recommended that VTE prophylaxis be given to all patients with severe or critical COVID-19.

While there is a lack of direct evidence that the prophylactic anticoagulant doses prescribed in our VTE recommendations completely alleviate the risk of VTE in women using oestrogen-containing contraception, it is likely that these doses are effective. Therefore, an increased risk of VTE during severe or critical COVID-19 is not considered a reason to stop oestrogen-containing contraception. Note that progestogen-only contraception methods are not associated with an increased VTE risk.

There is no evidence that women who are using oestrogen-containing contraception methods and who have mild or moderate COVID-19 have an increased risk of VTE. However, COVID-19 causes a hypercoagulable state in some people, which may worsen the VTE risk associated with combined hormonal contraception. The incidence of VTE in women of reproductive age with COVID-19 infection is currently not known.
There is a risk of unintended pregnancy when contraception is ceased. Women with severe or critical COVID-19 may not be well enough to take oral contraceptives, resulting in temporary cessation, but efforts should be made to ensure that recommencing contraception is not neglected. Where patients have stopped contraception, consider the need for emergency contraception.

**Rationale**

Severe or critical COVID-19 and oestrogen-containing contraceptives are both associated with an increased risk of venous thromboembolism (VTE). However, the increased risk is likely to be alleviated because (a) the risk of VTE is assessed when considering whether to prescribe oestrogen-containing contraceptives, and (b) it is recommended that patients with severe or critical COVID-19 are prescribed VTE prophylaxis.

While there is a lack of direct evidence that the prophylactic anticoagulant doses prescribed in our VTE recommendations completely alleviate the risk of VTE in women using oestrogen-containing contraception, it is likely that these doses are effective. Therefore, an increased risk of VTE during severe or critical COVID-19 is not considered a reason to stop oestrogen-containing contraception, and management as per usual care is recommended. It is useful to note, however, that usual care for people with severe or critical COVID-19 refers to stopping non-essential medications, as this reduces contact with patients thus reducing the risk of transmission to the healthcare worker. Note that progestogen-only contraception methods are not associated with an increased VTE risk.

There is no evidence that women who are using oestrogen-containing contraception methods and who have mild or moderate COVID-19 have an increased risk of VTE. However, COVID-19 causes a hypercoagulable state in some people, which may worsen the VTE risk associated with combined hormonal contraception. The incidence of VTE in women of reproductive age...
with COVID-19 infection is currently not known. Patients should be advised of this theoretical risk to allow informed choice of contraceptive option, however, at this time there is no evidence to support routine cessation. Management as per usual care is, therefore, recommended—where usual care refers to continuing oestrogen-containing contraception, unless contraindicated.

There is a risk of unintended pregnancy when contraception is ceased. Women with severe or critical COVID-19 may not be well enough to take oral contraceptives, resulting in temporary cessation, but efforts should be made to ensure that recommencing contraception is not neglected. Where patients have stopped contraception, consider the need for emergency contraception.
12. Timing of surgery following COVID-19 infection

**Conditional recommendation against**

Do not routinely perform elective surgery within eight weeks of recovery from acute illness, following a diagnosis of SARS-CoV-2 infection, unless outweighed by the risk of deferring surgery, such as disease progression or clinical priority.

*Informed consent and, where deemed necessary, shared decision-making with a valid substitute decision-maker, should include discussion about the potential increased risk of surgery following a diagnosis of COVID-19 and in the presence of post-acute COVID-19 symptoms.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

**Evidence To Decision**

**Benefits and harms**

In patients with a preoperative diagnosis of SARS-CoV-2 infection, there may be an increase in mortality and morbidity in those who have elective surgery within seven weeks. This risk needs to be considered with the individual patient's risk of deferring surgery, such as disease progression or clinical priority, to ensure any mortality benefit outweighs any potential harms associated with delaying surgery.

**Certainty of the Evidence**

Certainty of the evidence is low due to serious imprecision (reliance on a single study) and risk of bias.

**Preference and values**

We have no systematically collected information regarding patients' preferences and values. However, given the differing reasons individual patients will have for undergoing elective surgery, and the differing severity of acute and ongoing symptoms of COVID-19, substantial variability is expected.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit.

**Equity**

We have no systematically collected evidence regarding impact on equity. We acknowledge that multisystem preoperative assessment with a unit familiar with the assessment of people recovering from COVID-19 may be difficult to carry out in rural and remote areas. However, the recommendation considers it may be possible to be carried out via virtual consultation.

**Acceptability**

Although we have no systematically collected evidence regarding acceptability, there may be important issues with acceptability given the differing reasons individual patients will have for undergoing elective surgery and the differing severity of acute and ongoing symptoms of COVID-19.
**Feasibility**

We have no systematically collected evidence regarding feasibility.

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**Rationale**

In patients with a preoperative diagnosis of SARS-CoV-2 infection, there may be an increase in mortality and morbidity in those who have elective surgery within seven weeks.

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**Clinical Question/ PICO**

- **Population:** People with a diagnosis of SARS-CoV-2 infection
- **Intervention:** Surgery
- **Comparator:** No surgery

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**Summary**

Evidence indicates that there may be an increase in mortality and morbidity in patients who have elective surgery within seven weeks of a diagnosis of SARS-CoV-2 infection.

**What is the evidence informing this recommendation?**

Evidence comes from a multicentre, prospective, cohort study of patients undergoing elective or emergency surgery (140,231 patients from 116 countries) [444]. Surgical patients with preoperative SARS-CoV-2 infection (3127 patients) were compared with those without previous SARS-CoV-2 infection (137,104 patients).

The primary endpoint was 30-day postoperative mortality. The study reported adjusted analysis by patients whose symptoms had resolved. A sensitivity analysis was performed including only elective patients with preoperative SARS-CoV-2 infection (1762 patients) compared with those without previous SARS-CoV-2 infection (95,680 patients).

**Study characteristics**

The time from SARS-CoV-2 diagnosis to surgery was 0–2 weeks in 1138 patients (36%), 3–4 weeks in 461 patients (15%), 5–6 weeks in 326 patients (10%) and ≥ 7 weeks in 1202 patients (38%). Preoperative SARS-CoV-2 infection was confirmed with a RT-PCR swab in 80% (2486/3127) of patients. Symptomatic infection was reported in 55% (1726/3127) of preoperative SARS-CoV-2 infections. Of these symptomatic infections, 969 (56%) were not hospitalised, 497 (29%) were hospitalised for COVID-19 but did not require respiratory support, and 259 (15%) were hospitalised for COVID-19 and required respiratory support.

**What are the main results?**

In patients undergoing elective surgery, timing of surgery resulted in increased 30-day postoperative mortality at 0–2 weeks (OR 5.50, 95% CI 3.24 to 9.34), 3–4 weeks (OR 3.95, 95% CI 2.18 to 7.15) and at 5–6 weeks (OR 4.14, 95% CI 2.05 to 8.33) when compared with the reference standard (no preoperative SARS-CoV-2 diagnosis). However, this increase was not reported at ≥ 7 weeks (OR 1.03, 95% CI 0.50 to 2.09) from time of diagnosis with SARS-CoV-2. The trend was replicated in subgroup analyses by age, American Society of Anesthesiologists physical status, urgency, and grade of surgery.

The study also reported higher mortality in patients who reported ongoing symptoms at time of surgery at 0–2 weeks (OR 14.88, 95% CI 11.54 to 18.21), 3–4 weeks (OR 13.77, 95% CI 9.26 to 18.28), 5–6 weeks (OR 12.83, 95% CI 7.35 to 18.30) and at ≥ 7 weeks (OR 5.96, 95% CI 3.24 to 8.68). At ≥ 7 weeks, patients reporting ongoing symptoms still had higher mortality (6.0%, 95% CI 3.2 to 8.7) than patients whose symptoms had resolved (2.4%, 95% CI 1.4 to 3.4) or who had been asymptomatic (1.3%, 95% CI 0.6 to 2.0).

**Our confidence in the results**

Certainty of the evidence is low due to serious imprecision (only one study) and risk of bias.

**Additional information**

A rapid review by the Royal Australasian College of Surgeons (RACS) included 20 studies (12 peer reviewed) [446]. It included one case-control study and 18 case-series that reported on long-term clinical characteristics of COVID-19. The rapid review also included one prospective cohort study, which reported the risk of past SARS-CoV-2 infection on postoperative outcomes. (The study was a subgroup analysis of the previously reported prospective cohort study.) RACS recommends waiting 8–12 weeks, if possible.

The rapid review also identified five expert consensus guidance documents. The advice varied, with some advising a 2–4 week delay, some 8 weeks and others advising delaying until patients are no longer infectious and have recovered from COVID-19.

The Taskforce also notes another paper that contained recommendations from the Association of Anaesthetists, Centre for...
Evidence To Decision

Peri-operative Care, Federation of Surgical Specialty Associations, Royal College of Anaesthetists and Royal College of Surgeons of England [445]. They recommended no elective surgery within seven weeks of diagnosis with SARS-CoV-2 infection.

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<th>Certainty of the Evidence (Quality of evidence)</th>
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<tbody>
<tr>
<td>30-day postoperative mortality in elective surgery patients</td>
<td>Based on data from: 1,762 participants in 1 studies. (Observational (non-randomized))</td>
<td>No surgery</td>
<td>Surgery</td>
<td>Low Due to serious imprecision and risk of bias</td>
<td>Timing of surgery less than 7 weeks after COVID-19 diagnosis may increase risk of 30-day postoperative mortality in elective surgery patients.</td>
</tr>
</tbody>
</table>

1. **Risk of Bias:** serious. Residual confounding. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study. **Publication bias:** no serious.

**Conditional recommendation**

For people undergoing elective surgery following a diagnosis of SARS-CoV-2 infection, consider carrying out multisystem preoperative assessment in consultation with a unit familiar with the assessment of people recovering from COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

**Evidence To Decision**

**Benefits and harms**

In patients with a preoperative diagnosis of SARS-CoV-2 infection, there may be an increase in mortality and morbidity in those patients with ongoing symptoms following COVID-19 infection at the time of surgery. This risk needs to be considered with the individual patient’s risk of deferring surgery, such as disease progression or clinical priority, to ensure any mortality benefit outweighs any potential harms associated with delaying surgery.

**Certainty of the Evidence**

Certainty of the evidence is low due to serious imprecision (reliance on a single study) and risk of bias.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. However, given the differing reasons individual patients will have for undergoing elective surgery, and the differing severity of acute and ongoing symptoms of COVID-19, substantial variability is expected.
Given the likely variability in practice, the Consumer Panel believes that patients would value discussion with the treating physicians regarding the outcomes of preoperative assessment.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit.

**Equity**

We have no systematically collected evidence regarding impact on equity. We acknowledge that multisystem preoperative assessment with a unit familiar with the assessment of people recovering from COVID-19 may be difficult to carry out in rural and remote areas. However, the recommendation considers it may be possible to be carried out via virtual consultation.

**Acceptability**

Although we have no systematically collected evidence regarding acceptability, there may be important issues with acceptability given the differing reasons individual patients will have for undergoing elective surgery and the differing severity of acute and ongoing symptoms of COVID-19.

**Feasibility**

We have no systematically collected evidence regarding feasibility.

**Clinical Question/ PICO**

- **Population:** People with a diagnosis of SARS-CoV-2 infection
- **Intervention:** Surgery
- **Comparator:** No surgery

**Summary**

Evidence indicates that there may be an increase in mortality and morbidity in patients who have elective surgery within seven weeks of a diagnosis of SARS-CoV-2 infection.

**What is the evidence informing this recommendation?**

Evidence comes from a multicentre, prospective, cohort study of patients undergoing elective or emergency surgery (140,231 patients from 116 countries) [444]. Surgical patients with preoperative SARS-CoV-2 infection (3127 patients) were compared with those without previous SARS-CoV-2 infection (137,104 patients).

The primary endpoint was 30-day postoperative mortality. The study reported adjusted analysis by patients whose symptoms had resolved. A sensitivity analysis was performed including only elective patients with preoperative SARS-CoV-2 infection (1762 patients) compared with those without previous SARS-CoV-2 infection (95,680 patients).

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**What are the main results?**

In patients undergoing elective surgery, timing of surgery resulted in increased 30-day postoperative mortality at 0–2 weeks (OR 5.50, 95% CI 3.24 to 9.34), 3–4 weeks (OR 3.95, 95% CI 2.18 to 7.15) and at 5–6 weeks (OR 4.14, 95% CI 2.05 to 8.33)
when compared with the reference standard (no preoperative SARS-CoV-2 diagnosis). However, this increase was not reported at ≥ 7 weeks (OR 1.03, 95% CI 0.50 to 2.09) from time of diagnosis with SARS-CoV-2. The trend was replicated in subgroup analyses by age, American Society of Anesthesiologists physical status, urgency, and grade of surgery.

The study also reported higher mortality in patients who reported ongoing symptoms at time of surgery at 0–2 weeks (OR 14.88, 95% CI 11.54 to 18.21), 3–4 weeks (OR 13.77, 95% CI 9.26 to 18.28), 5–6 weeks (OR 12.83, 95% CI 7.35 to 18.30) and at ≥7 weeks (OR 5.96, 95% CI 3.24 to 8.68). At ≥ 7 weeks, patients reporting ongoing symptoms still had higher mortality (6.0%, 95% CI 3.2 to 8.7) than patients whose symptoms had resolved (2.4%, 95% CI 1.4 to 3.4) or who had been asymptomatic (1.3%, 95% CI 0.6 to 2.0).

Our confidence in the results
Certainty of the evidence is low due to serious imprecision (only one study) and risk of bias.

Additional information
A rapid review by the Royal Australasian College of Surgeons (RACS) included 20 studies (12 peer reviewed) [446]. It included one case-control study and 18 case-series that reported on long-term clinical characteristics of COVID-19. The rapid review also included one prospective cohort study, which reported the risk of past SARS-CoV-2 infection on postoperative outcomes. (The study was a subgroup analysis of the previously reported prospective cohort study.) RACS recommends waiting 8–12 weeks, if possible.

The rapid review also identified five expert consensus guidance documents. The advice varied, with some advising a 2–4 week delay, some 8 weeks and others advising delaying until patients are no longer infectious and have recovered from COVID-19.

The Taskforce also notes another paper that contained recommendations from the Association of Anaesthetists, Centre for Peri-operative Care, Federation of Surgical Specialty Associations, Royal College of Anaesthetists and Royal College of Surgeons of England [445]. They recommended no elective surgery within seven weeks of diagnosis with SARS-CoV-2 infection.

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13. Pregnancy and perinatal care

The primary panel for the recommendations in this section is the Pregnancy and Perinatal Care Panel. Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. The remaining panels review recommendations when relevant to their specific population group. In addition, all our recommendations are reviewed by the Consumer Panel.

Info Box

For recommendations on disease modifying treatments, chemoprophylaxis, venous thromboembolism (VTE) prophylaxis and respiratory support in pregnant or breastfeeding women, and ACE inhibitors in postpartum women, please see sections above. We are continually working on updating all recommendations to reflect special populations, including pregnant and breastfeeding women.

13.1 Antenatal corticosteroids

Consensus recommendation

The use of antenatal corticosteroids for women at risk of preterm birth is supported as part of standard care, independent of the presence of COVID-19.

There are clear benefits to using antenatal corticosteroids for women at risk of preterm birth at less than 34 weeks' gestation. There is currently no evidence to suggest that antenatal corticosteroids cause additional maternal or fetal harm in the setting of COVID-19 when used for this indication. They should therefore be given where indicated.

The Taskforce has separate recommendations regarding the use of dexamethasone as a disease-modifying treatment in pregnant or breastfeeding women for COVID-19. Women with COVID-19 who are on oxygen and receiving dexamethasone do not require additional doses of corticosteroids for fetal lung maturation. This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

There are substantial known benefits to using antenatal corticosteroids in preterm birth, which is supported as part of usual care. Antenatal corticosteroids reduce preterm newborn mortality and morbidities, including respiratory distress, necrotising enterocolitis and intra-ventricular haemorrhage [447]. There is currently no evidence to indicate that antenatal corticosteroids for preterm birth should not be used in a woman with confirmed COVID-19.

Certainty of the Evidence

No studies were identified that address the use of antenatal corticosteroids for women who have COVID-19 and are at risk of preterm birth.

Preference and values

There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

The Consumer Panel believes that most women would agree with the recommendation as the available evidence suggests...
no additional harm to mother or newborn.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19, irrespective of whether the baby is preterm or not, requires greater resources than for women without COVID-19.

Equity
There are no identified equity issues as the recommendation reflects usual care.

Acceptability
Although we have no systematically collected evidence regarding acceptability, this recommendation is likely to be acceptable to both patients and clinicians.

Feasibility
There are likely no important feasibility issues as the recommendation reflects usual care.

Rationale
There are substantial known benefits for using antenatal corticosteroids for this indication. There is currently no direct evidence to suggest additional harms of using antenatal corticosteroids for preterm birth in the setting of COVID-19. Antenatal corticosteroids should continue to be used as per usual care.

13.2 Magnesium sulfate

The use of magnesium sulfate in pregnancy for fetal neuroprotection for women at risk of preterm birth is supported as part of standard care, independent of the presence of COVID-19.

The use of magnesium sulfate in pregnancy for the management of severe pre-eclampsia or eclampsia is supported as part of standard care, independent of the presence of COVID-19.

There are clear benefits to using magnesium sulfate for fetal neuroprotection for women at risk of preterm birth, particularly prior to 32 weeks' gestation [571].

There are also clear benefits to using magnesium sulfate for women with severe pre-eclampsia or eclampsia [570].

There is currently no evidence to suggest that magnesium sulfate can cause additional maternal or fetal harm (such as pulmonary oedema) in the setting of COVID-19 when used for this indication. Magnesium sulfate should therefore be given where indicated.

In pregnant women with COVID-19 who are receiving magnesium sulfate, renal function and fluid balance should be monitored. If renal impairment develops, the dose of magnesium sulfate may need to be adjusted or withheld accordingly.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Evidence To Decision

Benefits and harms
There are substantial benefits to using magnesium sulfate for fetal neuroprotection in preterm birth and for women with severe pre-eclampsia or eclampsia. There is currently no evidence to indicate that magnesium sulfate should not be used in women with confirmed COVID-19.

Certainty of the Evidence
No studies were identified that address the use of magnesium sulfate for fetal neuroprotection in women who have COVID-19.

Preference and values
There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19, irrespective of whether the baby is preterm or not, requires greater resources than for women without COVID-19.

Equity
There are no identified equity issues as the recommendation reflects usual care.

Acceptability
Although we have no systematically collected evidence regarding acceptability, this recommendation is likely to be acceptable to both patients and clinicians.

Feasibility
There are likely no important feasibility issues as the recommendation reflects usual care.

Rationale
There are substantial benefits for using magnesium sulfate for fetal neuroprotection in preterm birth, and for management of pre-eclampsia and eclampsia. There is currently no direct evidence to suggest additional harms of using magnesium sulfate for fetal neuroprotection in the setting of COVID-19. This intervention should continue to be used as per usual care.

13.3 Mode of birth
Conditional recommendation

For pregnant women with COVID-19, mode of birth should remain as per usual care.

There is currently no evidence to indicate that caesarean section for women with COVID-19 reduces the risk of vertical transmission to the newborn. Mode of birth should continue as per usual care. Respiratory deterioration due to COVID-19 may prompt urgent delivery on an individual basis.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Evidence informing this recommendation comes from a systematic review of 49 studies comprising 655 women and 666 newborns, of whom 28 newborns (4.2%) had a COVID-19 infection. No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively by mode of birth (vaginal birth or caesarean section).

Certainty of the Evidence

Certainty of the evidence is very low due to reliance on case reports and case series. Evidence informing this recommendation comes from a systematic review estimating the risk of the newborn becoming infected with COVID-19 by mode of birth (vaginal or caesarean) in pregnant women with confirmed or suspected COVID-19 infection.

Preference and values

There is no systematically collected information regarding the preferences and values of pregnant women with COVID-19 at this point. Mode of birth should be individualised, based on clinical indications and taking into consideration individual preferences and values.

The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (regardless of mode of birth) requires greater resources than for women without COVID-19. The routine use of caesarean section for all pregnant women with COVID-19 would have additional resource implications.

Equity

For pregnant women with COVID-19, access to on-site paediatric support is needed at the time of birth. This may be more challenging for those women living in rural or remote areas.

Acceptability

Acceptability of different modes of birth by pregnant women is expected to vary and individual preferences should be taken into consideration. Clear communication from health professionals regarding the benefits and harms of different modes of birth is essential to aid discussion around individual preferences and acceptability.
**Feasibility**

There are no identified feasibility issues as the recommendation reflects usual care.

**Rationale**

There is currently no evidence to indicate that caesarean section for pregnant women with COVID-19 reduces the risk of vertical transmission. Usual care practices regarding clinical indications for caesarean section should be used.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively by mode of birth (vaginal birth or caesarean section). Therefore, the benefits and harms of mode of birth should be considered as per usual care, taking into consideration relevant clinical indications and a woman’s individual preferences. However, clinical deterioration due to worsening COVID-19 may prompt urgent delivery of the baby.

**Clinical Question/ PICO**

- **Population:** Pregnant women with COVID-19
- **Intervention:** Caesarean section
- **Comparator:** Vaginal birth

**Summary**

Evidence informing this recommendation comes from a systematic review that estimated the risk of the newborn becoming infected with COVID-19 by mode of birth (vaginal or caesarean) [448]. The review included 49 case reports or case series comprising 666 newborns. Cases were only included where the mother either had confirmed COVID-19 (based on a positive swab) or a high clinical suspicion of COVID-19 where a swab had not been taken. The incidence of COVID-19 infection in newborns is given in the table below.

<table>
<thead>
<tr>
<th>Mode of birth</th>
<th>Total newborns*</th>
<th>Infected</th>
<th>Not infected</th>
<th>Not tested</th>
<th>Died</th>
<th>% Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>292</td>
<td>8</td>
<td>261</td>
<td>21</td>
<td>7</td>
<td>2.7% (8/292)</td>
</tr>
<tr>
<td>Caesarean</td>
<td>374</td>
<td>20</td>
<td>313</td>
<td>26</td>
<td>1</td>
<td>5.3% (20/374)</td>
</tr>
</tbody>
</table>

*the review authors contacted the first author of the paper where there were missing newborn data (4 hospitals)

No cases of COVID-19 infection met the criteria for confirmed vertical transmission (positive PCR in umbilical cord blood, newborn blood collected within the first 12 hours of birth, or amniotic fluid collected prior to rupture of membranes). It was not possible to apply the classification developed by Shah et al [449] (confirmed, probable, possible, unlikely or not infected) due to lack of virological testing at birth or in first 12 hours of life.

Additional evidence is available from an observational cohort study in the US of newborns whose mothers had confirmed COVID-19 [461]. The Salvatore study reported on 106 newborns born to 116 mothers who were positive for COVID-19. Newborns were tested for SARS-CoV-2 by nasopharyngeal PCR at 12-24 hours (n=106), 5-7 days (n=79) and 14 days (n=72) of life.

Mode of birth was not affected by the mother’s SARS-CoV-2 status, with 59/106 (56%) born by vaginal birth and 43/106 (41%) by caesarean section. All newborns returned negative PCR test results for SARS-CoV-2 at all timepoints, indicating there was no vertical transmission.

**Additional information**

The Taskforce notes the publication of a WHO scientific brief on 8 February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 [450]. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.
13.4 Delayed umbilical cord clamping

Consensus recommendation

Delayed umbilical cord clamping is supported as part of standard care, independent of the presence of COVID-19.

There is currently no evidence that delayed umbilical cord clamping affects the risk of vertical transmission of COVID-19.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There is currently no evidence to indicate that delayed umbilical cord clamping increases the risk of SARS-CoV-19 transmission from mother to newborn. However, delayed umbilical cord clamping has several health benefits for term and preterm infants [451][452].

Certainty of the Evidence

There is currently no direct evidence on the transmission risk of delayed cord clamping between mothers with COVID-19 and their newborns.

Preference and values

No substantial variability expected

There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn.
Rationale
There is currently no evidence to indicate that delayed umbilical cord clamping affects the risk of vertical transmission of COVID-19. Usual care practices regarding delayed cord clamping of preterm and term newborns should be used.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Pregnant women with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Delayed cord clamping</td>
</tr>
<tr>
<td>Comparator:</td>
<td></td>
</tr>
</tbody>
</table>

Summary
There remains significant uncertainty whether delayed cord clamping affects SARS-CoV-2 transmission.

What is the evidence informing this recommendation?
Evidence comes from a systematic review that assessed success of different perinatal practices in preventing SARS-CoV-2 transmission between positive mothers and their infants [557]. The review included 28 studies (four prospective observational, one multicentre cohort, three retrospective chart reviews, seven case series, and 13 case reports). Six studies were rated as good quality, one as moderate, and 21 as poor quality.

Study characteristics
The review included five studies that documented early or delayed cord clamping practices. Four studies were case reports or case series, and one an observational study involving 403 women with SARS-CoV-2 infection admitted for childbirth across 70 centres in Spain [453]. It was generally not possible to assess how rigorously infection prevention and control practices had been implemented, though it is likely that such practices varied between studies. The vaccination status of women and the COVID-19 variant/s were not reported in these studies.

What are the main results?
Diagnosis with COVID-19 occurred in 5/138 (3.6%) babies in the delayed cord clamping group and 2/222 (0.9%) babies in the early cord clamping group. All infants who tested positive were asymptomatic. There is insufficient evidence to conclude whether cord clamping practices affect COVID-19 transmission.

Our confidence in the results
Evidence comes from retrospective observational studies with very few events, which are likely to be at high risk of bias.

Additional information
The Taskforce notes the publication of a WHO scientific brief on 8 February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 [450]. The brief acknowledges the limited evidence on the
extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

**How up to date is this evidence?**
The evidence in this summary was last updated on 6 September 2021. We continually monitor COVID-19 research and update our recommendations when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

## 13.5 Skin-to-skin contact

**Consensus recommendation**

Early skin-to-skin contact after birth and during the postnatal period is supported, independent of the presence of COVID-19. However, parents with COVID-19 should use infection prevention and control measures (mask and hand hygiene).

**Early skin-to-skin contact** refers to placing the naked baby prone on the parent’s bare chest immediately after birth.

Skin-to-skin contact should be encouraged and continue as per usual practice in other postnatal and neonatal settings, such as neonatal ICU and postnatal wards, providing infection prevention and control measures are maintained.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

**Evidence To Decision**

**Benefits and harms**

There are substantial known benefits for skin-to-skin contact between mother and newborn, including significantly reduced newborn mortality and morbidity and improved newborn and parental attachment [454][455]. There is currently no evidence to indicate that a woman with a known COVID-19 infection should not practice skin-to-skin with her newborn to prevent transmission of COVID-19, provided they use infection prevention and control measures (mask and hand hygiene) [557].
Certainty of the Evidence
There is currently no direct evidence on the transmission risk of skin-to-skin contact between mothers with COVID-19 and their newborns.

Preference and values
There is currently no direct evidence on the transmission risk of skin-to-skin contact between mothers with COVID-19 and their newborns.

The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for women and newborns without COVID-19.

Equity
There are likely no important equity issues.

Acceptability
Acceptability of skin-to-skin contact between mothers with COVID-19 and their newborns is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the benefits and harms of skin-to-skin contact is essential to aid discussion around individual preferences and acceptability.

Feasibility
There are likely no important feasibility issues as the recommendation reflects usual care.

Rationale
There is currently no evidence to indicate that skin-to-skin contact affects the risk of vertical transmission of COVID-19. Usual care practices regarding skin-to-skin contact should be used.

Clinical Question/ PICO
Population: Women with COVID-19 who have given birth
Intervention: Skin-to-skin contact
Comparator: No skin-to-skin contact

Summary
There remains significant uncertainty whether early skin-to-skin contact affects SARS-CoV-2 transmission.

What is the evidence informing this recommendation?
Evidence comes from a systematic review that assessed success of different perinatal practices in preventing SARS-CoV-2 transmission between positive mothers and their infants [557]. The review included 28 studies (four prospective observational, one multicentre cohort, three retrospective chart reviews, seven case series, and 13 case reports). Six studies were rated as good quality, one as moderate, and 21 as poor quality.
Study characteristics
The review included 12 studies (38 newborns) that documented early skin-to-skin contact (variably described "kangaroo care", "immediate skin-to-skin contact" or "immediate bonding", as compared to "strict isolation measures" or "separated immediately after delivery"). It was generally not possible to assess how rigorously infection prevention and control practices had been implemented, though it is likely that such practices varied between studies. The vaccination status of women and the COVID-19 variant/s were not reported in these studies.

What are the main results?
In the early skin-to-skin contact group, 4/16 (25%) neonates tested positive for COVID-19, while in the comparator group 2/22 (9%) neonates tested positive. All infants who tested positive were asymptomatic. There is insufficient evidence to conclude whether early skin-to-skin contact affects COVID-19 transmission.

Our confidence in the results
Evidence comes from retrospective observational studies with very few events, which are likely to be at high risk of bias.

Additional information
The Taskforce notes the publication of a WHO scientific brief on 8 February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 [450]. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

How up to date is this evidence?
The evidence in this summary was last updated on 6 September 2021. We continually monitor COVID-19 research and update our recommendations when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

### Outcome

<table>
<thead>
<tr>
<th>Study results and measurements</th>
<th>Comparator No skin-to-skin contact</th>
<th>Intervention Skin-to-skin contact</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of infected newborns</strong></td>
<td><strong>1</strong>Within 30 days of exposure</td>
<td><strong>9</strong>Critical</td>
<td>Very low Due to very serious risk of bias and imprecision, and serious indirectness</td>
<td>We are uncertain whether skin-to-skin contact increases or decreases the number of infected newborns.</td>
</tr>
<tr>
<td>Based on data from: 106 participants in 1 studies. (Observational (non-randomized))</td>
<td>See summary for details. Included 106 newborns born to 116 mothers with confirmed SARS-CoV-2 infection. Newborns were tested for infection at 12–24 hours, 5–7 days and 14 days of life. All newborns returned negative test results at all timepoints.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. **Number of infected neonates within 30 days of birth**
2. **Risk of Bias:** very serious. Evidence is derived from a single observational study. **Indirectness:** serious. Number of newborns receiving skin-to-skin care not reported. **Imprecision:** very serious. Only data from one observational study; no direct data of skin-to-skin care. **Publication bias:** no serious.

### 13.6 Breastfeeding
Breastfeeding is supported irrespective of the presence of COVID-19. However, women with COVID-19 who are breastfeeding should use infection prevention and control measures (mask and hand hygiene) while infectious.

There is currently no evidence to indicate that breastfeeding increases the risk of vertical transmission to the newborn. As there are substantial known benefits for breastfeeding, women should be supported to initiate or continue breastfeeding. If the baby is being fed with expressed breast milk or formula, the same infection prevention and control measures (mask and hand hygiene) should be used.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

There are substantial known benefits for breastfeeding for the health and well-being of mothers and newborns, which is supported as part of usual care. Breastfeeding reduces child mortality, promotes newborn development and reduces the risk of infectious and chronic disease. For mothers, breastfeeding reduces the risk of ovarian and breast cancer [457]. There is currently no evidence to indicate that a woman with a known COVID-19 infection should not breastfeed her newborn to prevent transmission, provided they use infection prevention and control measures (mask and hand hygiene).

Certainty of the Evidence

Certainty of the evidence is very low due to reliance on case reports and case series.

Preference and values

There is no systematically collected information regarding the preferences and values of pregnant women with COVID-19 at this point. Breastfeeding is an individual decision based on consideration of individual preferences and values.

The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn. The panel notes that some women might still choose not to breastfeed based on reasons unrelated to COVID-19.

Resources and other considerations

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, there is not expected to be any substantial resource considerations for breastfeeding compared to not breastfeeding. Caring for pregnant women and newborns with COVID-19 (irrespective of breastfeeding) requires greater resources than for women and newborns without COVID-19.

Equity

No important issues with the recommended alternative

There are likely no important equity issues.

Acceptability

Important issues, or potential issues not investigated

Acceptability of infant feeding practices by pregnant and postpartum women is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the benefits and harms of different feeding practices is essential to aid discussion around individual preferences and acceptability.
Rationale

There is currently no evidence to indicate that breastfeeding affects the risk of vertical transmission of COVID-19. Usual care practices regarding breastfeeding of newborns should be used.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively for different feeding practices, though evidence is currently limited.

Breastfeeding should be considered as per usual care, taking into consideration relevant clinical situation and a woman's individual preferences.

Clinical Question/ PICO

Population: Newborns of mothers with confirmed COVID-19
Intervention: Breastfeeding or breast milk
Comparator: No breastfeeding or breast milk

Summary

There remains significant uncertainty whether SARS-CoV-2 transmission via breast milk is possible.

What is the evidence informing this recommendation?

Evidence comes from three systematic reviews:

1. Living systematic review of 67 studies reporting newborn SARS-CoV-2 infection status and detection of SARS-CoV-2 in breast milk from mothers with confirmed SARS-CoV-2 infection [458].
2. Systematic review of 50 studies (four cohort studies, one case control, 18 case series and 27 case reports) regarding the presence of SARS-CoV-2 genome and antibodies in breast milk [459].
3. Systematic review of 28 studies that assessed success of different perinatal practices (including breastfeeding) in preventing SARS-CoV-2 transmission between positive mothers and their infants [557].

Study characteristics

1. Living systematic review [458]: SARS-CoV-2 infection status by feeding type from 66 studies (485 newborns and infants) where breast milk samples were available. Breast milk samples were tested for SARS-CoV-2 RNA using RT-PCR analysis (n=413) or ELISA for antibody detection only (n=72).
2. Systematic review [459]: among 213 women with SARS-CoV-2 infection, 183 women had SARS-CoV-2 genome testing of their breast milk, 30 had antibody testing of their breast milk and 89 had both genome and antibody testing.
3. Systematic review [557]: 25 studies (342 newborns) documented breast or bottle-feeding practices—190 neonates were in the breastfeeding group and 152 in the bottle-feeding group. Studies were largely of poor quality. It was generally not possible to assess how rigorously infection prevention and control practices had been implemented, though it is likely that such practices varied between studies. The vaccination status of women and the COVID-19 variant were not reported in these studies.

What are the main results?

1. Living systematic review [458]:
   - Of the 66 included studies where breast milk samples were available, 34/350 (9.7%) newborns had confirmed COVID-19, diagnosed either by viral RNA detection or serology (Table 1).
   - Of the 85 newborns who were breastfed (n=44) or received mixed feeding (n=41), 17 (20%) had COVID-19 confirmed by viral RNA detection (Table 1).
   - Of the 303 included studies where breast milk samples were not available, 110/917 (12.0%) newborns were diagnosed with COVID-19 by viral RNA detection. Of the 163 newborns who were breastfed or received mixed feeding, 19 (11.7%) were diagnosed with COVID-19 by viral RNA detection (Table 2).
   - 13/413 (3.1%) breast milk samples collected from COVID-19 positive mothers tested positive for SARS-CoV-2 via RT-PCR assay. Of the 11 newborns and infants who were known to be exposed to breast milk with detectable viral RNA, 6 (55%) tested positive and 5 (45%) tested negative for SARS-CoV-2.
The authors of the living systematic review note the following important considerations:

- Evidence of possible transmission through breast milk is still limited, particularly for older infants.
- The limited available breast milk samples were tested by RT-PCR assays. It is possible that viral RNA detection in breast milk was affected by the component of breast milk tested, as it has been shown to affect the assay sensitivity. The presence of viral RNA in breast milk does not necessarily indicate viral infectivity.
- Further research is needed to understand timing of maternal and infant exposure, breast milk viral load, duration of infection, and the presence of protective antibodies in breast milk and their effects on vertical transmission.

2. Systematic review [459]:

- Of the 214 infants, 32 (15%) tested positive for SARS-CoV-2 viral genome in the nasopharyngeal swab and one tested positive for anti-SARS-CoV-2 antibodies in serum.
- 12 women had breast milk samples that were positive for SARS-CoV-2 on RT-PCR testing. Among their infants, six tested positive for SARS-CoV-2 via nasopharyngeal swab and four were symptomatic (three confirmed positive).
- Presence of SARS-CoV-2 genome in breast milk is uncommon in mothers with confirmed SARS-CoV-2 infection, while the presence of antibodies in breast milk is more prevalent.

3. Systematic review [557]:

- The review pooled available data from 28 studies without adjustment for study size or study quality. The proportion of neonates who tested positive in the breastfeeding group was 11.5% (22/190). This was significantly higher than the positivity rate of 2.6% (4/152) in the bottle-fed group.
- Sensitivity analysis (excluding studies with sample size < 5) showed COVID-19 positivity rates of 8.4% (15/178) for the breastfed group and 2.1% (3/141) for infants fed by other modes.
- Almost all infants who tested positive for COVID-19 were asymptomatic—two neonates developed low-grade fevers but without respiratory symptoms, and one preterm infant had respiratory symptoms, which were presumed to be related to prematurity rather than COVID-19—indicating that transmission did not translate into newborn harms.

Our confidence in the results

Certainty of the evidence (across all three reviews) is very low due to the inclusion of case reports and case series likely to be at high risk of bias (including publication bias), possible duplication of cases between studies, and few events in individual studies. Inconsistent masking or hygiene protocols between studies may also be a factor. The higher transmission rate in the third systematic review [557] might be affected by respiratory droplet transmission due to poor hand hygiene or poor mask adherence during feeding.

Table 1 Studies (n=66) in the living systematic review where breast milk samples were available

<table>
<thead>
<tr>
<th>Feeding type</th>
<th>Confirmed COVID-19</th>
<th>Negative COVID-19</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newborns ≤ 28 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>15</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>Mixed feeding</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Formula</td>
<td>3</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Not reported feeding practice</td>
<td>6</td>
<td>222</td>
<td>228</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>14</td>
<td>58</td>
<td>72</td>
</tr>
<tr>
<td><strong>Infants &gt; 28 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Mixed feeding</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Formula</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not reported feeding practice</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 2 Studies (n=303) in the living systematic review where breast milk samples were not available

<table>
<thead>
<tr>
<th>Feeding type</th>
<th>Confirmed COVID-19</th>
<th>Negative COVID-19</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newborns ≤ 28 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>16</td>
<td>137</td>
<td>153</td>
</tr>
<tr>
<td>Mixed feeding</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Formula</td>
<td>15</td>
<td>67</td>
<td>82</td>
</tr>
<tr>
<td>Not reported feeding practice</td>
<td>76</td>
<td>596</td>
<td>672</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>110</td>
<td>807</td>
<td>917</td>
</tr>
<tr>
<td><strong>Infants &gt; 28 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Mixed feeding</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Formula</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Not reported feeding practice</td>
<td>125</td>
<td>2</td>
<td>127</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>146</td>
<td>2</td>
<td>148</td>
</tr>
</tbody>
</table>

Additional information

The Taskforce notes the publication of a WHO scientific brief on 8 February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 [450]. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

Further, a WHO scientific brief on breastfeeding and COVID-19 from June 2020 concluded that data were insufficient to conclude that SARS-CoV-2 can be transmitted postnatally from an infected mother to her infant through breast milk and that the benefits of breastfeeding (with infection prevention and control measures) outweigh potential risks [460].

How up to date is this evidence?
The evidence in this summary was last updated on 6 September 2021. We continually monitor COVID-19 research and update our recommendations when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infected newborns (No breast milk testing) 1</td>
<td>Based on data from: 1,142 participants in 340 studies. 2 (Observational (non-randomized))</td>
<td>No breastfeeding or breast milk</td>
<td>Breastfeeding or breast milk</td>
<td>Very low</td>
<td>We are uncertain whether breastfeeding increases or decreases the number of infected newborns born to mothers with confirmed COVID-19 (where breast milk was not tested).</td>
</tr>
</tbody>
</table>
### 13.7 Rooming-in

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparator</th>
<th>Study results and measurements</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rooming-in</td>
<td>No breastfeeding or breast milk</td>
<td>Based on data from: 485 participants in 67 studies. (^4) (Observational (non-randomized))</td>
<td>Breastfeeding or breast milk</td>
<td>Very low Due to very serious risk of bias, serious inconsistency, imprecision and publication bias (^5)</td>
<td>We are uncertain whether breastfeeding or breast milk increases or decreases number of infected newborns born to mothers with confirmed COVID-19 (where breast milk was tested).</td>
</tr>
</tbody>
</table>

1. Number of infected newborns within 30 days of breastfeeding or receiving expressed breastmilk
3. **Risk of Bias:** very serious. Evidence is derived from case studies and case reports. **Inconsistency:** serious. Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities. **Indirectness:** serious. Differences between the outcomes of interest and those reported. Testing of breast milk not reported. **Imprecision:** serious. Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities. **Publication bias:** serious. Due to case reports being more likely to report positive cases.
4. Systematic review \([458]\).
5. **Risk of Bias:** very serious. Evidence derived from case series and case reports. **Inconsistency:** serious. Variations in disease severity of infected mothers and availability of different testing modalities. **Indirectness:** no serious. **Imprecision:** serious. Low number of breast milk samples tested. **Publication bias:** serious. Due to case reports being more likely to report positive cases.

**Conditional recommendation**

For women with COVID-19 who have given birth, support rooming-in of mother and newborn in the birth suite and on the postnatal ward when both mother and baby are well. However, women with COVID-19 should use infection prevention and control measures (mask and hand hygiene).

There is currently no evidence to indicate that a woman with a known COVID-19 infection should be separated from her newborn to prevent transmission. As there are substantial known benefits for keeping mother and newborn together postpartum, women should be supported to be with their newborn as per usual care.

Women with COVID-19 should be encouraged and supported in using good hand hygiene before and after handling their baby, and using a mask while in close contact with their baby. To the extent possible, these women should practice physical distancing when not feeding or caring for the baby.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.
Evidence To Decision

Benefits and harms

There are substantial known benefits for keeping mother and newborn together postpartum, which is supported as part of usual care. Rooming-in of mother and newborn promotes bonding and increases exclusive breastfeeding at discharge [462] as well as duration of breastfeeding [463]. There is currently no evidence to indicate that a woman with a known COVID-19 infection should be separated from her newborn to prevent transmission, provided they use infection prevention and control measures (mask and hand hygiene).

Certainty of the Evidence

Certainty of the evidence is very low due to reliance on case reports and case series.

Preference and values

There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point. The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for women and newborns without COVID-19.

Equity

There are likely no important equity issues.

Acceptability

Acceptability of rooming-in is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the benefits and harms of rooming-in is essential to aid discussion around individual preferences and acceptability.

Feasibility

There are likely no important feasibility issues as the recommendation reflects usual care.

Rationale

There is currently no evidence to indicate that rooming-in affects the risk of vertical transmission of COVID-19. Usual care practices regarding rooming-in of newborns should be used, taking into consideration the relevant clinical situation and a woman’s individual preferences.

Clinical Question/ PICO

Population: Women with COVID-19 who have given birth
Intervention: Rooming-in
Comparator: No rooming-in
Summary
There remains significant uncertainty whether rooming-in practices affect SARS-CoV-2 transmission.

What is the evidence informing this recommendation?
Evidence comes from a systematic review that assessed success of different perinatal practices in preventing SARS-CoV-2 transmission between positive mothers and their infants [557]. The review included 28 studies (four prospective observational, one multicentre cohort, three retrospective chart reviews, seven case series, and 13 case reports). Six studies were rated as good quality, one as moderate, and 21 as poor quality.

Study characteristics
The review included 23 studies (403 newborns) that assessed COVID-19 transmission in rooming-in versus isolation measures. These measures were not consistently defined or applied across studies, with variable terms such as “no isolation”, “roomed-in”, “kept in separate room”, “immediate separation”, “isolation and separation” and “followed in isolation rooms” being used to define groups. Studies were largely of poor quality. It was generally not possible to assess how rigorously infection prevention and control practices had been implemented, though it is likely that such practices varied between studies. The vaccination status of women and the COVID-19 variant/s were not reported in these studies.

What are the main results?
The rooming-in group included 103 neonates, 20 (19.4%) of whom tested positive for SARS-CoV-2. The isolation group consisted of 300 neonates, five (1.7%) of whom tested positive for the virus. After excluding case reports and case series with < 5 cases, the positivity rate in rooming-in group was 15.5% (15/97), while in the isolation group it was 1.0%(3/289). None of the infants who tested positive for COVID-19 exhibited symptoms, indicating that transmission did not translate into newborn harms.

Our confidence in the results
Evidence comes from observational studies, most of which are low-quality studies, with few events. These are likely to be at high risk of bias. In addition, inconsistent masking or hygiene protocols or inadequate ventilation may be a contributing factor.

Additional information
The Taskforce notes the publication of a WHO scientific brief on 8 February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 [450]. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

How up to date is this evidence?
The evidence in this summary was last updated on 6 September 2021. We continually monitor COVID-19 research and update our recommendations when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
</table>
| **Number of infected newborns** 1  
Within 30 days of exposure | Based on data from: 666 participants in 49 studies. (Observational (non-randomized)) | No rooming-in | Rooming-in | **Very low**  
Due to very serious risk of bias, and serious imprecision, indirectness and inconsistency 2 | **We are uncertain whether rooming-in increases or decreases the number of infected newborns.** |

1. Number of infected neonates within 30 days of breastfeeding or receiving expressed breast milk
2. **Risk of Bias: very serious.** Evidence is derived from case studies and case reports.. **Inconsistency: serious.** Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities.. **Indirectness:**
serious. Differences between the outcomes of interest and those reported. Testing of breast milk not reported. Imprecision: serious. Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities. Publication bias: no serious.
14. Child and adolescent care

The primary panel for the recommendations in this section is the Paediatric and Adolescent Care Panel.

Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. The remaining panels review recommendations when relevant to their specific population group. In addition, all our recommendations are reviewed by the Consumer Panel.

14.1 Paediatric Inflammatory Multisystem Syndrome (PIMS-TS)

Since late April, clinicians have described a condition among severely ill children and adolescents of fever and significant inflammation, often with abdominal pain, rash or shock. This condition has occurred in settings with substantial community incidence of COVID-19 and these children often have evidence of prior SARS-CoV-2 infection. The condition has provisionally been named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by clinicians from the United Kingdom [467]. The US Centers for Disease Control and Prevention has named it multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) [465]. WHO has also defined this condition and used the label MIS-C [466].

In Australia, the Acute Inflammatory Vasculitis working group, the Paediatric Active Enhanced Disease Surveillance (PAEDS) network and the Royal Australasian College of Physicians have issued a statement on PIMS-TS [464]. The Taskforce aligns with this statement, pending further evidence. In assessing the international literature on this condition, the Taskforce favours the PIMS-TS case definition from the Royal College of Paediatrics and Child Health (UK) [467] as we judge this to be most aligned with current Australian practice. The Taskforce will, however, review and include evidence to inform our recommendations from data using any of the three case definitions (listed below for comparison). Click here for a side-by-side comparison of the three definitions (adapted from [468]).

Royal College of Paediatrics and Child Health (PIMS-TS) case definition [467]

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated C-reactive protein (CRP) and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features*. This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).

3. SARS-CoV-2 polymerase chain reaction (PCR) testing may be positive or negative. All stable children should be discussed as soon as possible with specialist services to ensure prompt treatment (paediatric infectious disease / cardiology / rheumatology). There should be a low threshold for referral to paediatric intensive care using normal pathways.

* Additional features include:

** These assays are not widely available. CRP can be used as a surrogate marker for IL-6.

Info Box

For recommendations on disease-modifying treatments, chemoprophylaxis and respiratory support in children and adolescents please see sections above. We are continually working on updating all recommendations to reflect special populations, including children and adolescents.
CDC MIS-C case definition [465]

An individual aged under 21 years of age presenting with fever*, laboratory evidence of inflammation** and evidence of clinically severe illness requiring hospitalisation, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)

AND

No alternative plausible diagnoses

AND

Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

* Fever > 38.0°C for ≥ 24 hours or report of subjective fever lasting ≥ 24 hours
**Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Additional comments: some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C. Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

WHO MIS-C case definition [466]

Children and adolescents 0–19 years of age with fever > 3 days.

AND

Two of the following:
• rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet)
• hypotension or shock
• features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)
• evidence of coagulopathy (by prothrombin time (PT), partial thromboplastin time (PTT), elevated D-dimers)
• acute gastrointestinal problems (diarrhoea, vomiting or abdominal pain)

AND

Elevated markers of inflammation such as erythrocyte sedimentation rate, C-reactive protein or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test or serology positive) or likely contact with patients with COVID-19.
14.1.1 Intravenous immunoglobulin (IVIG) plus corticosteroids

Info Box

The Taskforce endorses the PIMS-TS case definition from the Royal College of Paediatrics and Child Health (United Kingdom) [467].

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated C-reactive protein (CRP) and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features*. This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).

3. SARS-CoV-2 PCR testing may be positive or negative. All stable children should be discussed as soon as possible with specialist services to ensure prompt treatment (paediatric infectious disease / cardiology / rheumatology). There should be a low threshold for referral to paediatric intensive care using normal pathways.

* Additional features include:

Clinical

- All: persistent fever > 38.5°C
- Most: oxygen requirement, hypotension
- Some: abdominal pain, confusion, conjunctivitis, cough, diarrhoea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting

Imaging and electrocardiogram (ECG)

- Echocardiogram and ECG: myocarditis, valvulitis, pericardial effusion, coronary artery dilatation
- Chest x-ray: patchy symmetrical infiltrates, pleural effusion
- Abdominal ultrasound scan: colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly
- Computed tomography (CT) chest: as for chest x-ray—may demonstrate coronary artery abnormalities if with contrast

Laboratory

- All: abnormal fibrinogen, absence of potential causative organisms (other than SARS-CoV-2), high CRP, high D-dimers, high ferritin, hypoalbuminaemia, lymphopaenia, neutrophilia in most – normal neutrophils in some
- Some: acute kidney injury, anaemia, coagulopathy, high IL-10 (if available)**, high IL-6 (if available)**, neutrophilia, proteinuria, raised creatine kinase (CK), raised lactic acid dehydrogenase (LDH), raised triglycerides, raised troponin, thrombocytopenia, transaminits

** These assays are not widely available. CRP can be used as a surrogate marker for IL-6.

Additionally, in Australia the PAEDS network definition may be used for case reporting and identification of suspected cases. For a comparison of PIMS-TS / MIS-C international definitions click here.

Consensus recommendation

Children and adolescents who have suspected or confirmed PIMS-TS should be managed by and discussed with a multidisciplinary team. Because of the potential for rapid deterioration, early consultation with experts and consideration of early transfer to a paediatric hospital with intensive care facilities to manage children are recommended for patients with suspected or confirmed PIMS-TS.

14.1.1 Intravenous immunoglobulin (IVIG) plus corticosteroids
Practical Info

Primary classification of PIMS-TS should be based on the presenting phenotype (adapted from Harwood [473]):

1. Kawasaki disease-like: complete and incomplete, classified using the American Heart Association criteria [474]
2. Non-specific: children presenting with shock or fever (or both) and symptoms that might include abdominal pain, gastrointestinal, respiratory or neurological symptoms that do not meet the criteria for Kawasaki disease.

Currently, the suggested dosing for methylprednisolone or other systemic intravenous corticosteroids remains unclear. Contact your local expert for further advice on dosing.

Evidence To Decision

**Conditional recommendation**

Consider using intravenous immunoglobulin (2 g/kg per dose) in combination with methylprednisolone in children and adolescents who meet PIMS-TS criteria.

*Intravenous immunoglobulin should be considered for all children with complete or incomplete Kawasaki disease, irrespective of whether it may be related to COVID-19. Depending on the age and the phenotype expression of PIMS-TS, combination therapy of IVIG and corticosteroids should be considered as a first-line therapy. This is particularly relevant for older children with myocardial dysfunction, as opposed to younger children with a more Kawasaki disease-like phenotype.*

*Note that the oncotic load from a large IVIG dose should be considered when administering this agent to children with myocardial dysfunction. For selected cases of PIMS-TS with severe myocardial dysfunction, corticosteroid treatment alone and/or delayed use of IVIG may be beneficial.*

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

**Benefits and harms**

There are proven benefits to using intravenous immunoglobulin in children and adolescents for other diseases, particularly in Kawasaki disease, which shares characteristics and partially overlaps with PIMS-TS. Benefits outweigh the risks for using intravenous immunoglobulin in this population.

**Certainty of the Evidence**

Three observational studies has been found exploring the combination of intravenous immunoglobulin and corticosteroids versus intravenous immunoglobulin alone. Certainty of the evidence is deemed moderate for escalation or adjunctive immunomodulatory therapy requirement and low for left ventricular dysfunction and composite cardiovascular outcomes.

**Preference and values**

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. As intravenous immunoglobulin is a blood-derived product, some may decline this intervention and prefer corticosteroids alone.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.
Three observational studies on the management of PIMS-TS have been identified [472][519][520].

McArdle 2021 is an international observational cohort study that compared treatment of Intravenous immunoglobulin (IVIG) plus glucocorticoids with IVIG alone and glucocorticoids alone in children with multisystem inflammatory syndrome after suspected COVID-19 infection [520]. The primary outcomes were a composite of inotropic support or mechanical ventilation (invasive or non-invasive) by day 2 or later or death, and reduction in disease severity. The study found that IVIG plus steroids compared with IVIG alone made no difference to receipt of inotropic or ventilatory support or death (OR 0.77, 95% CI 0.33 to 1.82; 410 patients) or when compared with steroids alone (OR 0.54, 95% CI 0.22 to 1.33; 307 patients).

Son 2021 is a cohort study conducted in the USA that compared IVIG plus glucocorticoids with glucocorticoids alone [519]. The primary outcome was cardiovascular dysfunction on or after day 2 until discharge, or shock that resulted in the use of vasopressors. The study found that IVIG plus steroids compared with IVIG alone was associated with lower cardiovascular dysfunction after day 2 (RR 0.56, 95% CI 0.34 to 0.94; 212 patients).

Data from these two studies were pooled with the previously included study by Ouldali 2021 [472]. IVIG combined with steroids compared with IVIG alone probably reduces the need for escalation or adjunctive immunomodulatory therapy (moderate certainty evidence – upgraded due to large treatment effect) and may decrease left ventricular dysfunction (low certainty evidence).

**Rationale**

Three observational studies on the management of PIMS-TS have been identified [472][519][520].

**Clinical Question/ PICO**

**Population:** Children and adolescents with COVID-19  
**Intervention:** Intravenous immunoglobulin plus methylprednisolone  
**Comparator:** Intravenous immunoglobulin

**Summary**

Three observational studies on the management of PIMS-TS have been identified [472][519][520]. McArdle 2021 is an international observational cohort study that compared treatment of Intravenous immunoglobulin (IVIG) plus glucocorticoids with IVIG alone and glucocorticoids alone in children with multisystem inflammatory syndrome after suspected COVID-19 infection [520]. The primary outcomes were a composite of inotropic support or mechanical ventilation (invasive or non-invasive) by day 2 or later or death, and reduction in...
disease severity. The study found that IVIG plus steroids compared with IVIG alone made no difference to receipt of inotropic or ventilatory support or death (OR 0.77, 95% CI 0.33 to 1.82; 410 patients) or when compared with steroids alone (OR 0.54, 95% CI 0.22 to 1.33; 307 patients).

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Data from these two studies were pooled with the previously included study [472]. IVIG combined with steroids compared with IVIG alone probably reduces the need for escalation or adjunctive immunomodulatory therapy (moderate certainty evidence – upgraded due to large treatment effect) and may decrease left ventricular dysfunction (low certainty evidence).
<table>
<thead>
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<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
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</tr>
</thead>
</table>
| Left ventricular dysfunction    | Important | Relative risk 0.34 (CI 95% 0.15 — 0.77)  
5 Important                                                                                                                                                                                                                                                                                                                                                           | IVIG       | IVIG + MP            | Low                                              | IVIG + MP may decrease left ventricular dysfunction                                                       |
|                                 |           | Based on data from 256 participants in 2 studies.  
7 (Observational (non-randomized))                                                                                                                                                                                                                                                                                                                               |            |                      |                                                   |                                                                                                             |
| Death                           |           | Odds Ratio 0.32 (CI 95% 0.05 — 1.86)  
Based on data from 430 participants in 1 studies.  
8 (Observational (non-randomized))                                                                                                                                                                                                                                                                 |            |                      | Very low                                         | We are uncertain whether IVIG + MP increases or decreases death                                           |
|                                 |           | Odds Ratio 0.9 (CI 95% 0.48 — 1.69)  
Based on data from 454 participants in 1 studies.  
(Observational (non-randomized))  
Follow up: 2 days.                                                                                                                                                                                                                                                                                     |            |                      | Very low                                         | We are uncertain whether IVIG + MP increases or decreases reduction of disease severity                     |
| Reduction of disease severity    |           | Odds Ratio 0.77 (CI 95% 0.33 — 1.82)  
Based on data from 454 participants in 1 studies.  
(Observational (non-randomized))                                                                                                                                                                                                                                                                       |            |                      | Very low                                         | We are uncertain whether IVIG + MP increases or decreases composite of inotropic support or mechanical ventilation or death |
| Composite of inotropic support or mechanical ventilation or death |           | Odds Ratio 0.18 (CI 95% 0.1 — 0.33)  
Based on data from 414 participants in 1 studies.  
13 (Observational (non-randomized))                                                                                                                                                                                                                                                                  |            |                      | Low                                              | IVIG + MP may decrease an escalation of immunomodulatory treatment                                       |
| Escalation of immunomodulatory treatment |         | Odds Ratio 0.46 (CI 95% 0.3 — 0.69)  
Based on data from 811 participants in 3 studies.  
15 (Observational (non-randomized))                                                                                                                                                                                                                                                                  |            |                      | Moderate                                         | IVIG + MP probably decreases the need for escalation or adjunctive immunomodulatory therapy               |
| Escalation or adjunctive immunomodulatory therapy required |         | Relative risk 0.46 (CI 95% 0.3 — 0.69)  
Based on data from 811 participants in 3 studies.  
15 (Observational (non-randomized))                                                                                                                                                                                                                                                                  |            |                      |                                                   |                                                                                                             |
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator IVIG</th>
<th>Intervention IVIG + MP</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite cardiovascular outcomes</td>
<td>Relative risk 0.56 (CI 95% 0.34 — 0.94) Based on data from 206 participants in 1 studies.</td>
<td>175 per 1000</td>
<td>98 per 1000</td>
<td>Low Due to serious imprecision, Upgraded due to Large magnitude of effect</td>
<td>IVIG + MP may decrease composite cardiovascular outcomes</td>
</tr>
<tr>
<td>Persistent or recurrent fever</td>
<td>Relative risk 0.78 (CI 95% 0.53 — 1.13) Based on data from 202 participants in 1 studies.</td>
<td>40 per 1000</td>
<td>31 per 1000</td>
<td>Very low Due to serious imprecision</td>
<td>We are uncertain whether IVIG + MP increases or decreases persistent or recurrent fever</td>
</tr>
<tr>
<td>Duration of PICU stay</td>
<td>Lower better Based on data from: 106 participants in 1 studies. (Observational (non-randomized))</td>
<td>6 (Median)</td>
<td>4 (Median)</td>
<td>Very low Due to serious imprecision</td>
<td>We are uncertain whether IVIG + MP increases or decreases duration of PICU stay.</td>
</tr>
<tr>
<td>Time to improvement in disease severity</td>
<td>Based on data from: 454 participants in 1 studies. (Observational (non-randomized))</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, Due to serious imprecision</td>
<td>We are uncertain whether glucocorticoids increases or decreases time to improvement in disease severity</td>
</tr>
</tbody>
</table>

1. **Risk of Bias:** no serious, due to observational study. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study. **Publication bias:** no serious.


3. **Imprecision:** serious. **Publication bias:** no serious.

4. **Imprecision:** serious.

5. LVEF < 55% occurring at least 1 day after first line therapy introduction

6. **Imprecision:** serious.

7. Systematic review with included studies: [472], [519]. **Baseline/comparator:** Control arm of reference used for intervention.

8. Systematic review with included studies: [520]. **Baseline/comparator:** Control arm of reference used for intervention.

9. **Risk of Bias:** serious, Serious - concerns about cross-over into other treatment arms. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Wide confidence intervals, Only data from one study. **Publication bias:** no serious.

10. Reduction on ordinal scale on seven-point ordinal scale between day 0 and day 2. The levels of disease severity from worst to least were as follows: receipt of mechanical ventilation and inotropic support, receipt of mechanical ventilation alone, receipt of inotropic support alone, receipt of oxygen alone, no supportive therapy with a C-reactive protein level of 50 mg per litre or more, no supportive therapy with a C-reactive protein level of less

11. **Risk of Bias:** serious, Serious - concerns about cross-over into other arms, and unclear blinding of outcome assessors. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study. **Publication bias:** no serious.
14.1.2 Corticosteroids

**Consensus recommendation**

Consider using corticosteroids (irrespective of oxygen status) as adjuvant therapy for children and adolescents diagnosed with PIMS-TS.

*Intravenous corticosteroids (e.g. methylprednisolone) may be given before, or in combination with, intravenous immunoglobulin. Corticosteroids should be considered as the next treatment option for children who remain unwell (tachycardia, need for vasoactive support) 24 hours after infusion of intravenous immunoglobulin, particularly if they have ongoing pyrexia or have not received corticosteroids as a first-line treatment.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

**Practical Info**

Primary classification of PIMS-TS should be based on the presenting phenotype (adapted from Harwood [470]):

1. Kawasaki disease-like: complete and incomplete, classified using the American Heart Association criteria [471]
2. Non-specific: children presenting with shock or fever (or both) and symptoms that might include abdominal pain, gastrointestinal, respiratory or neurological symptoms that do not meet the criteria for Kawasaki disease.
**Evidence To Decision**

**Benefits and harms**

There are proven benefits to using corticosteroids in children and adolescents for other diseases, particularly in Kawasaki disease, which shares characteristics and partially overlaps with PIMS-TS. Corticosteroids are generally considered safe in this population. However, there may be risks to consider, particularly with regards to unmasking other infections (e.g. strongyloidiasis).

**Certainty of the Evidence**

Only one observational study has been found exploring the combination of intravenous immunoglobulin and corticosteroids versus intravenous immunoglobulin alone. Certainty of the evidence is deemed very low (due to only one study and low numbers of events/patients).

**Preference and values**

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. However, we expect the intervention would be generally acceptable as it is occasionally used for the treatment of Kawasaki disease.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment for COVID-19. The panel recognises that some informed patients, parents, carers, families and guardians may prefer to wait until the available evidence is clearer.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. There are unlikely to be issues as corticosteroids are widely available.

**Equity**

It is unlikely that the use of corticosteroids will create equity issues as they are widely available.

**Acceptability**

Corticosteroids are generally a well-accepted intervention, and there are no important issues regarding acceptability.

**Feasibility**

There are no expected feasibility issues.

**Rationale**

Corticosteroids are used for the treatment of several conditions and, in particular, in high risk of refractory cases of Kawasaki disease. One observational study has found a potential benefit of the combination therapy in comparison with immunoglobulin alone [472].

Children of older age and with more manifestations of myocardial dysfunction may benefit especially from the combination therapy.
Clinical Question/ PICO

**Population:** Children and adolescents with COVID-19  
**Intervention:** Intravenous immunoglobulin plus methylprednisolone  
**Comparator:** Intravenous immunoglobulin

Summary

Three observational studies on the management of PIMS-TS have been identified [472][519][520]. McArdle 2021 is an international observational cohort study that compared treatment of Intravenous immunoglobulin (IVIG) plus glucocorticoids with IVIG alone and glucocorticoids alone in children with multisystem inflammatory syndrome after suspected COVID-19 infection [520]. The primary outcomes were a composite of inotropic support or mechanical ventilation (invasive or non-invasive) by day 2 or later or death, and reduction in disease severity. The study found that IVIG plus steroids compared with IVIG alone made no difference to receipt of inotropic or ventilatory support or death (OR 0.77, 95% CI 0.33 to 1.82; 410 patients) or when compared with steroids alone (OR 0.54, 95% CI 0.22 to 1.33; 307 patients).

Son 2021 is a cohort study conducted in the USA that compared IVIG plus glucocorticoids with glucocorticoids alone [519]. The primary outcome was cardiovascular dysfunction on or after day 2 until discharge, or shock that resulted in the use of vasopressors. The study found that IVIG plus steroids compared with IVIG alone was associated with lower cardiovascular dysfunction after day 2 (RR 0.56, 95% CI 0.34 to 0.94; 212 patients).

Data from these two studies were pooled with the previously included study [472]. IVIG combined with steroids compared with IVIG alone probably reduces the need for escalation or adjunctive immunomodulatory therapy (moderate certainty evidence – upgraded due to large treatment effect) and may decrease left ventricular dysfunction (low certainty evidence).

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator IVIG</th>
<th>Intervention IVIG + MP</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>Odds Ratio 0.25 (CI 95% 0.09 – 0.7) Based on data from 106 participants in 1 studies. (Observational (non-randomized))</td>
<td>375 per 1000</td>
<td>130 per 1000</td>
<td>Very low Due to serious imprecision ¹</td>
<td>We are uncertain whether IVIG + MP improves or worsens treatment failure.</td>
</tr>
<tr>
<td>OLD Second-line treatment</td>
<td>Odds Ratio 0.19 (CI 95% 0.06 – 0.61) Based on data from 106 participants in 1 studies. (Observational (non-randomized))</td>
<td>310 per 1000</td>
<td>79 per 1000</td>
<td>Very low Due to serious imprecision ²</td>
<td>We are uncertain whether IVIG + MP improves or worsens need for second-line treatment.</td>
</tr>
<tr>
<td>Need for hemodynamic support</td>
<td>Odds Ratio 0.21 (CI 95% 0.06 – 0.76) Based on data from 106 participants in 1 studies.</td>
<td>230 per 1000</td>
<td>59 per 1000</td>
<td>Very low Due to serious imprecision ³</td>
<td>We are uncertain whether IVIG + MP improves or worsens the need for hemodynamic support.</td>
</tr>
</tbody>
</table>

¹ We are uncertain whether IVIG + MP improves or worsens treatment failure.  
² We are uncertain whether IVIG + MP improves or worsens need for second-line treatment.  
³ We are uncertain whether IVIG + MP improves or worsens the need for hemodynamic support.
<table>
<thead>
<tr>
<th>Outcome</th>
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<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLD Acute left ventricular dysfunction</td>
<td>5</td>
<td>Odds Ratio 0.2 (CI 95% 0.06 — 0.66) Based on data from 106 participants in 1 studies.</td>
<td>IVIG</td>
<td>IVIG + MP</td>
<td>Very low</td>
<td>We are uncertain whether IVIG + MP improves or worsens acute left ventricular dysfunction.</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>5</td>
<td>Relative risk 0.34 (CI 95% 0.15 — 0.77) Based on data from 256 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>IVIG + MP may decrease left ventricular dysfunction</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
<td>Odds Ratio 0.32 (CI 95% 0.05 — 1.86) Based on data from 430 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether IVIG + MP increases or decreases death</td>
</tr>
<tr>
<td>Reduction of disease severity</td>
<td>10</td>
<td>Odds Ratio 0.9 (CI 95% 0.48 — 1.69) Based on data from 454 participants in 1 studies. (Observational (non-randomized)) Follow up: 2 days.</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether IVIG + MP increases or decreases reduction of disease severity</td>
</tr>
<tr>
<td>Composite of inotropic support or mechanical ventilation or death</td>
<td>10</td>
<td>Odds Ratio 0.77 (CI 95% 0.33 — 1.82) Based on data from 454 participants in 1 studies. (Observational (non-randomized))</td>
<td></td>
<td></td>
<td>Very low</td>
<td>We are uncertain whether IVIG + MP increases or decreases composite of inotropic support or mechanical ventilation or death</td>
</tr>
<tr>
<td>OLD Escalation of immunomodulatory treatment</td>
<td>10</td>
<td>Odds Ratio 0.18 (CI 95% 0.1 — 0.33) Based on data from 414 participants in 1 studies. (Observational (non-randomized))</td>
<td></td>
<td></td>
<td>Low</td>
<td>IVIG + MP may decrease an escalation of immunomodulatory treatment</td>
</tr>
</tbody>
</table>

Relative risk 0.34 (CI 95% 0.15 — 0.77) Based on data from 256 participants in 2 studies. (Observational (non-randomized))

Odds Ratio 0.9 (CI 95% 0.33 — 1.82) Based on data from 454 participants in 1 studies. (Observational (non-randomized)) Follow up: 2 days.

Odds Ratio 0.77 (CI 95% 0.48 — 1.69) Based on data from 430 participants in 1 studies. (Observational (non-randomized))
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escalation or adjunctive immunomodulatory therapy required</td>
<td>Relative risk 0.46 (CI 95% 0.3 – 0.69) Based on data from 811 participants in 3 studies.</td>
<td>539 per 1000</td>
<td>248 per 1000</td>
<td>Moderate Upgraded due to Large magnitude of effect</td>
<td>IVIG + MP probably decreases the need for escalation or adjunctive immunomodulatory therapy</td>
</tr>
<tr>
<td>Composite cardiovascular outcomes</td>
<td>Relative risk 0.56 (CI 95% 0.34 – 0.94) Based on data from 206 participants in 1 studies.</td>
<td>175 per 1000</td>
<td>98 per 1000</td>
<td>Low Due to serious imprecision, Upgraded due to Large magnitude of effect</td>
<td>IVIG + MP may decrease composite cardiovascular outcomes</td>
</tr>
<tr>
<td>Persistent or recurrent fever</td>
<td>Relative risk 0.78 (CI 95% 0.53 – 1.13) Based on data from 202 participants in 1 studies.</td>
<td>40 per 1000</td>
<td>31 per 1000</td>
<td>Very low Due to serious imprecision</td>
<td>We are uncertain whether IVIG + MP increases or decreases persistent or recurrent fever</td>
</tr>
<tr>
<td>Duration of PICU stay</td>
<td>Lower better Based on data from: 106 participants in 1 studies.</td>
<td>6 (Median)</td>
<td>4 (Median)</td>
<td>Very low Due to serious imprecision</td>
<td>We are uncertain whether IVIG + MP increases or decreases duration of PICU stay.</td>
</tr>
<tr>
<td>Time to improvement in disease severity</td>
<td>Based on data from: 454 participants in 1 studies.</td>
<td>IVIG + MP compared to IVIG alone made no difference to time to improvement in disease severity (HR 0.89, 95%CI 0.67, 1.19).</td>
<td></td>
<td>Very low Due to serious risk of bias, Due to serious imprecision</td>
<td>We are uncertain whether glucocorticoids increases or decreases time to improvement in disease severity</td>
</tr>
</tbody>
</table>

4. Imprecision: serious.
5. LVEF < 55% occurring at least 1 day after first line therapy introduction
7. Systematic review with included studies: [472], [519]. Baseline/comparator: Control arm of reference used for...
14.1.3 Other immunomodulatory agents
Additional immunomodulatory agents for PIMS-TS (anti IL-1, anti IL-6 or anti-TNF) should be considered as a third-line option in children and adolescents with PIMS-TS who do not respond to intravenous immunoglobulin and corticosteroids.

Before initiating additional immunomodulatory therapies, all PIMS-TS patients need to be discussed with a multidisciplinary team and interventions carefully considered. Immunomodulatory agents previously used that have an acceptable risk–benefit ratio include:

- Anakinra (IL-1 receptor antagonist)
- Infliximab (TNF inhibitor)
- Tocilizumab (IL-6 receptor antagonist)

Consider testing for infections that may be unmasked by the use of these agents.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

There are proven benefits of immunomodulatory therapy in children and adolescents for other diseases, but its effectiveness in treating PIMS-TS remains unknown. There are known harms of using immunomodulatory therapies, especially in relation to immunosuppression and the increased risk of infection (e.g. using these therapies in the context of undiagnosed bacterial sepsis). Depending on the agent used, a different ratio of risk and harms may be considered.

Certainty of the Evidence

No randomised trials have been identified assessing the use of immunomodulatory agents for the treatment of PIMS-TS.

Preference and values

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. However, we expect the intervention would be generally acceptable as it is regularly used for treating other conditions in this population.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the agent used, the potential costs to be considered may vary as well as its availability.

Equity

There is a risk of creating inequity as people who live in rural and remote areas may have limited access to immunomodulatory agents.
Immunomodulatory agents are routinely used to treat a range of rheumatological conditions in children and adolescents and may limit the hyperinflammatory state associated with this syndrome. Given the partial characterisation of PIMS-TS, immunomodulatory agents have occasionally been used for its treatment in international cohorts [473][474].

14.1.4 Aspirin and antithrombotic agents

Consensus recommendation

Children who are treated for PIMS-TS with intravenous immunoglobulin or other agents should also be prescribed low-dose aspirin (3–5 mg per kg once daily for at least 6 weeks).

Additional measures to be considered to prevent venous thrombosis associated with PIMS-TS include:

- Anticoagulation therapy
- Compression stockings (in children older than 12 years of age)

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Aspirin is not routinely recommended in children due to the risk of Reye's syndrome. However, there are potential benefits of using aspirin in children and adolescents, particularly in Kawasaki disease, which shares common characteristics and partially overlaps with PIMS-TS. There are also other well-known harms to consider when administering aspirin at higher doses, such as increased risk of gastrointestinal bleeding, acute kidney injury, tinnitus or bronchospasm.

Certainty of the Evidence

No randomised trials have been identified assessing the use of aspirin or antithrombotic agents for the treatment of PIMS-TS.

Preference and values

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. However, we expect the intervention would be generally acceptable as it is regularly used for the treatment of Kawasaki disease.
The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

### Resources and other considerations

We have no systematically collected evidence regarding cost-benefit.

### Equity

It is unlikely that the use of aspirin will create equity issues as it is widely available.

### Acceptability

Aspirin is generally a well-accepted intervention, and there are no important issues regarding acceptability.

### Feasibility

Feasibility is affected by prompt diagnosis of PIMS-TS and access to a multidisciplinary team for discussion.

### Rationale

Aspirin is used as an antithrombotic to prevent coronary artery thrombosis in Kawasaki disease.
15. Post-COVID-19

Post-COVID-19 or long COVID describes the symptoms that may arise in the weeks or months following resolution of a SARS-CoV-2 infection. A range of symptoms have been reported in both adults and children, with variation in the duration of symptoms and clinical history [606][607]. For instance, symptoms may be experienced by people who had either mild or severe COVID-19. Some symptoms may subside gradually with self-directed care alone, while other symptoms may require care from a health professional, or new symptoms may arise.

15.1 Assessment and diagnosis of post-COVID-19 condition

**Good practice statement**

**Assessing the probability diagnosis**

- Confirm that the person had COVID-19 (by checking that they had a positive PCR test), or is likely to have had COVID-19 (by checking that they have had symptoms consistent with a SARS-CoV-2 infection and/or known contact with a positive case or high-risk setting). Document details of the acute illness.
- Check the current symptoms and ask the person about their concerns, functioning and wishes in terms of their needs.
- Assess whether the current symptoms are likely to be related to acute COVID-19.
- Assess whether the symptoms may be related to, or are exacerbated by, comorbid conditions [618].
Consensus recommendation

The following symptoms and signs have been described by people with post-COVID-19 infection [606][607][608]:

- **Pulmonary symptoms**
  - Shortness of breath
  - Cough

- **Neurological symptoms**
  - Fatigue
  - Headache
  - Cognitive dysfunction
  - Sleep disturbance
  - Loss of smell
  - Paraesthesia

- **Renal disease**
- **Thromboembolism**
- **Psychological symptoms**
  - Anxiety
  - Depression
  - Mood swings
  - Note that fatigue and sleep disturbance may also indicate the emergence of a mental health condition

- **Cardiac symptoms**
  - Chest pain

- **Musculoskeletal symptoms**
  - Non-specific pain
  - Myalgia

- **Fever**
  - Low-grade fevers

- **Reduced activity and functional level**
- **Reduced nutritional status and weight loss**
- **Post-intensive care syndrome (PICS)**
  - PICS refers to one or more of the following symptoms that people experience following care in ICU: anxiety, depression, cognitive impairment, memory loss, muscle weakness, dysphagia and reduced quality of life [610][611].

In some people, both adults and children, symptoms corresponding to multisystem inflammatory syndrome [CDC 2021] have been reported [609].

This list of symptoms and signs will be updated as new evidence emerges.

### 15.2 Management and care of people with post-COVID-19 condition

Our understanding of effective management approaches is still emerging. As such, recommendations for the management of people with post-COVID-19 will be updated here as new evidence emerges. In the interim, we direct readers to the Post-COVID-19 flowchart, This flowchart outlines aspects of care and treatment based on current best-practice approaches.
## 16. Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACEIs</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>AEs</td>
<td>Adverse events</td>
</tr>
<tr>
<td>AHPPC</td>
<td>Australian Health Protection Principal Committee</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANZICS</td>
<td>Australian and New Zealand Intensive Care Society</td>
</tr>
<tr>
<td>ANZPID</td>
<td>Australia and New Zealand Paediatric Infectious Diseases Group</td>
</tr>
<tr>
<td>ARBs</td>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>BiPAP</td>
<td>Bilevel positive airway pressure</td>
</tr>
<tr>
<td>BSA</td>
<td>Body surface area</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration equation</td>
</tr>
<tr>
<td>CMA</td>
<td>Combined metabolic activators</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 2019 (disease caused by the virus SARS-CoV-2)</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>CPR</td>
<td>Cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical study report</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>DMARDs</td>
<td>Disease-modifying anti-rheumatic drugs</td>
</tr>
<tr>
<td>DMTs</td>
<td>Disease-modifying treatments</td>
</tr>
<tr>
<td>DOI</td>
<td>Digital Object Identifier</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECHO</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>FiO2</td>
<td>Fraction of inspired oxygen</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of recommendations, assessment, development and evaluation</td>
</tr>
<tr>
<td>HCP</td>
<td>Healthcare professionals</td>
</tr>
<tr>
<td>HFNC</td>
<td>High-flow nasal cannula</td>
</tr>
<tr>
<td>HFNO</td>
<td>High-flow nasal oxygen</td>
</tr>
<tr>
<td>HFOV</td>
<td>High-frequency oscillatory ventilation</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>hUC-MSCs</td>
<td>Human umbilical cord mesenchymal stem cells</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
</tr>
<tr>
<td>IFN-κ</td>
<td>Interferon kappa</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IHPS</td>
<td>Infantile hypertrophic pyloric stenosis</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IU</td>
<td>International units</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of diet in renal disease</td>
</tr>
<tr>
<td>MERS</td>
<td>Middle East respiratory syndrome</td>
</tr>
<tr>
<td>MET</td>
<td>Medical Emergency Team</td>
</tr>
<tr>
<td>MIS-C</td>
<td>Multisystem inflammatory syndrome in children</td>
</tr>
<tr>
<td>mIU</td>
<td>Milli-international units</td>
</tr>
<tr>
<td>MHT</td>
<td>Menopausal hormone therapy</td>
</tr>
<tr>
<td>NAe</td>
<td>Neutralising antibodies</td>
</tr>
<tr>
<td>NC19CET</td>
<td>National COVID-19 Clinical Evidence Taskforce</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Non-invasive positive pressure ventilation</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-invasive ventilation</td>
</tr>
<tr>
<td>NMBAe</td>
<td>Neuromuscular blocking agents</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PaO2</td>
<td>Partial pressure of arterial oxygen</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>PICU</td>
<td>Paediatric intensive care unit</td>
</tr>
<tr>
<td>PICS</td>
<td>Post-intensive care syndrome</td>
</tr>
<tr>
<td>PIMS-TS</td>
<td>Paediatric multisystem inflammatory syndrome - temporally associated with SARS-CoV-2</td>
</tr>
<tr>
<td>PPE</td>
<td>Personal protective equipment</td>
</tr>
<tr>
<td>RACS</td>
<td>Royal Australasian College of Surgeons</td>
</tr>
<tr>
<td>rhG-CSF</td>
<td>Recombinant human granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td>RR</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcription-polymerase chain reaction</td>
</tr>
<tr>
<td>SAEs</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe acute respiratory syndrome</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus 2 (the virus that causes the disease COVID-19)</td>
</tr>
<tr>
<td>SOT</td>
<td>Supplementary oxygen therapy</td>
</tr>
<tr>
<td>SpO2</td>
<td>Oxygen saturation</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>TFF2</td>
<td>Trefoil factor 2</td>
</tr>
<tr>
<td>TID</td>
<td>Three times a day</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>VA ECMO</td>
<td>Venoarterial extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>VV ECMO</td>
<td>Venovenous extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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