Australian guidelines for the clinical care of people with COVID-19

NATIONAL
COVID-19
CLINICAL
EVIDENCE
TASKFORCE

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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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Summary of recommendations

1. Reading Guide

2. Introduction

3. Methods and processes

4. Definition of disease severity

4.1. Definition of disease severity for adults

Consensus recommendation

Mild illness	Adults not presenting any clinical features suggestive of moderate or severe disease or a complicated course of illness. Characteristics: • no symptoms • or mild upper respiratory tract symptoms • or cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation
Moderate illness	Stable adult patient presenting with respiratory and/or systemic symptoms or signs. Able to maintain oxygen saturation above 92% (or above 90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs. Characteristics: • prostration, severe asthenia, fever > 38˚C or persistent cough • clinical or radiological signs of lung involvement • no clinical or laboratory indicators of clinical severity or respiratory impairment
Severe illness	Adult patients meeting any of the following criteria: • respiratory rate ≥ 30 breaths/min • oxygen saturation ≤ 92% at a rest state • arterial partial pressure of oxygen (PaO2)/ inspired oxygen fraction (FiO2) ≤ 300
Critical illness	Adult patient meeting any of the following criteria: Respiratory failure • Occurrence of severe respiratory failure (PaO2/FiO2 < 200), respiratory distress or acute respiratory distress syndrome (ARDS). This includes patients deteriorating despite advanced forms of respiratory support (non-invasive ventilation (NIV), high-flow nasal oxygen (HFNO)) OR patients requiring mechanical ventilation. OR other signs of significant deterioration • hypotension or shock • impairment of consciousness • other organ failure

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.

	Feeding / hydration / conscious state	**Respiratory / vital signs**	**Oxygen requirement**[1]
Mild illness	Normal or mildly reduced feeding	No or mild upper respiratory tract symptoms OR No or mild work of breathing	No supplemental oxygen required to maintain SpO_2 > 92%
Moderate illness	Poor feeding, unable to maintain hydration without nasogastric or IV fluids AND Normal conscious state	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)	Requires low-flow oxygen (nasal prongs or mask) to maintain SpO_2 > 92%
Severe illness	Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable	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)	Requires high-flow oxygen at 2 L/kg/min[3] to maintain SpO_2 > 92%
Critical illness	Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious	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	Requires advanced modes of support to maintain oxygenation High-flow nasal oxygen at > 2 L/kg/min[3] OR Non-invasive ventilation OR Intubation and mechanical ventilation OR Extracorporeal membrane oxygenation (ECMO)

[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.

6. Disease-modifying treatments

6.1. Baricitinib

6.1.1. Baricitinib for adults

Conditional recommendation

Consider using baricitinib for adults hospitalised with COVID-19 who require supplemental oxygen, high-flow oxygen and/or non-invasive ventilation.

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.

Given the uncertainty regarding the effectiveness of bariticinib in patients who require mechanical ventilation, further evidence is required to inform care in this population.

6.1.2. Baricitinib for pregnant or breastfeeding women

6.2. Corticosteroids

6.2.1. 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.

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.

6.2.2. 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).

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

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.

6.2.3. Corticosteroids for children or 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.

Conditional recommendation against

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

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

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

6.3. Remdesivir

6.3.1. Remdesivir for adults

Conditional recommendation

Consider using remdesivir for adults 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.

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 *[52]*. 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.

Not recommended

Do not start remdesivir in adults 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).

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.

6.3.2. Remdesivir for pregnant or breastfeeding women

Conditional recommendation

Consider using remdesivir for 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 *[52]*. 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, 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 *[47]*.

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.

6.3.3. Remdesivir for children or adolescents

Conditional recommendation against

Use of remdesivir for children or 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.

Due to antagonism observed *in vitro*, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended *[47]*.

6.4. Sarilumab

6.4.1. 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.

6.4.2. Sarilumab for pregnant or breastfeeding women

6.5. Tocilizumab

6.5.1. 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).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved. 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 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.

6.5.2. Tocilizumab for pregnant or breastfeeding women

Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 for 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, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved. 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.

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.

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

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.

6.5.3. Tocilizumab for children or 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 and adolescents. (The Taskforce notes that RECOVERY is recruiting children and adolescents with PIMS-TS for their trial of tocilizumab *[90]*.) Tocilizumab should be administered as a single intravenous infusion over 60 minutes, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved. 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 *[89]*
- < 30 kg: 12 mg/kg
- ≥ 30 kg: 8 mg/kg (max 800 mg)

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.

6.6. 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.

6.7. 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.

6.8. Convalescent plasma

Not recommended

Do not use convalescent plasma 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 convalescent plasma may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include convalescent plasma.

6.9. 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.

6.10. 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.

6.11. 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.

6.12. Interferon β-1a plus lopinavir-ritonavir

Not recommended

Do not use intravenous interferon β-1a plus lopinavir-ritonavir 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 intravenous interferon β-1a nor lopinavir-ritonavir as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

6.13. Lopinavir-ritonavir

Not recommended

Do not use lopinavir-ritonavir 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 lopinavir-ritonavir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include lopinavir-ritonavir.

6.14. Disease-modifying treatments not recommended outside of clinical trials

6.14.1. Angiotensin 2 receptor agonist (C21)

Not recommended

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.

6.14.2. Anakinra

Not recommended

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.

6.14.3. Aprepitant

Not recommended

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.

6.14.4. Baloxavir marboxil

Not recommended

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.

6.14.5. Bamlanivimab

Not recommended

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.

6.14.6. Bamlanivimab plus etesevimab

Not recommended

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.

6.14.7. Bromhexine hydrochloride

Not recommended

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.

6.14.8. Budesonide

Not recommended

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

Remark: Budesonide 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 budesonide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

6.14.9. Camostat mesilate

Not recommended

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.

6.14.10. Chloroquine

Not recommended

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.

6.14.11. Combined metabolic cofactor supplementation (CMCS)

Not recommended

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

Remark: Combined metabolic cofactor supplementation (CMCS) 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 CMCS to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

6.14.12. CT-P59 monoclonal antibody

Not recommended

Do not use the monoclonal antibody CT-P59 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 CT-P59 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

6.14.13. Darunavir-cobicistat

Not recommended

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.

6.14.14. Dutasteride

Not recommended

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.

6.14.15. Enisamium

Not recommended

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.

6.14.16. Favipiravir

Not recommended

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.

6.14.17. Fluvoxamine

Not recommended

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.

6.14.18. Human umbilical cord mesenchymal stem cells

Not recommended

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.

6.14.19. Interferon β-1a (inhaled)

Not recommended

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.

6.14.20. Interferon β-1b

Not recommended

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.

6.14.21. Interferon gamma

Not recommended

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

Remark: 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.

6.14.22. Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)

Not recommended

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.

6.14.23. Intravenous immunoglobulin

Not recommended

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.

6.14.24. Intravenous immunoglobulin plus methylprednisolone

Not recommended

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.

6.14.25. Ivermectin

Not recommended

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.

6.14.26. Ivermectin plus doxycycline

Not recommended

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.

6.14.27. Lenzilumab

Not recommended

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.

6.14.28. N-acetylcysteine

Not recommended

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.

6.14.29. Nitazoxanide

Not recommended

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.

6.14.30. Peginterferon lambda

Not recommended

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.

6.14.31. Recombinant human granulocyte colony-stimulating factor (rhG-CSF)

Not recommended

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.

6.14.32. REGN-COV2

Not recommended

Do not use REGN-COV2 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 REGN-COV2 for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

6.14.33. Ruxolitinib

Not recommended

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.

6.14.34. Sofosbuvir-daclatasvir

Not recommended

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.

6.14.35. Sulodexide

Not recommended

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

Remark: 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.

6.14.36. Telmisartan

Not recommended

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.

6.14.37. Triazavirin

Not recommended

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.

6.14.38. Umifenovir

Not recommended

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.

6.14.39. Vitamin C

Not recommended

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.

6.14.40. Vitamin D analogues (calcifediol/cholecalciferol)

Not recommended

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.

6.14.41. Zinc

Not recommended

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.

6.14.42. 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.

6.15. Disease-modifying treatments under review

6.15.1. Aspirin

6.15.2. Sotrovimab

7. Chemoprophylaxis

7.1. 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.

7.2. Hydroxychloroquine for post-exposure prophylaxis

Not recommended

For people exposed to individuals with severe acute respiratory syndrome coronavirus 2 (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.

8. Respiratory support in adults

Consensus recommendation

Guiding principles of care
For patients with COVID-19 for whom respiratory support (HFNO/NIV) is being considered, decisions should balance likelihood of patient benefit against the risk of infection for healthcare workers. For patients with COVID-19 receiving respiratory support (HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place. Closed circuit NIV should be used.

Remark: The relative risk of infection to healthcare workers associated with specific oxygen therapies remains uncertain and may vary from site to site.

8.1. High-flow nasal oxygen therapy

Info Box

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where oxygen is delivered, often in conjunction with compressed air and humidification. It delivers high flow oxygen via large diameter nasal cannula that is humidified and heated. Flow rates can be given up to 60 L/min with an oxygen/air blender supplying oxygen at 21–100%.

High-flow humidified oxygen should be considered when unable to maintain SaO2 ≥ 92% despite conventional oxygen delivery at > 6 L/min or an FiO2 = 0.4.

Conditional recommendation

Consider using HFNO therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If HFNO is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only.

Remark: Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

Not recommended

Do not use HFNO therapy for patients with hypoxaemia associated with COVID-19 in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval.

8.2. Non-invasive ventilation

Info Box

Non-invasive ventilation (NIV), also known as non-invasive positive pressure ventilation (NIPPV) or bilevel positive pressure support (BiPAP), is a form of respiratory support. Bilevel positive pressure is delivered throughout the respiratory cycle by a firm-fitting nasal-face mask. The patient breathes spontaneously and triggers the device to cycle.

A higher level of pressure is provided during the inspiratory phase to enhance ventilation, while a lower level of continuous positive pressure is delivered during the expiratory phase (also known as positive end-expiratory pressure or PEEP). Supplemental oxygen can also be delivered through the device.

Conditional recommendation

Consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If NIV is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only.

Not recommended

Do not use NIV therapy for patients with hypoxaemia associated with COVID-19 in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval.

Conditional recommendation

In patients with COVID-19 for whom NIV is appropriate for an alternate clinical presentation (e.g. concomitant chronic obstructive pulmonary disease (COPD) with type 2 respiratory failure and hypercapnia, acute pulmonary oedema), ensure airborne and other infection control precautions are optimised.

8.3. 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.

8.4. 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.

8.5. 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.

8.6. 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.

8.7. 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.

8.7.1. 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.

Consensus 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 it 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: 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 particularly 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, there is limited evidence to suggest prone positioning could be effective in improving oxygenation in patients 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.

8.7.2. 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.

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.

8.8. Recruitment manoeuvres

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.

8.9. 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.

8.9.1. 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.

8.9.2. 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

10. Venous thromboembolism (VTE) prophylaxis

10.1. VTE prophylaxis for adults

Consensus 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 or dalteparin 2500 IU 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.

Conditional recommendation against

Do not routinely offer therapeutic anticoagulant dosing in adults with 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.

Info Box

The Taskforce acknowledges the publication of two joint media releases from the REMAP-CAP, ACTIV-4 and ATTACC trial teams on 22 December 2020 [here] and 22 January 2021 [here]. The media releases noted that therapeutic doses of anticoagulation drugs may be more beneficial than lower doses for the prevention of VTE in hospitalised patients. However, among critically ill COVID-19 patients requiring intensive care unit (ICU) support, therapeutic doses of anticoagulation drugs did not reduce the need for organ support and a potential for harm in this subgroup could not be excluded; all trial sites have paused enrolment of this group of patients.

The results from the REMAP-CAP, ACTIV-4 and ATTACC study groups have been published for critical patients and have been used to inform current recommendations *[427]*. The Taskforce notes the preprint publication of the results in hospitalised non-critical patients (posted to medRxiv on 17 May 2021). These results are currently under review and an updated recommendation will be included in a future version of the guideline.

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.

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.

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.

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.

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.

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: 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

13.2. 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.

13.3. 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.

13.4. Skin-to-skin contact

Consensus recommendation

Early skin-to-skin contact after birth and during the postnatal period is supported, irrespective 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.

13.5. 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 breastmilk or formula, these same infection prevention and control measures should be used.

13.6. 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.

14. Child and adolescent care

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.

14.1. Paediatric Inflammatory Multisystem Syndrome (PIMS-TS)

Info Box

The Taskforce endorses the PIMS-TS case definition from the Royal College of Paediatrics and Child Health (United Kingdom) *[475]*.

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, thrombocytopaenia, 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

Consensus 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.

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 prior to, 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.

For selected cases of PIMS-TS with severe myocardial dysfunction, corticosteroid treatment alone and/or delayed use of IVIG may be beneficial.

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.

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)

15. 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.

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 newly discovered 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 *[369]*.

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
- CRANAplus
- National Aboriginal Community Controlled Health Organisation
- 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

Australian Government
National Health and Medical Research Council

Version 28 of these guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 11 February 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 28 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

- [APA style] National COVID-19 Clinical Evidence Taskforce. (2021 version 40.1). Australian guidelines for the clinical care of people with COVID-19. https://covid19evidence.net.au/
- [Vancouver style] National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. 2021 [version 40.1]. Available from: https://covid19evidence.net.au/

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

- Weekly updates of national living evidence-based guidelines: Methods for the Australian Living Guidelines for Care of People with COVID-19. Tendal et al. 2020 J Clin Epidemiol doi: 10.1016/j.jclinepi.2020.11.005.
- Clinical care of pregnant and postpartum women with COVID-19: Living recommendations from the National COVID-19 Clinical Evidence Taskforce. Vogel et al. 2020 ANZJOG doi: 10.1111/ajo.13270.

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

Definitions of disease severity for adults were developed by the Primary and Chronic Care Panel, Hospital and Acute Care Panel and Critical Care Panel. Definitions of disease severity for children and adolescents were developed by the Paediatric and Adolescent Care Panel.

Definitions were reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. In addition, all our definitions are reviewed by the Consumer Panel.

4.1. Definition of disease severity for adults

Consensus recommendation

Mild illness	Adults not presenting any clinical features suggestive of moderate or severe disease or a complicated course of illness. Characteristics: • no symptoms • or mild upper respiratory tract symptoms • or cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation
Moderate illness	Stable adult patient presenting with respiratory and/or systemic symptoms or signs. Able to maintain oxygen saturation above 92% (or above 90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs. Characteristics: • prostration, severe asthenia, fever > 38˚C or persistent cough • clinical or radiological signs of lung involvement • no clinical or laboratory indicators of clinical severity or respiratory impairment
Severe illness	Adult patients meeting any of the following criteria: • respiratory rate ≥ 30 breaths/min • oxygen saturation ≤ 92% at a rest state • arterial partial pressure of oxygen (PaO2)/ inspired oxygen fraction (FiO2) ≤ 300
Critical illness	Adult patient meeting any of the following criteria: Respiratory failure • Occurrence of severe respiratory failure (PaO2/FiO2 < 200), respiratory distress or acute respiratory distress syndrome (ARDS). This includes patients deteriorating despite advanced forms of respiratory support (non-invasive ventilation (NIV), high-flow nasal oxygen (HFNO)) OR patients requiring mechanical ventilation. OR other signs of significant deterioration • hypotension or shock • impairment of consciousness • other organ failure

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.

	Feeding / hydration / conscious state	**Respiratory / vital signs**	**Oxygen requirement**[1]
Mild illness	Normal or mildly reduced feeding	No or mild upper respiratory tract symptoms OR No or mild work of breathing	No supplemental oxygen required to maintain SpO_2 > 92%
Moderate illness	Poor feeding, unable to maintain hydration without nasogastric or IV fluids AND Normal conscious state	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)	Requires low-flow oxygen (nasal prongs or mask) to maintain SpO_2 > 92%
Severe illness	Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable	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)	Requires high-flow oxygen at 2 L/kg/min[3] to maintain SpO_2 > 92%
Critical illness	Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious	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	Requires advanced modes of support to maintain oxygenation High-flow nasal oxygen at > 2 L/kg/min[3] OR Non-invasive ventilation OR Intubation and mechanical ventilation OR Extracorporeal membrane oxygenation (ECMO)

[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 *[369]*, National Institute for the Infectious Diseases (Italy) *[16]* and Surviving Sepsis Campaign *[367]*. Wording has been adapted for clarity and applicability to the Australian context.

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

Category	Therapy
Agents that may have activity against SARS-CoV-2	Antimalarials Antivirals Convalescent plasma
Agents that may have activity against the associated cytokine-release syndrome	Tocilizumab Anakinra (IL1RA) Corticosteroids
Other and ancillary agents	ACE inhibitors NSAIDs
Blood purification systems for reducing cytokines in ICU	Cytokine removal

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. Baricitinib

6.1.1. Baricitinib for adults

Conditional recommendation

Consider using baricitinib for adults hospitalised with COVID-19 who require supplemental oxygen, high-flow oxygen and/or non-invasive ventilation.

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.

Given the uncertainty regarding the effectiveness of bariticinib in patients who require mechanical ventilation, further evidence is required to inform care in this population.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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 Moderate

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 Substantial variability is expected or uncertain

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 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

We have no systematically collected evidence regarding impact on equity, however this may be affected by geographic area and access to baricitinib.

Acceptability No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

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

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

Population: Patients 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 *[22]*, and one that compared baricitinib with standard care in 1525 adults with mild to severe COVID-19 *[24]*.

Publication status

One study is only available as a preprint (Marconi et al. posted to medRxiv on 3 May 2021) and has therefore not been peer reviewed.

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 Marconi et al., patients also received 4 mg baricitinib. Pregnant and breastfeeding women were ineligible.

What are the main results?

Baricitinib probably decreases mortality (40 fewer deaths per 1000 patients (RR 0.63, CI 95% 0.48 to 0.81; 2558 patients in 2 studies)) and serious adverse events (40 fewer SAEs per 1000 patients (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 & 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, known harms associated with baricitinib include an increased risk of serious infections, gastrointestinal disorders, thrombosis and headaches *[25]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.63 (CI 95% 0.48 — 0.81) Based on data from 2,558 patients in 2 studies. [1] (Randomized controlled)	107 per 1000	67 per 1000 Difference: **40 fewer** per 1000 (CI 95% 56 fewer — 20 fewer)	**Moderate** Due to serious imprecision [2]	Baricitinib probably decreases death slightly.
Invasive mechanical ventilation or ECMO End of follow-up 9 Critical	Relative risk 0.66 (CI 95% 0.46 — 0.93) Based on data from 922 patients in 1 studies. [3] (Randomized controlled)	152 per 1000	100 per 1000 Difference: **52 fewer** per 1000 (CI 95% 82 fewer — 11 fewer)	**Low** Due to very serious imprecision [4]	Baricitinib may decrease requirement for invasive mechanical ventilation or ECMO slightly (116 events).
Non-invasive ventilation or HFNO End of follow-up 6 Important	Relative risk 0.83 (CI 95% 0.63 — 1.1) Based on data from 706 patients in 1 studies. [5] (Randomized controlled)	236 per 1000	196 per 1000 Difference: **40 fewer** per 1000 (CI 95% 87 fewer — 24 more)	**Low** Due to very serious imprecision [6]	Baricitinib may decrease requirement for NIV / HFNO slightly (152 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.79 (CI 95% 0.67 — 0.94) Based on data from 2,518 patients in 2 studies. [7] (Randomized controlled)	192 per 1000	152 per 1000 Difference: **40 fewer** per 1000 (CI 95% 63 fewer — 12 fewer)	**Moderate** Due to serious imprecision [8]	Baricitinib probably reduces serious adverse events slightly.
Adverse events End of follow-up 6 Important	Relative risk 0.95 (CI 95% 0.87 — 1.04) Based on data from 2,535 patients in 2 studies. [9] (Randomized controlled)	451 per 1000	428 per 1000 Difference: **23 fewer** per 1000 (CI 95% 59 fewer — 18 more)	**Moderate** Due to serious imprecision [10]	Baricitinib probably has little or no difference on adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 0.8 (CI 95% 0.57 — 1.12) Based on data from 1,502 patients in 1 studies. [11] (Randomized controlled)	93 per 1000	74 per 1000 Difference: **19 fewer** per 1000 (CI 95% 40 fewer — 11 more)	**Low** Due to very serious imprecision [12]	Baricitinib may have little or no difference on discontinuation due to adverse events (126 events).
Clinical recovery End of follow-up	Relative risk 1.07 (CI 95% 1.01 — 1.14) Based on data from	784	839	**Low** Due to very serious	Baricitinib may increase clinical recovery.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	1,033 patients in 1 studies. [13] (Randomized controlled)	per 1000 Difference: 55 more per 1000 (CI 95% 8 more — 110 more)	per 1000	imprecision [14]	
Duration of hospitalisation Mean (days) 6 Important	Lower better (Randomized controlled)	13.7 (Mean) Difference: MD 0.8 lower CI 95%	12.9 (Mean)	**Low** Due to very serious imprecision [15]	We are uncertain whether baricitinib increases or decreases duration of hospitalisation.
Time to recovery Median (days) 6 Important	Lower better (Randomized controlled)	11 (Median) CI 95%	10 (Median)	**Low** Due to very serious imprecision [16]	We are uncertain whether baricitinib increases or decreases time to recovery.

1. Systematic review [23] with included studies: Marconi 2021, Kalil 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** due to only 2 studies.
3. Systematic review [21] with included studies: Kalil 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
5. Systematic review [21] with included studies: Kalil 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
7. Systematic review [23] with included studies: Kalil 2020, Marconi 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Serious.** due to 2 studies.
9. Systematic review [23] with included studies: Kalil 2020, Marconi 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Serious.** Wide confidence intervals.
11. Systematic review [23] with included studies: Marconi 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
13. Systematic review [21] with included studies: Kalil 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **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.**
15. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
16. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals.

6.1.2. Baricitinib for pregnant or breastfeeding women

6.2. Corticosteroids

6.2.1. 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).

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.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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

Moderate

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

No substantial variability expected

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 No important issues with the recommended alternative

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 No important issues with the recommended alternative

We have no systematically collected evidence regarding impact on equity. Since corticosteroids are widely available and affordable, no negative impact is expected.

Acceptability No important issues with the recommended alternative

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 No important issues with the recommended alternative

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 recent meta-analysis and associated living guidance *[28]* of seven randomised trials of patients with critical COVID-19 *[32][33][34][35][36][37][38]*, one study of patients with moderate, severe and critical COVID-19 *[39]*, and one study of patients with severe COVID-19 *[40]*. 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 *[29]* and sepsis *[30]*—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 *[37][35][39]*, three compared hydrocortisone with standard care *[36][34][32]* and three compared methylprednisolone with standard care *[33][38][40]*.

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
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 patients in 9 studies. [1] (Randomized controlled)	316 per 1000	265 per 1000 Difference: **51 fewer** per 1000 (CI 95% 85 fewer — 6 fewer)	**Moderate** Due to some inconsistency [2]	Corticosteroids probably decrease death at day 28 in adults who require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 patients in 6 studies. [3] (Randomized controlled)	234 per 1000	187 per 1000 Difference: **47 fewer** per 1000 (CI 95% 110 fewer — 44 more)	**Moderate** Due to serious inconsistency [4]	Corticosteroids probably have little impact on serious adverse events in adults who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 patients in 1 studies. [6] (Randomized controlled)	320 per 1000	282 per 1000 Difference: **38 fewer** per 1000 (CI 95% 67 fewer — 10 fewer)	**Moderate** Due to only one study [7]	Corticosteroids probably decrease invasive mechanical ventilation or death in adults who require oxygen.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 patients in 2 studies. [8] (Randomized controlled)	582 per 1000	640 per 1000 Difference: **58 more** per 1000 (CI 95% 35 more — 87 more)	**Moderate** Due to serious inconsistency [9]	Corticosteroids probably increases discharge from hospital in adults who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 patients in 1 studies. [10] (Randomized controlled)	140 per 1000	178 per 1000 Difference: **38 more** per 1000 (CI 95% 0 fewer — 85 more)	**Moderate** Due to only one study [11]	Corticosteroids probably increase death in adults who do not require oxygen.
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days of	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 patients in 1 studies. [12] (Randomized controlled)	155 per 1000	194 per 1000 Difference: **39 more** per 1000 (CI 95% 0 fewer — 88 more)	**Moderate** Due to only one study [13]	Corticosteroids probably increase invasive mechanical ventilation or death in adults who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
commencing treatment 9 Critical					
Discharge from hospital [adults not requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 patients in 1 studies. [14] (Randomized controlled)	804 per 1000	772 per 1000 Difference: **32 fewer** per 1000 (CI 95% 80 fewer — 8 more)	**Moderate** Due to only one study [15]	Corticosteroids may have little impact on discharge from hospital in adults who do not require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 patients in 30 studies. [16]	48 per 1000	51 per 1000 Difference: **3 more** per 1000 (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 patients in 32 studies. [17]	186 per 1000	188 per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 patients in 24 studies. [18]	286 per 1000	332 per 1000 Difference: **46 more** per 1000 (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 patients in 8 studies. [19]	69 per 1000	75 per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 patients in 7 studies. [20]	35 per 1000	28 per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.

1. Systematic review [26] with included studies: CAPE COVID 2020, CoDEX 2020, Steroids-SARI 2020, DEXA-COVID 19 2020, Edalatifard 2020, REMAP-CAP 2020, RECOVERY, COVID STEROID 2020, METCOVID 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies.
3. Systematic review [27] with included studies: DEXA-COVID 19 2020, REMAP-CAP 2020, COVID STEROID 2020, CoDEX 2020, Steroids-SARI 2020, CAPE COVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: Serious.** Only data from one study.
8. Systematic review [26] with included studies: RECOVERY, RECOVERY, Edalatifard 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [27] 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 [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Imprecision: Serious.** Only data from one study.
14. Systematic review [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Imprecision: Serious.** Only data from one study.
16. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
20. Systematic review [28] . **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.

Evidence To Decision

Benefits and harms Important 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 Low

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 expect few to want the intervention

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 — No important issues with the recommended alternative

There are no identified resource issues as the recommendation reflects usual care.

Equity — No important issues with the recommended alternative

There are no identified equity issues as the recommendation reflects usual care.

Acceptability — Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility — No important issues with the recommended alternative

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 recent meta-analysis and associated living guidance *[28]* of seven randomised trials of patients with critical COVID-19 *[32][33][34][35][36][37][38]*, one study of patients with moderate, severe and critical COVID-19 *[39]*, and one study of patients with severe COVID-19 *[40]*. 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 *[29]* and sepsis *[30]*—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 *[37][35][39]*, three compared hydrocortisone with standard care *[36][34][32]* and three compared methylprednisolone with standard care *[33][38][40]*.

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
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [adults requiring oxygen] Within 28 days of	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 patients in 9 studies. [1] (Randomized	316 per 1000 Difference: **51 fewer** per 1000	265 per 1000	**Moderate** Due to some inconsistency [2]	Corticosteroids probably decrease death at day 28 in adults who require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
commencing treatment 9 Critical	controlled)	(CI 95% 85 fewer — 6 fewer)			
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 patients in 6 studies. [3] (Randomized controlled)	234 per 1000	187 per 1000 Difference: **47 fewer** per 1000 (CI 95% 110 fewer — 44 more)	**Moderate** Due to serious inconsistency [4]	Corticosteroids probably have little impact on serious adverse events in adults who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 patients in 1 studies. [6] (Randomized controlled)	320 per 1000	282 per 1000 Difference: **38 fewer** per 1000 (CI 95% 67 fewer — 10 fewer)	**Moderate** Due to only one study [7]	Corticosteroids probably decrease invasive mechanical ventilation or death in adults who require oxygen.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 patients in 2 studies. [8] (Randomized controlled)	582 per 1000	640 per 1000 Difference: **58 more** per 1000 (CI 95% 35 more — 87 more)	**Moderate** Due to serious inconsistency [9]	Corticosteroids probably increases discharge from hospital in adults who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 patients in 1 studies. [10] (Randomized controlled)	140 per 1000	178 per 1000 Difference: **38 more** per 1000 (CI 95% 0 fewer — 85 more)	**Moderate** Due to only one study [11]	Corticosteroids probably increase death in adults who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 patients in 1 studies. [12] (Randomized controlled)	155 per 1000	194 per 1000 Difference: 39 more per 1000 (CI 95% 0 fewer — 88 more)	Moderate Due to only one study [13]	Corticosteroids probably increase invasive mechanical ventilation or death in adults who do not require oxygen.
Discharge from hospital [adults not requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 patients in 1 studies. [14] (Randomized controlled)	804 per 1000	772 per 1000 Difference: 32 fewer per 1000 (CI 95% 80 fewer — 8 more)	Moderate Due to only one study [15]	Corticosteroids may have little impact on discharge from hospital in adults who do not require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 patients in 30 studies. [16]	48 per 1000	51 per 1000 Difference: 3 more per 1000 (CI 95% 7 fewer — 16 more)	Low Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 patients in 32 studies. [17]	186 per 1000	188 per 1000 Difference: 2 more per 1000 (CI 95% 19 fewer — 24 more)	Low Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 patients in 24 studies. [18]	286 per 1000	332 per 1000 Difference: 46 more per 1000 (CI 95% 23 more — 72 more)	Moderate Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 patients in 8 studies. [19]	69 per 1000	75 per 1000 Difference: 6 more per 1000 (CI 95% 10 fewer — 27 more)	Low Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 patients in 7 studies. [20]	35 per 1000	28 per 1000 Difference: 7 fewer per 1000 (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.

1. Systematic review [26] with included studies: CAPE COVID 2020, CoDEX 2020, Steroids-SARI 2020, DEXA-COVID 19 2020, Edalatifard 2020, REMAP-CAP 2020, RECOVERY, COVID STEROID 2020, METCOVID 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies.
3. Systematic review [27] with included studies: DEXA-COVID 19 2020, REMAP-CAP 2020, COVID STEROID 2020, CoDEX 2020, Steroids-SARI 2020, CAPE COVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: Serious.** Only data from one study.
8. Systematic review [26] with included studies: RECOVERY, RECOVERY, Edalatifard 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [27] 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 [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Imprecision: Serious.** Only data from one study.
14. Systematic review [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
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19. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
20. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.

6.2.2. 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).

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*

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

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 *[?]*.

Certainty of the Evidence — Low

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 — No substantial variability expected

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 — No important issues with the recommended alternative

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 — No important issues with the recommended alternative

We have no systematically collected evidence regarding impact on equity. Since corticosteroids are widely available and affordable, no negative impact is expected.

Acceptability — No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, corticosteroids are likely to be acceptable to both patients and clinicians.

Feasibility No important issues with the recommended alternative

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 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).

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 recent meta-analysis and associated living guidance *[28]* of seven randomised trials of patients with critical COVID-19 *[32][33][34][35][36][37][38]*, one study of patients with moderate, severe and critical COVID-19 *[39]* and one study of patients with severe COVID-19 *[40]*. 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 *[29]* and sepsis *[30]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[37][35][39]*, three compared hydrocortisone with standard care *[36][34][32]* and three compared methylprednisolone with standard care *[33][38][40]*.

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** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 patients in 9 studies. [1] (Randomized controlled)	316 per 1000	265 per 1000 Difference: **51 fewer** per 1000 (CI 95% 85 fewer — 6 fewer)	**Low** Due to serious inconsistency and serious indirectness [2]	Corticosteroids may decrease death at day 28 in patients who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 patients in 6 studies. [3] (Randomized controlled)	234 per 1000	187 per 1000 Difference: **47 fewer** per 1000 (CI 95% 110 fewer — 44 more)	**Low** Due to serious inconsistency and indirectness [4]	Corticosteroids may have little impact on serious adverse events in patients who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days after commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 patients in 1 studies. [6] (Randomized controlled)	320 per 1000	282 per 1000 Difference: **38 fewer** per 1000 (CI 95% 67 fewer — 10 fewer)	**Low** Due to only one study and serious indirectness [7]	Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 patients in 1 studies. [8] (Randomized controlled)	140 per 1000	178 per 1000 Difference: **38 more** per 1000 (CI 95% 0 fewer — 85 more)	**Low** Due to only one study and serious indirectness [9]	Corticosteroids may increase death in patients who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 patients in 1 studies. [10] (Randomized controlled)	155 per 1000	194 per 1000 Difference: **39 more** per 1000 (CI 95% 0 fewer — 88 more)	**Low** Due to only one study and serious indirectness [11]	Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 patients in 1 studies. [12] (Randomized controlled)	804 per 1000	772 per 1000 Difference: **32 fewer** per 1000 (CI 95% 80 fewer — 8 more)	**Low** Due to only one study and serious indirectness [13]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 patients in 30 studies. [14]	48 per 1000	51 per 1000 Difference: **3 more** per 1000 (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 patients in 32 studies. [15]	186 per 1000	188 per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 patients in 24 studies. [16]	286 per 1000	332 per 1000 Difference: **46 more** per 1000 (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 patients in 8 studies. [17]	69 per 1000	75 per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 patients in 7 studies. [18]	35 per 1000	28 per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 patients in 2 studies. [19] (Randomized controlled)	582 per 1000	640 per 1000 Difference: **58 more** per 1000 (CI 95% 35 more — 87 more)	**Low** Due to serious inconsistency and serious indirectness [20]	Corticosteroids may increase discharge from hospital in patients who require oxygen.

1. Systematic review [41] with included studies: COVID STEROID 2020, REMAP-CAP 2020, Edalatifard 2020, RECOVERY, Steroids-SARI 2020, DEXA-COVID 19 2020, CAPE COVID 2020, METCOVID 2020, CoDEX 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [27] with included studies: Steroids-SARI 2020, REMAP-CAP 2020, CAPE COVID 2020, CoDEX 2020, DEXA-COVID 19 2020, COVID STEROID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [27] 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 [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study, Wide confidence intervals.
10. Systematic review [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
12. Systematic review [27] 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 [28] . **Baseline/comparator:** Control arm of reference used for intervention.
15. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.

18. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [41] with included studies: RECOVERY, RECOVERY, Edalatifard 2020. **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 **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.

Evidence To Decision

Benefits and harms — Important 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 — Low

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 expect few to want the intervention

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 — No important issues with the recommended alternative

There are no identified resource issues as the recommendation reflects usual care.

Equity — No important issues with the recommended alternative

There are no identified equity issues as the recommendation reflects usual care.

Acceptability — Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility No important issues with the recommended alternative

There are no identified feasibility issues as the recommendation reflects usual care.

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 recent meta-analysis and associated living guidance *[28]* of seven randomised trials of patients with critical COVID-19 *[32][33][34][35][36][37][38]*, one study of patients with moderate, severe and critical COVID-19 *[39]* and one study of patients with severe COVID-19 *[40]*. 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 *[29]* and sepsis *[30]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[37][35][39]*, three compared hydrocortisone with standard care *[36][34][32]* and three compared methylprednisolone with standard care *[33][38][40]*.

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** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 patients in 9 studies. [1] (Randomized controlled)	316 per 1000	265 per 1000 Difference: **51 fewer** per 1000 (CI 95% 85 fewer — 6 fewer)	**Low** Due to serious inconsistency and serious indirectness [2]	Corticosteroids may decrease death at day 28 in patients who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 patients in 6 studies. [3] (Randomized controlled)	234 per 1000	187 per 1000 Difference: **47 fewer** per 1000 (CI 95% 110 fewer — 44 more)	**Low** Due to serious inconsistency and indirectness [4]	Corticosteroids may have little impact on serious adverse events in patients who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days after commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 patients in 1 studies. [6] (Randomized controlled)	320 per 1000	282 per 1000 Difference: **38 fewer** per 1000 (CI 95% 67 fewer — 10 fewer)	**Low** Due to only one study and serious indirectness [7]	Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days after commencing	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 patients in 1 studies. [8] (Randomized controlled)	140 per 1000	178 per 1000 Difference: **38 more** per 1000 (CI 95% 0 fewer — 85 more)	**Low** Due to only one study and serious indirectness [9]	Corticosteroids may increase death in patients who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
treatment 9 Critical					
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 patients in 1 studies. [10] (Randomized controlled)	155 per 1000	194 per 1000 Difference: **39 more** per 1000 (CI 95% 0 fewer — 88 more)	**Low** Due to only one study and serious indirectness [11]	Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 patients in 1 studies. [12] (Randomized controlled)	804 per 1000	772 per 1000 Difference: **32 fewer** per 1000 (CI 95% 80 fewer — 8 more)	**Low** Due to only one study and serious indirectness [13]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 patients in 30 studies. [14]	48 per 1000	51 per 1000 Difference: **3 more** per 1000 (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 patients in 32 studies. [15]	186 per 1000	188 per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 patients in 24 studies. [16]	286 per 1000	332 per 1000 Difference: **46 more** per 1000 (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 patients in 8 studies. [17]	69 per 1000	75 per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 patients in 7 studies. [18]	35 per 1000	28 per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 patients in 2 studies. [19] (Randomized controlled)	582 per 1000	640 per 1000 Difference: **58 more** per 1000 (CI 95% 35 more — 87 more)	**Low** Due to serious inconsistency and serious indirectness [20]	Corticosteroids may increase discharge from hospital in patients who require oxygen.

1. Systematic review [41] with included studies: COVID STEROID 2020, REMAP-CAP 2020, Edalatifard 2020, RECOVERY, Steroids-SARI 2020, DEXA-COVID 19 2020, CAPE COVID 2020, METCOVID 2020, CoDEX 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [27] with included studies: Steroids-SARI 2020, REMAP-CAP 2020, CAPE COVID 2020, CoDEX 2020, DEXA-COVID 19 2020, COVID STEROID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [27] 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 [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study, Wide confidence intervals.
10. Systematic review [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
12. Systematic review [27] 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 [28] . **Baseline/comparator:** Control arm of reference used for intervention.
15. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [41] with included studies: RECOVERY, RECOVERY, Edalatifard 2020. **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.

6.2.3. Corticosteroids for children or 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.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

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 — Low

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 — No substantial variability expected

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.

Resources No important issues with the recommended alternative

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 No important issues with the recommended alternative

We have no systematically collected evidence regarding impact on equity. Since corticosteroids are widely available and affordable, no negative impact is expected.

Acceptability No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, corticosteroids are likely to be acceptable to both patients and clinicians.

Feasibility No important issues with the recommended alternative

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 considering using corticosteroids in children and adolescents with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

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 recent meta-analysis and associated living guidance *[28]* of seven randomised trials of patients with critical COVID-19 *[32][33][34][35][36][37][38]*, one study of patients with moderate, severe and critical COVID-19 *[39]* and one study of patients with severe COVID-19 *[40]*. 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 *[29]* and sepsis *[30]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[37][35][39]*, three compared hydrocortisone with standard care *[36][34][32]* and three compared methylprednisolone with standard care *[33][38][40]*.

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** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 patients in 9 studies. [1] (Randomized controlled)	316 per 1000	265 per 1000 Difference: **51 fewer** per 1000 (CI 95% 85 fewer — 6 fewer)	**Low** Due to serious inconsistency and serious indirectness [2]	Corticosteroids may decrease death at day 28 in patients who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 patients in 6 studies. [3] (Randomized controlled)	234 per 1000	187 per 1000 Difference: **47 fewer** per 1000 (CI 95% 110 fewer — 44 more)	**Low** Due to serious inconsistency and indirectness [4]	Corticosteroids may have little impact on serious adverse events in patients who require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important **Invasive mechanical ventilation or death [adults requiring oxygen]** [5] Within 28 days after commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 patients in 1 studies. [6] (Randomized controlled)	320 per 1000	282 per 1000 Difference: **38 fewer** per 1000 (CI 95% 67 fewer — 10 fewer)	**Low** Due to only one study and serious indirectness [7]	Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 patients in 1 studies. [8] (Randomized controlled)	140 per 1000	178 per 1000 Difference: **38 more** per 1000 (CI 95% 0 fewer — 85 more)	**Low** Due to only one study and serious indirectness [9]	Corticosteroids may increase death in patients who do not require oxygen.
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 patients in 1 studies. [10] (Randomized controlled)	155 per 1000	194 per 1000 Difference: **39 more** per 1000 (CI 95% 0 fewer — 88 more)	**Low** Due to only one study and serious indirectness [11]	Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 patients in 1 studies. [12] (Randomized controlled)	804 per 1000	772 per 1000 Difference: **32 fewer** per 1000 (CI 95% 80 fewer — 8 more)	**Low** Due to only one study and serious indirectness [13]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important					
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 patients in 30 studies. [14]	48 per 1000	51 per 1000 Difference: **3 more** per 1000 (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 patients in 32 studies. [15]	186 per 1000	188 per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 patients in 24 studies. [16]	286 per 1000	332 per 1000 Difference: **46 more** per 1000 (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 patients in 8 studies. [17]	69 per 1000	75 per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 patients in 7 studies. [18]	35 per 1000	28 per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 patients in 2 studies. [19] (Randomized controlled)	582 per 1000	640 per 1000 Difference: **58 more** per 1000 (CI 95% 35 more — 87 more)	**Low** Due to serious inconsistency and serious indirectness [20]	Corticosteroids may increase discharge from hospital in patients who require oxygen.

1. Systematic review [41] with included studies: COVID STEROID 2020, REMAP-CAP 2020, Edalatifard 2020,

RECOVERY, Steroids-SARI 2020, DEXA-COVID 19 2020, CAPE COVID 2020, METCOVID 2020, CoDEX 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [27] with included studies: Steroids-SARI 2020, REMAP-CAP 2020, CAPE COVID 2020, CoDEX 2020, DEXA-COVID 19 2020, COVID STEROID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [27] 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 [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study, Wide confidence intervals.
10. Systematic review [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
12. Systematic review [27] 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 [28] . **Baseline/comparator:** Control arm of reference used for intervention.
15. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [41] with included studies: RECOVERY, RECOVERY, Edalatifard 2020. **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 or adolescents who do not require oxygen**.

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

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

Evidence To Decision

Benefits and harms Important 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 Low

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 expect few to want the intervention

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 No important issues with the recommended alternative

There are no identified resource issues as the recommendation reflects usual care.

Equity No important issues with the recommended alternative

There are no identified equity issues as the recommendation reflects usual care.

Acceptability Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility No important issues with the recommended alternative

There are no identified feasibility 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 recent meta-analysis and associated living guidance *[28]* of seven randomised trials of patients with critical COVID-19 *[32][33][34][35][36][37][38]*, one study of patients with moderate, severe and critical COVID-19 *[39]* and one study of patients with severe COVID-19 *[40]*. 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 *[29]* and sepsis *[30]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[37][35][39]*, three compared hydrocortisone with standard care *[36][34][32]* and three compared methylprednisolone with standard care *[33][38][40]*.

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** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text 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 patients in 9 studies. [1] (Randomized controlled)	316 per 1000	265 per 1000 Difference: **51 fewer** per 1000 (CI 95% 85 fewer — 6 fewer)	**Low** Due to serious inconsistency and serious indirectness [2]	Corticosteroids may decrease death at day 28 in patients who require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical **Serious adverse events [adults requiring oxygen]** Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 patients in 6 studies. [3] (Randomized controlled)	234 per 1000	187 per 1000 Difference: **47 fewer** per 1000 (CI 95% 110 fewer — 44 more)	**Low** Due to serious inconsistency and indirectness [4]	Corticosteroids may have little impact on serious adverse events in patients who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days after commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 patients in 1 studies. [6] (Randomized controlled)	320 per 1000	282 per 1000 Difference: **38 fewer** per 1000 (CI 95% 67 fewer — 10 fewer)	**Low** Due to only one study and serious indirectness [7]	Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 patients in 1 studies. [8] (Randomized controlled)	140 per 1000	178 per 1000 Difference: **38 more** per 1000 (CI 95% 0 fewer — 85 more)	**Low** Due to only one study and serious indirectness [9]	Corticosteroids may increase death in patients who do not require oxygen.
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days after commencing treatment	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 patients in 1 studies. [10] (Randomized controlled)	155 per 1000	194 per 1000 Difference: **39 more** per 1000 (CI 95% 0 fewer — 88 more)	**Low** Due to only one study and serious indirectness [11]	Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical					
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 patients in 1 studies. [12] (Randomized controlled)	804 per 1000	772 per 1000 Difference: **32 fewer** per 1000 (CI 95% 80 fewer — 8 more)	**Low** Due to only one study and serious indirectness [13]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.
6 Important					
Gastrointestinal bleeding End of treatment	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 patients in 30 studies. [14]	48 per 1000	51 per 1000 Difference: **3 more** per 1000 (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
6 Important					
Super infections End of treatment	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 patients in 32 studies. [15]	186 per 1000	188 per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
6 Important					
Hyperglycaemia End of treatment	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 patients in 24 studies. [16]	286 per 1000	332 per 1000 Difference: **46 more** per 1000 (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
6 Important					
Neuromuscular weakness End of treatment	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 patients in 8 studies. [17]	69 per 1000	75 per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.
6 Important					
Neuropsychiatric effects End of treatment	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 patients in 7 studies. [18]	35 per 1000	28 per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.
6 Important					

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 patients in 2 studies. [19] (Randomized controlled)	582 per 1000	640 per 1000 Difference: 58 more per 1000 (CI 95% 35 more — 87 more)	**Low** Due to serious inconsistency and serious indirectness [20]	Corticosteroids may increase discharge from hospital in patients who require oxygen.

1. Systematic review [41] with included studies: COVID STEROID 2020, REMAP-CAP 2020, Edalatifard 2020, RECOVERY, Steroids-SARI 2020, DEXA-COVID 19 2020, CAPE COVID 2020, METCOVID 2020, CoDEX 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [27] with included studies: Steroids-SARI 2020, REMAP-CAP 2020, CAPE COVID 2020, CoDEX 2020, DEXA-COVID 19 2020, COVID STEROID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [27] 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 [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study, Wide confidence intervals.
10. Systematic review [27] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
12. Systematic review [27] 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 [28] . **Baseline/comparator:** Control arm of reference used for intervention.
15. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [28] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [41] with included studies: RECOVERY, RECOVERY, Edalatifard 2020. **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.

6.3. Remdesivir

6.3.1. Remdesivir for adults

Conditional recommendation

Consider using remdesivir for adults 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.

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 [52]. 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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Moderate

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

No substantial variability expected

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 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, 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

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 Important issues, or potential issues not investigated

On 10 July, the Therapeutic Goods Administration granted provisional approval to use remdesivir in hospitalised adults with severe COVID-19 symptoms (requiring oxygen or high-level support to breathe). 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 *[52]*. 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: 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 five randomised trials that compared remdesivir with standard care in 7415 adults hospitalised with COVID-19 *[44][45][48][51][62]*. The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 5451 and 1062 patients with moderate to critical COVID-19 *[51][44]*.

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).

Disease severity	Number of patients	References
Moderate	666	*[48][62]*
Moderate-Critical	6513	*[44][51]*
Severe-Critical	236	*[45]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (22 fewer deaths per 1000 patients (RR 0.76, CI 95% 0.57 to 1.02; 6400 patients in 5 studies)), and probably increases death at day 28 in patients who require ventilation (50 more deaths per 1000 patients (RR 1.20 CI 95% 0.98 to 1.47; 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 eight-point WHO ordinal scale *[44]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[48]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[48]* or 6-point ordinal scale *[45]*.

Compared with standard care, remdesivir probably reduces serious adverse events (63 fewer SAEs per 1000 patients (RR 0.75, CI 95% 0.68 to 0.89; 1865 patients in 3 studies)). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation and number of patients discharged from hospital at day 28. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock, adverse events and discontinuation due to adverse events.

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, 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 & 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 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 *[47]*.

Pregnant and breastfeeding women
An additional study was identified but did not meet the inclusion criteria due to its observational design *[63]*. 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.

Children and adolescents
Remdesivir has been used anecdotally for the treatment of COVID-19 in this population, however, it remains uncertain that the benefits outweigh the harms. Currently, there are trials recruiting children.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [hospital, no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.76 (CI 95% 0.57 — 1.02) Based on data from 6,400 patients in 7 studies. [1] (Randomized controlled)	90 per 1000	68 per 1000 Difference: **22 fewer** per 1000 (CI 95% 39 fewer — 2 more)	**Moderate** Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.2 (CI 95% 0.98 — 1.47) Based on data from 1,004 patients in 4 studies. [3] (Randomized controlled)	248 per 1000	298 per 1000 Difference: **50 more** per 1000 (CI 95% 5 fewer — 117 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 patients in 2 studies. [5] (Randomized controlled)	143 per 1000	113 per 1000 Difference: **30 fewer** per 1000 (CI 95% 93 fewer — 112 more)	**Low** Due to serious inconsistency and serious imprecision [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (132 events).
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 patients in 1 studies. [7] (Randomized controlled)	225 per 1000	128 per 1000 Difference: **97 fewer** per 1000 (CI 95% 131 fewer — 47 fewer)	**Low** Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 patients in 3 studies. [9] (Randomized controlled)	711 per 1000	704 per 1000 Difference: **7 fewer** per 1000 (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [10]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 patients in 2 studies. [11] (Randomized controlled)	114 per 1000	119 per 1000 Difference: **5 more** per 1000 (CI 95% 13 fewer — 24 more)	**Moderate** Due to serious imprecision [12]	Remdesivir probably has no impact on number of patients requiring ventilation.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 patients in 2 studies. [13] (Randomized controlled)	10 per 1000	10 per 1000 Difference: **0 fewer** per 1000 (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.75 (CI 95% 0.63 — 0.89) Based on data from 1,865 patients in 3 studies. [15] (Randomized controlled)	253 per 1000	190 per 1000 Difference: **63 fewer** per 1000 (CI 95% 94 fewer — 28 fewer)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly (340 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 1,880 patients in 3 studies. [17] (Randomized controlled)	548 per 1000	570 per 1000 Difference: **22 more** per 1000 (CI 95% 60 fewer — 115 more)	**Low** Due to serious risk of bias and serious inconsistency [18]	We are uncertain whether remdesivir increases or decreases adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 patients in 3 studies. [19] (Randomized controlled)	93 per 1000	161 per 1000 Difference: **68 more** per 1000 (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.96 — 1.03) Based on data from 5,533 patients in 2 studies. [21] (Randomized controlled)	711 per 1000	704 per 1000 Difference: **7 fewer** per 1000 (CI 95% 28 fewer — 21 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days 6 Important	Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.
Time to improvement Days 6 Important	Hazard Ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [61] with included studies: SOLIDARITY 2020 low/hi flow, Wang 2020, Beigel 2020 lo-flow, Mahajan 2021, SOLIDARITY 2020 no O2, Spinner 2020, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [57] with included studies: Wang 2020, Beigel 2020 Inv vent, Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [53] with included studies: Beigel 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Low number of patients, Only data from one study.
9. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **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.
11. Systematic review [61] with included studies: Mahajan 2021, SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Serious.** Wide confidence intervals.
13. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **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 bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
17. Systematic review [53] with included studies: Wang 2020, Spinner 2020, Beigel 2020, Spinner 2020. **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. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies.
19. Systematic review [53] with included studies: Spinner 2020, Beigel 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
21. Systematic review [61] with included studies: SOLIDARITY 2020, Mahajan 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

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 *[46][48]*.

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 deaths per 1000 patients (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 deaths per 1000 patients (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 *[46]*, lack of blinding), serious imprecision (too few who died) 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) *[46]*. 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 *[47]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.73 (CI 95% 0.4 — 1.33) Based on data from 781 patients in 2 studies. [1] (Randomized controlled)	59 per 1000	43 per 1000 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 mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.67 (CI 95% 0.11 — 3.99) Based on data from 384 patients in 1 studies. [3] (Randomized controlled)	16 per 1000	11 per 1000 Difference: **5 fewer** per 1000 (CI 95% 14 fewer — 48 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether remdesivir 5-day treatment increases or decreases death at 28 days (5 deaths).
Acute respiratory failure or ARDS	Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 patients in 1 studies. [5]	117 per 1000	55 per 1000	**Low** Due to very serious	Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (34

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Within 30 days of commencing treatment 9 Critical	(Randomized controlled)	Difference: **62 fewer** per 1000 (CI 95% 89 fewer — 7 fewer)		imprecision [6]	events).
Septic shock Within 30 days of commencing treatment 6 Important	Relative risk 0.39 (CI 95% 0.08 — 2.01) Based on data from 397 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision [8]	We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (7 events).
Clinical recovery Within 14 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 1.02 — 1.41) Based on data from 397 patients in 1 studies. [9] (Randomized controlled)	**538** per 1000 Difference: **108 more** per 1000 (CI 95% 11 more — 221 more)	**646** per 1000	**Low** Due to serious risk of bias and imprecision [10]	Remdesivir 5-day treatment may improve clinical recovery slightly (235 events).
Serious adverse events End of follow up 6 Important	Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 patients in 2 studies. [11] (Randomized controlled)	**200** per 1000 Difference: **72 fewer** per 1000 (CI 95% 106 fewer — 26 fewer)	**128** per 1000	**Moderate** Due to serious risk of bias [12]	Remdesivir 5-day treatment probably decreases serious adverse events slightly (129 events).
Adverse events End of follow up 6 Important	Relative risk 0.93 (CI 95% 0.84 — 1.03) Based on data from 781 patients in 2 studies. [13] (Randomized controlled)	**662** per 1000 Difference: **46 fewer** per 1000 (CI 95% 106 fewer — 20 more)	**616** per 1000	**Moderate** Due to serious risk of bias [14]	Remdesivir 5-day treatment probably makes little or no difference to adverse events (503 events).
Discontinuation due to adverse events During treatment 6 Important	Relative risk 0.59 (CI 95% 0.3 — 1.15) Based on data from 781 patients in 2 studies. [15] (Randomized controlled)	**56** per 1000 Difference: **23 fewer** per 1000 (CI 95% 39 fewer — 8 more)	**33** per 1000	**Low** 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).
Discharged from hospital Within 14 days of commencing treatment	Relative risk 1.06 (CI 95% 0.93 — 1.2) Based on data from 781 patients in 2 studies. [17] (Randomized controlled)	**638** per 1000 Difference: **38 more** per 1000 (CI 95% 45 fewer — 128 more)	**676** per 1000	**Moderate** 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)

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important **Discharged from hospital** Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.92 — 1.06) Based on data from 384 patients in 1 studies. [19] (Randomized controlled)	902 per 1000	893 per 1000 Difference: **9 fewer** per 1000 (CI 95% 72 fewer — 54 more)	**Low** 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).

1. Systematic review [50] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** due to few events.
3. Systematic review [50] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Only data from one study, due to few events.
5. Systematic review [50] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Low number of patients, Only data from one study.
7. Systematic review [50] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [50] with included studies: Goldman 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Only data from one study.
11. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [50] with included studies: Spinner 2020, Goldman 2020. **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 bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** due to few events.
17. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **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.
19. Systematic review [50] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Imprecision: Very serious.** Low number of patients, Only data from one study.

Not recommended

Do not start remdesivir in adults 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).

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.

Evidence To Decision

Benefits and harms — Important 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 — Moderate

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 expect few to want the intervention

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 — No important issues with the recommended alternative

There are no identified resource issues as the recommendation reflects usual care.

Equity — No important issues with the recommended alternative

There are no identified equity issues as the recommendation reflects usual care.

Acceptability — No important issues with the recommended alternative

There are no identified acceptability issues as the recommendation reflects usual care.

Feasibility No important issues with the recommended alternative

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 five randomised trials that compared remdesivir with standard care in 7415 adults hospitalised with COVID-19 *[44][45][48][51][62]*. The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 5451 and 1062 patients with moderate to critical COVID-19 *[51][44]*.

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).

Disease severity	Number of patients	References
Moderate	666	*[48][62]*
Moderate-Critical	6513	*[44][51]*
Severe-Critical	236	*[45]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (22 fewer deaths per 1000 patients (RR 0.76, CI 95% 0.57 to 1.02; 6400 patients in 5 studies)), and probably increases death at day 28 in patients who require ventilation (50 more deaths per 1000 patients (RR 1.20 CI 95% 0.98 to 1.47; 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 eight-point WHO ordinal scale *[44]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[48]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[48]* or 6-point ordinal scale *[45]*.

Compared with standard care, remdesivir probably reduces serious adverse events (63 fewer SAEs per 1000 patients (RR 0.75, CI 95% 0.68 to 0.89; 1865 patients in 3 studies)). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation and number of patients discharged from hospital at day 28. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock, adverse events and discontinuation due to adverse events.

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, 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 & 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 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 *[47]*.

Pregnant and breastfeeding women
An additional study was identified but did not meet the inclusion criteria due to its observational design *[63]*. 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.

Children and adolescents
Remdesivir has been used anecdotally for the treatment of COVID-19 in this population, however, it remains uncertain that the benefits outweigh the harms. Currently, there are trials recruiting children.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [hospital, no ventilation] Within 28 days of commencing treatment	Relative risk 0.76 (CI 95% 0.57 — 1.02) Based on data from 6,400 patients in 7 studies. [1] (Randomized controlled)	90 per 1000	68 per 1000 Difference: 22 fewer per 1000 (CI 95% 39 fewer — 2 more)	**Moderate** Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical					
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.2 (CI 95% 0.98 — 1.47) Based on data from 1,004 patients in 4 studies. [3] (Randomized controlled)	248 per 1000	298 per 1000 Difference: **50 more** per 1000 (CI 95% 5 fewer — 117 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 patients in 2 studies. [5] (Randomized controlled)	143 per 1000	113 per 1000 Difference: **30 fewer** per 1000 (CI 95% 93 fewer — 112 more)	**Low** Due to serious inconsistency and serious imprecision [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (132 events).
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 patients in 1 studies. [7] (Randomized controlled)	225 per 1000	128 per 1000 Difference: **97 fewer** per 1000 (CI 95% 131 fewer — 47 fewer)	**Low** Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 patients in 3 studies. [9] (Randomized controlled)	711 per 1000	704 per 1000 Difference: **7 fewer** per 1000 (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [10]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 patients in 2 studies. [11] (Randomized controlled)	114 per 1000	119 per 1000 Difference: **5 more** per 1000 (CI 95% 13 fewer — 24 more)	**Moderate** Due to serious imprecision [12]	Remdesivir probably has no impact on number of patients requiring ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 patients in 2 studies. [13] (Randomized controlled)	10 per 1000	10 per 1000 Difference: **0 fewer** per 1000 (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.75 (CI 95% 0.63 — 0.89) Based on data from 1,865 patients in 3 studies. [15] (Randomized controlled)	253 per 1000	190 per 1000 Difference: **63 fewer** per 1000 (CI 95% 94 fewer — 28 fewer)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly (340 events).
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 1,880 patients in 3 studies. [17] (Randomized controlled)	548 per 1000	570 per 1000 Difference: **22 more** per 1000 (CI 95% 60 fewer — 115 more)	**Low** Due to serious risk of bias and serious inconsistency [18]	We are uncertain whether remdesivir increases or decreases adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 patients in 3 studies. [19] (Randomized controlled)	93 per 1000	161 per 1000 Difference: **68 more** per 1000 (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.96 — 1.03) Based on data from 5,533 patients in 2 studies. [21] (Randomized controlled)	711 per 1000	704 per 1000 Difference: **7 fewer** per 1000 (CI 95% 28 fewer — 21 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days 6 Important	Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.
Time to improvement Days 6 Important	Hazard Ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [61] with included studies: SOLIDARITY 2020 low/hi flow, Wang 2020, Beigel 2020 lo-flow, Mahajan 2021, SOLIDARITY 2020 no O2, Spinner 2020, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [57] with included studies: Wang 2020, Beigel 2020 Inv vent, Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [53] with included studies: Beigel 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Low number of patients, Only data from one study.
9. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **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.
11. Systematic review [61] with included studies: Mahajan 2021, SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Serious.** Wide confidence intervals.
13. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **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 bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
17. Systematic review [53] with included studies: Wang 2020, Spinner 2020, Beigel 2020, Spinner 2020. **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. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies.
19. Systematic review [53] with included studies: Spinner 2020, Beigel 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
21. Systematic review [61] with included studies: SOLIDARITY 2020, Mahajan 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.3.2. Remdesivir for pregnant or breastfeeding women

Conditional recommendation

Consider using remdesivir for 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 [52]. 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, 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 [47].

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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 *[63]*.

Certainty of the Evidence

Low

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 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

On 10 July 2020, the Therapeutic Goods Administration granted provisional approval to use remdesivir in adults hospitalised with severe COVID-19 symptoms (requiring oxygen or high-level support to breathe). 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 *[52]*. 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: 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 five randomised trials that compared remdesivir with standard care in 7415 adults hospitalised with COVID-19 *[44][45][48][51][62]*. The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 5451 and 1062 patients with moderate to critical COVID-19 *[51][44]*.

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).

Disease severity	Number of patients	References
Moderate	666	*[48][62]*
Moderate-Critical	6513	*[44][51]*
Severe-Critical	236	*[45]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (22 fewer deaths per 1000 patients (RR 0.76, CI 95% 0.57 to 1.02; 6400 patients in 5 studies)), and probably increases death at day 28 in patients who require ventilation (50 more deaths per 1000 patients (RR 1.20 CI 95% 0.98 to 1.47; 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 eight-point WHO ordinal scale *[44]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[48]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[48]* or 6-point ordinal scale *[45]*.

Compared with standard care, remdesivir probably reduces serious adverse events (63 fewer SAEs per 1000 patients (RR 0.75, CI 95% 0.68 to 0.89; 1865 patients in 3 studies)). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation and number of patients discharged from hospital at day 28. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock, adverse events and discontinuation due to adverse events.

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, 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 & 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 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 *[47]*.

Pregnant and breastfeeding women
An additional study was identified but did not meet the inclusion criteria due to its observational design *[63]*. 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.

Children and adolescents
Remdesivir has been used anecdotally for the treatment of COVID-19 in this population, however, it remains uncertain that the benefits outweigh the harms. Currently, there are trials recruiting children.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [hospital, no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.76 (CI 95% 0.57 — 1.02) Based on data from 6,400 patients in 7 studies. [1] (Randomized controlled)	90 per 1000	68 per 1000 Difference: **22 fewer** per 1000 (CI 95% 39 fewer — 2 more)	**Moderate** Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.2 (CI 95% 0.98 — 1.47) Based on data from 1,004 patients in 4 studies. [3] (Randomized controlled)	248 per 1000	298 per 1000 Difference: **50 more** per 1000 (CI 95% 5 fewer — 117 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.
Respiratory failure or ARDS Within 28 days of commencing treatment	Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 patients in 2 studies. [5] (Randomized	143 per 1000	113 per 1000 Difference: **30 fewer** per 1000	**Low** Due to serious inconsistency and serious imprecision [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (132 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical	controlled)	(CI 95% 93 fewer — 112 more)			
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 patients in 1 studies. [7] (Randomized controlled)	225 per 1000	128 per 1000 Difference: **97 fewer** per 1000 (CI 95% 131 fewer — 47 fewer)	**Low** Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 patients in 3 studies. [9] (Randomized controlled)	711 per 1000	704 per 1000 Difference: **7 fewer** per 1000 (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [10]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 patients in 2 studies. [11] (Randomized controlled)	114 per 1000	119 per 1000 Difference: **5 more** per 1000 (CI 95% 13 fewer — 24 more)	**Moderate** Due to serious imprecision [12]	Remdesivir probably has no impact on number of patients requiring ventilation.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 patients in 2 studies. [13] (Randomized controlled)	10 per 1000	10 per 1000 Difference: **0 fewer** per 1000 (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.75 (CI 95% 0.63 — 0.89) Based on data from 1,865 patients in 3 studies. [15] (Randomized controlled)	253 per 1000	190 per 1000 Difference: **63 fewer** per 1000 (CI 95% 94 fewer — 28 fewer)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly (340 events).
Adverse events End of follow-up	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from	548 per 1000	570 per 1000	**Low** Due to serious risk of bias and	We are uncertain whether remdesivir increases or decreases

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	1,880 patients in 3 studies. [17] (Randomized controlled)	Difference: **22 more** per 1000 (CI 95% 60 fewer — 115 more)		serious inconsistency [18]	adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 patients in 3 studies. [19] (Randomized controlled)	**93** per 1000	**161** per 1000 Difference: **68 more** per 1000 (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.96 — 1.03) Based on data from 5,533 patients in 2 studies. [21] (Randomized controlled)	**711** per 1000	**704** per 1000 Difference: **7 fewer** per 1000 (CI 95% 28 fewer — 21 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days 6 Important	Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.
Time to improvement Days 6 Important	Hazard Ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [61] with included studies: SOLIDARITY 2020 low/hi flow, Wang 2020, Beigel 2020 lo-flow, Mahajan 2021, SOLIDARITY 2020 no O2, Spinner 2020, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [57] with included studies: Wang 2020, Beigel 2020 Inv vent, Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [53] with included studies: Beigel 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

Imprecision: Serious. Low number of patients, Only data from one study.
9. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **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.
11. Systematic review [61] with included studies: Mahajan 2021, SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Serious.** Wide confidence intervals.
13. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **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 bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
17. Systematic review [53] with included studies: Wang 2020, Spinner 2020, Beigel 2020, Spinner 2020. **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. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies.
19. Systematic review [53] with included studies: Spinner 2020, Beigel 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
21. Systematic review [61] with included studies: SOLIDARITY 2020, Mahajan 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

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 *[46][48]*.

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 deaths per 1000 patients (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 deaths per 1000 patients (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 *[46]*, lack of blinding), serious imprecision (too few who died) 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) *[46]*. 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 *[47]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.73 (CI 95% 0.4 — 1.33) Based on data from 781 patients in 2 studies. [1] (Randomized controlled)	59 per 1000	43 per 1000 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 mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.67 (CI 95% 0.11 — 3.99) Based on data from 384 patients in 1 studies. [3] (Randomized controlled)	16 per 1000	11 per 1000 Difference: **5 fewer** per 1000 (CI 95% 14 fewer — 48 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether remdesivir 5-day treatment increases or decreases death at 28 days (5 deaths).
Acute respiratory failure or ARDS Within 30 days of commencing treatment	Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 patients in 1 studies. [5] (Randomized controlled)	117 per 1000	55 per 1000 Difference: **62 fewer** per 1000 (CI 95% 89 fewer — 7 fewer)	**Low** Due to very serious imprecision [6]	Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (34 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical					
Septic shock Within 30 days of commencing treatment 6 Important	Relative risk 0.39 (CI 95% 0.08 — 2.01) Based on data from 397 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision [8]	We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (7 events).
Clinical recovery Within 14 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 1.02 — 1.41) Based on data from 397 patients in 1 studies. [9] (Randomized controlled)	538 per 1000	646 per 1000 Difference: **108 more** per 1000 (CI 95% 11 more — 221 more)	**Low** Due to serious risk of bias and imprecision [10]	Remdesivir 5-day treatment may improve clinical recovery slightly (235 events).
Serious adverse events End of follow up 6 Important	Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 patients in 2 studies. [11] (Randomized controlled)	200 per 1000	128 per 1000 Difference: **72 fewer** per 1000 (CI 95% 106 fewer — 26 fewer)	**Moderate** Due to serious risk of bias [12]	Remdesivir 5-day treatment probably decreases serious adverse events slightly (129 events).
Adverse events End of follow up 6 Important	Relative risk 0.93 (CI 95% 0.84 — 1.03) Based on data from 781 patients in 2 studies. [13] (Randomized controlled)	662 per 1000	616 per 1000 Difference: **46 fewer** per 1000 (CI 95% 106 fewer — 20 more)	**Moderate** Due to serious risk of bias [14]	Remdesivir 5-day treatment probably makes little or no difference to adverse events (503 events).
Discontinuation due to adverse events During treatment 6 Important	Relative risk 0.59 (CI 95% 0.3 — 1.15) Based on data from 781 patients in 2 studies. [15] (Randomized controlled)	56 per 1000	33 per 1000 Difference: **23 fewer** per 1000 (CI 95% 39 fewer — 8 more)	**Low** 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).
Discharged from hospital Within 14 days of commencing treatment 6 Important	Relative risk 1.06 (CI 95% 0.93 — 1.2) Based on data from 781 patients in 2 studies. [17] (Randomized controlled)	638 per 1000	676 per 1000 Difference: **38 more** per 1000 (CI 95% 45 fewer — 128 more)	**Moderate** 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)

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Discharged from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.92 — 1.06) Based on data from 384 patients in 1 studies. [19] (Randomized controlled)	902 per 1000	893 per 1000 Difference: **9 fewer** per 1000 (CI 95% 72 fewer — 54 more)	**Low** 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).

1. Systematic review [50] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** due to few events.
3. Systematic review [50] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Only data from one study, due to few events.
5. Systematic review [50] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Low number of patients, Only data from one study.
7. Systematic review [50] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [50] with included studies: Goldman 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Only data from one study.
11. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [50] with included studies: Spinner 2020, Goldman 2020. **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 bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** due to few events.
17. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **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.
19. Systematic review [50] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Imprecision: Very serious.** Low number of patients, Only data from one study.

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.

Evidence To Decision

Benefits and harms — Important 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 — Low

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 expect few to want the intervention

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 — No important issues with the recommended alternative

There are no identified resource issues as the recommendation reflects usual care.

Equity — No important issues with the recommended alternative

There are no identified equity issues as the recommendation reflects usual care.

Acceptability — No important issues with the recommended alternative

There are no identified acceptability issues as the recommendation reflects usual care.

Feasibility — No important issues with the recommended alternative

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 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 five randomised trials that compared remdesivir with standard care in 7415 adults hospitalised with COVID-19 *[44][45][48][51][62]*. The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 5451 and 1062 patients with moderate to critical COVID-19 *[51][44]*.

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).

Disease severity	Number of patients	References
Moderate	666	*[48][62]*
Moderate-Critical	6513	*[44][51]*
Severe-Critical	236	*[45]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (22 fewer deaths per 1000 patients (RR 0.76, CI 95% 0.57 to 1.02; 6400 patients in 5 studies)), and probably increases death at day 28 in patients who require ventilation (50 more deaths per 1000 patients (RR 1.20 CI 95% 0.98 to 1.47; 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 eight-point WHO ordinal scale *[44]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[48]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[48]* or 6-point ordinal scale *[45]*.

Compared with standard care, remdesivir probably reduces serious adverse events (63 fewer SAEs per 1000 patients (RR 0.75, CI 95% 0.68 to 0.89; 1865 patients in 3 studies)). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation and number of patients discharged from hospital at day 28. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock, adverse events and discontinuation due to adverse events.

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, 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 & 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 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 *[47]*.

Pregnant and breastfeeding women
An additional study was identified but did not meet the inclusion criteria due to its observational design *[63]*. 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.

Children and adolescents
Remdesivir has been used anecdotally for the treatment of COVID-19 in this population, however, it remains uncertain that the benefits outweigh the harms. Currently, there are trials recruiting children.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [hospital, no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.76 (CI 95% 0.57 — 1.02) Based on data from 6,400 patients in 7 studies. [1] (Randomized controlled)	90 per 1000	68 per 1000 Difference: **22 fewer** per 1000 (CI 95% 39 fewer — 2 more)	**Moderate** Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.2 (CI 95% 0.98 — 1.47) Based on data from 1,004 patients in 4 studies. [3] (Randomized controlled)	248 per 1000	298 per 1000 Difference: **50 more** per 1000 (CI 95% 5 fewer — 117 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 patients in 2 studies. [5] (Randomized controlled)	143 per 1000	113 per 1000 Difference: **30 fewer** per 1000 (CI 95% 93 fewer — 112 more)	**Low** Due to serious inconsistency and serious imprecision [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (132 events).
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 patients in 1 studies. [7] (Randomized controlled)	225 per 1000	128 per 1000 Difference: **97 fewer** per 1000 (CI 95% 131 fewer — 47 fewer)	**Low** Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 patients in 3 studies. [9] (Randomized controlled)	711 per 1000	704 per 1000 Difference: **7 fewer** per 1000 (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [10]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 patients in 2 studies. [11] (Randomized controlled)	114 per 1000	119 per 1000 Difference: **5 more** per 1000 (CI 95% 13 fewer — 24 more)	**Moderate** Due to serious imprecision [12]	Remdesivir probably has no impact on number of patients requiring ventilation.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 patients in 2 studies. [13] (Randomized controlled)	10 per 1000	10 per 1000 Difference: **0 fewer** per 1000 (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.75 (CI 95% 0.63 — 0.89) Based on data from 1,865 patients in 3 studies. [15] (Randomized controlled)	253 per 1000	190 per 1000 Difference: **63 fewer** per 1000 (CI 95% 94 fewer — 28 fewer)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly (340 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 1,880 patients in 3 studies. [17] (Randomized controlled)	548 per 1000	570 per 1000 Difference: **22 more** per 1000 (CI 95% 60 fewer — 115 more)	**Low** Due to serious risk of bias and serious inconsistency [18]	We are uncertain whether remdesivir increases or decreases adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 patients in 3 studies. [19] (Randomized controlled)	93 per 1000	161 per 1000 Difference: **68 more** per 1000 (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.96 — 1.03) Based on data from 5,533 patients in 2 studies. [21] (Randomized controlled)	711 per 1000	704 per 1000 Difference: **7 fewer** per 1000 (CI 95% 28 fewer — 21 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days 6 Important	Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.
Time to improvement Days 6 Important	Hazard Ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [61] with included studies: SOLIDARITY 2020 low/hi flow, Wang 2020, Beigel 2020 lo-flow, Mahajan 2021, SOLIDARITY 2020 no O2, Spinner 2020, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [57] with included studies: Wang 2020, Beigel 2020 Inv vent, Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [53] with included studies: Beigel 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Low number of patients, Only data from one study.
9. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **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.
11. Systematic review [61] with included studies: Mahajan 2021, SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Serious.** Wide confidence intervals.
13. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **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 bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
17. Systematic review [53] with included studies: Wang 2020, Spinner 2020, Beigel 2020, Spinner 2020. **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. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies.
19. Systematic review [53] with included studies: Spinner 2020, Beigel 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
21. Systematic review [61] with included studies: SOLIDARITY 2020, Mahajan 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.3.3. Remdesivir for children or adolescents

Conditional recommendation against

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

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.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [47].

Practical Info

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 *[64]*:

- 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 < 40kg

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

In adults who are hospitalised with moderate COVID-19 and who do not require oxygen but not 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 — Low

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 — Substantial variability is expected or uncertain

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 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.

Equity Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 *[44][46][48]*.

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 five randomised trials that compared remdesivir with standard care in 7415 adults hospitalised with COVID-19 *[44][45][48][51][62]*. The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials,

which randomised 5451 and 1062 patients with moderate to critical COVID-19 *[51][44]*.

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).

Disease severity	Number of patients	References
Moderate	666	*[48][62]*
Moderate-Critical	6513	*[44][51]*
Severe-Critical	236	*[45]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (22 fewer deaths per 1000 patients (RR 0.76, CI 95% 0.57 to 1.02; 6400 patients in 5 studies)), and probably increases death at day 28 in patients who require ventilation (50 more deaths per 1000 patients (RR 1.20 CI 95% 0.98 to 1.47; 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 eight-point WHO ordinal scale *[44]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[48]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[48]* or 6-point ordinal scale *[45]*.

Compared with standard care, remdesivir probably reduces serious adverse events (63 fewer SAEs per 1000 patients (RR 0.75, CI 95% 0.68 to 0.89; 1865 patients in 3 studies)). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation and number of patients discharged from hospital at day 28. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock, adverse events and discontinuation due to adverse events.

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, 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 & 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 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 *[47]*.

Pregnant and breastfeeding women
An additional study was identified but did not meet the inclusion criteria due to its observational design *[63]*. 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.

Children and adolescents
Remdesivir has been used anecdotally for the treatment of COVID-19 in this population, however, it remains uncertain that the benefits outweigh the harms. Currently, there are trials recruiting children.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [hospital, no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.76 (CI 95% 0.57 — 1.02) Based on data from 6,400 patients in 7 studies. [1] (Randomized controlled)	90 per 1000	68 per 1000 Difference: **22 fewer** per 1000 (CI 95% 39 fewer — 2 more)	**Moderate** Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.2 (CI 95% 0.98 — 1.47) Based on data from 1,004 patients in 4 studies. [3] (Randomized controlled)	248 per 1000	298 per 1000 Difference: **50 more** per 1000 (CI 95% 5 fewer — 117 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 patients in 2 studies. [5] (Randomized controlled)	143 per 1000	113 per 1000 Difference: **30 fewer** per 1000 (CI 95% 93 fewer — 112 more)	**Low** Due to serious inconsistency and serious imprecision [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (132 events).
Invasive mechanical ventilation or ECMO Within 28 days of	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 patients in 1 studies. [7] (Randomized controlled)	225 per 1000	128 per 1000 Difference: **97 fewer** per 1000	**Low** Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
commencing treatment 9 Critical		(CI 95% 131 fewer — 47 fewer)			
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 patients in 3 studies. [9] (Randomized controlled)	711 per 1000	704 per 1000 Difference: **7 fewer** per 1000 (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [10]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 patients in 2 studies. [11] (Randomized controlled)	114 per 1000	119 per 1000 Difference: **5 more** per 1000 (CI 95% 13 fewer — 24 more)	**Moderate** Due to serious imprecision [12]	Remdesivir probably has no impact on number of patients requiring ventilation.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 patients in 2 studies. [13] (Randomized controlled)	10 per 1000	10 per 1000 Difference: **0 fewer** per 1000 (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.75 (CI 95% 0.63 — 0.89) Based on data from 1,865 patients in 3 studies. [15] (Randomized controlled)	253 per 1000	190 per 1000 Difference: **63 fewer** per 1000 (CI 95% 94 fewer — 28 fewer)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly (340 events).
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 1,880 patients in 3 studies. [17] (Randomized controlled)	548 per 1000	570 per 1000 Difference: **22 more** per 1000 (CI 95% 60 fewer — 115 more)	**Low** Due to serious risk of bias and serious inconsistency [18]	We are uncertain whether remdesivir increases or decreases adverse events.
Discontinuation due to adverse events During treatment	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 patients in 3 studies. [19] (Randomized	93 per 1000	161 per 1000 Difference: **68 more** per 1000 (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	controlled)				
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.96 — 1.03) Based on data from 5,533 patients in 2 studies. [21] (Randomized controlled)	711 per 1000	704 per 1000 Difference: 7 fewer per 1000 (CI 95% 28 fewer — 21 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days 6 Important	Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.
Time to improvement Days 6 Important	Hazard Ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 patients in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [61] with included studies: SOLIDARITY 2020 low/hi flow, Wang 2020, Beigel 2020 lo-flow, Mahajan 2021, SOLIDARITY 2020 no O2, Spinner 2020, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [57] with included studies: Wang 2020, Beigel 2020 Inv vent, Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [53] with included studies: Beigel 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Low number of patients, Only data from one study.
9. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **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.
11. Systematic review [61] with included studies: Mahajan 2021, SOLIDARITY 2020. **Baseline/comparator:** Control

arm of reference used for intervention.
12. **Imprecision: Serious.** Wide confidence intervals.
13. Systematic review [53] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [53] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **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 bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
17. Systematic review [53] with included studies: Wang 2020, Spinner 2020, Beigel 2020, Spinner 2020. **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. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies.
19. Systematic review [53] with included studies: Spinner 2020, Beigel 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
21. Systematic review [61] with included studies: SOLIDARITY 2020, Mahajan 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

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 *[46][48]*.

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 deaths per 1000 patients (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 deaths per 1000 patients (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 *[46]*, lack of blinding), serious imprecision (too few who died) 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) *[46]*. 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 *[47]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.73 (CI 95% 0.4 — 1.33) Based on data from 781 patients in 2 studies. [1] (Randomized controlled)	59 per 1000	43 per 1000 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 mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.67 (CI 95% 0.11 — 3.99) Based on data from 384 patients in 1 studies. [3] (Randomized controlled)	16 per 1000	11 per 1000 Difference: **5 fewer** per 1000 (CI 95% 14 fewer — 48 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether remdesivir 5-day treatment increases or decreases death at 28 days (5 deaths).
Acute respiratory failure or ARDS Within 30 days of commencing treatment 9 Critical	Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 patients in 1 studies. [5] (Randomized controlled)	117 per 1000	55 per 1000 Difference: **62 fewer** per 1000 (CI 95% 89 fewer — 7 fewer)	**Low** Due to very serious imprecision [6]	Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (34 events).
Septic shock Within 30 days of commencing treatment	Relative risk 0.39 (CI 95% 0.08 — 2.01) Based on data from 397 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision [8]	We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (7 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important					
Clinical recovery Within 14 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 1.02 — 1.41) Based on data from 397 patients in 1 studies. [9] (Randomized controlled)	538 per 1000	646 per 1000 Difference: **108 more** per 1000 (CI 95% 11 more — 221 more)	**Low** Due to serious risk of bias and imprecision [10]	Remdesivir 5-day treatment may improve clinical recovery slightly (235 events).
Serious adverse events End of follow up 6 Important	Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 patients in 2 studies. [11] (Randomized controlled)	200 per 1000	128 per 1000 Difference: **72 fewer** per 1000 (CI 95% 106 fewer — 26 fewer)	**Moderate** Due to serious risk of bias [12]	Remdesivir 5-day treatment probably decreases serious adverse events slightly (129 events).
Adverse events End of follow up 6 Important	Relative risk 0.93 (CI 95% 0.84 — 1.03) Based on data from 781 patients in 2 studies. [13] (Randomized controlled)	662 per 1000	616 per 1000 Difference: **46 fewer** per 1000 (CI 95% 106 fewer — 20 more)	**Moderate** Due to serious risk of bias [14]	Remdesivir 5-day treatment probably makes little or no difference to adverse events (503 events).
Discontinuation due to adverse events During treatment 6 Important	Relative risk 0.59 (CI 95% 0.3 — 1.15) Based on data from 781 patients in 2 studies. [15] (Randomized controlled)	56 per 1000	33 per 1000 Difference: **23 fewer** per 1000 (CI 95% 39 fewer — 8 more)	**Low** 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).
Discharged from hospital Within 14 days of commencing treatment 6 Important	Relative risk 1.06 (CI 95% 0.93 — 1.2) Based on data from 781 patients in 2 studies. [17] (Randomized controlled)	638 per 1000	676 per 1000 Difference: **38 more** per 1000 (CI 95% 45 fewer — 128 more)	**Moderate** 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)
Discharged from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.92 — 1.06) Based on data from 384 patients in 1 studies. [19] (Randomized controlled)	902 per 1000	893 per 1000 Difference: **9 fewer** per 1000 (CI 95% 72 fewer — 54 more)	**Low** 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).

1. Systematic review [50] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** due to few events.
3. Systematic review [50] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Only data from one study, due to few events.
5. Systematic review [50] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Low number of patients, Only data from one study.
7. Systematic review [50] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [50] with included studies: Goldman 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Only data from one study.
11. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [50] with included studies: Spinner 2020, Goldman 2020. **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 bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** due to few events.
17. Systematic review [50] with included studies: Goldman 2020, Spinner 2020. **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.
19. Systematic review [50] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Imprecision: Very serious.** Low number of patients, Only data from one study.

6.4. Sarilumab

6.4.1. 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.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

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 *[318]*.

Children and adolescents
The safety profile in children and adolescents with COVID-19 has not been established.

Certainty of the Evidence — Moderate

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 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 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 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 No important issues with the recommended alternative

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 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

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) *[86]* and 2238 patients hospitalised with severe–critical COVID-19 *[320][483]*.

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 mortality 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 mortality, 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 & 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 Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness *[318]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [all patients] Within 21-29 days after commencing treatment 9 Critical	Relative risk 0.9 (CI 95% 0.73 — 1.1) Based on data from 2,303 patients in 3 studies. [1] (Randomized controlled)	294 per 1000	265 per 1000 Difference: 29 fewer per 1000 (CI 95% 79 fewer — 29 more)	**Moderate** Due to serious imprecision [2]	Sarilumab probably decreases death slightly.
Requiring ventilation (HFNO, NIV, MV) End of follow-up 6 Important	Relative risk 1.15 (CI 95% 0.66 — 1.99) Based on data from 416 patients in 1 studies. [3] (Randomized controlled)	155 per 1000	178 per 1000 Difference: 23 more per 1000 (CI 95% 53 fewer — 153 more)	**Low** Due to very serious imprecision [4]	Sarilumab may have little impact on number of patients requiring ventilation.
Serious adverse events End of follow-up 6 Important	Relative risk 1.02 (CI 95% 0.89 — 1.18) Based on data from 2,315 patients in 3 studies. [5] (Randomized controlled)	199 per 1000	203 per 1000 Difference: 4 more per 1000 (CI 95% 22 fewer — 36 more)	**Moderate** Due to serious imprecision [6]	Sarilumab probably has little impact on serious adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.98 — 1.19) Based on data from 1,865 patients in 2 studies. [7] (Randomized controlled)	539 per 1000	582 per 1000 Difference: **43 more** per 1000 (CI 95% 11 fewer — 102 more)	**Moderate** Due to serious imprecision [8]	Sarilumab probably increases adverse events slightly.
Admission to ICU During treatment 6 Important	Relative risk 1.06 (CI 95% 0.49 — 2.29) Based on data from 268 patients in 1 studies. [9] (Randomized controlled)	125 per 1000	132 per 1000 Difference: **7 more** per 1000 (CI 95% 64 fewer — 161 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether sarilumab increases or decreases admission to ICU (35 events).
Clinical improvement Within 22 days after commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.87 — 1.1) Based on data from 1,097 patients in 1 studies. [11] (Randomized controlled)	608 per 1000	596 per 1000 Difference: **12 fewer** per 1000 (CI 95% 79 fewer — 61 more)	**Low** Due to very serious imprecision [12]	Sarilumab may have little impact on clinical improvement.
Clinical recovery Within 22 days after commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.89 — 1.1) Based on data from 1,449 patients in 1 studies. [13] (Randomized controlled)	589 per 1000	583 per 1000 Difference: **6 fewer** per 1000 (CI 95% 65 fewer — 59 more)	**Low** Due to very serious imprecision [14]	Sarilumab may have little impact on clinical recovery.
Discharge from hospital End of follow-up 6 Important	Relative risk 0.99 (CI 95% 0.92 — 1.07) Based on data from 1,513 patients in 2 studies. [15] (Randomized controlled)	590 per 1000	584 per 1000 Difference: **6 fewer** per 1000 (CI 95% 47 fewer — 41 more)	**Moderate** Due to serious imprecision [16]	Sarilumab probably has little impact on discharge from hospital.

1. Systematic review [322] with included studies: REMAP-CAP sarilumab, Sivapalasingam 2021, Lescure 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [322] with included studies: Lescure 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
5. Systematic review [322] with included studies: Sivapalasingam 2021, Lescure 2021, REMAP-CAP sarilumab. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [322] with included studies: Lescure 2021, Sivapalasingam 2021. **Baseline/comparator:** Control arm of reference used for intervention.

8. **Imprecision: Serious.** Wide confidence intervals.
9. Systematic review [322] with included studies: Lescure 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
11. Systematic review [322] with included studies: Sivapalasingam 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
13. Systematic review [322] with included studies: Sivapalasingam 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
15. Systematic review [322] with included studies: Sivapalasingam 2021, Lescure 2021. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Imprecision: Serious.** Wide confidence intervals.

6.4.2. Sarilumab for pregnant or breastfeeding women

6.5. Tocilizumab

6.5.1. 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).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved. 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 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.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

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 *[85]*.

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 — Moderate

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).

Preference and values — Substantial variability is expected or uncertain

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 — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

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 — No important issues with the recommended alternative

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 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

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.

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 10 randomised trials that compared tocilizumab with standard care in 6570 adults hospitalised with COVID-19 *[69][70][72][73][82][86][87][88][91][93]*. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate to critical COVID-19 *[91]*. 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 *[86]*. 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 *[87]*, which included 108 patients with critical illness.

To determine whether differences in observed effect on mortality 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. *[82]*, 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 (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 1: Disease severity of patients within included trials

Disease severity	Number of patients	References
Moderate–Severe	1132	*[69][70][72][73][88][93]*
Moderate–Critical	4683	*[82][87][91]*
Critical	755	*[86]*

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

Study	Tocilizumab	Control
RECOVERY	Median (IQR): 143 (107–203)	Median (IQR): 144 (106–205)
REMAP-CAP	Median (IQR): 150 (85–221)	Median (IQR): 130 (71–208)
Hermine 2020	Median (IQR): 120 (75–220)	Median (IQR): 127 (84–171)
Rosas 2021	Mean (SD): 168 (101)	Mean (SD): 173 (114)
Salama 2020	Mean (SD): 152 (177)	Mean (SD): 203 (405)
Salvarini 2020	Median (IQR): 105 (50–146)	Median (IQR): 65 (32–118)
Stone 2020	Median (IQR): 116 (67–191)	Median (IQR): 94 (58–142)
Veiga 2021	Mean (SD): 160 (104)	Mean (SD): 193 (283)

What are the main results?
Tocilizumab probably decreases mortality slightly (32 fewer deaths per 1000 patients; RR 0.89, CI 95% 0.82 to 0.98; 6481 patients in 9 studies) and the need for invasive mechanical ventilation (30 fewer per 1000; RR 0.81, CI 95% 0.70 to 0.93; 4248 patients in 4 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), 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 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 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 (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 & 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 adverse effects related to tocilizumab are generally mild and include headache, dizziness, infections and injection site reactions *[67]*. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab.

Children and adolescents
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.

Pregnant and breastfeeding women
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [All patients] Day 21-28 after commencing treatment 9 Critical	Relative risk 0.89 (CI 95% 0.82 — 0.98) Based on data from 6,481 patients in 9 studies. [1] (Randomized controlled)	290 per 1000	258 per 1000 Difference: **32 fewer** per 1000 (CI 95% 52 fewer — 6 fewer)	**Moderate** Due to serious imprecision [2]	Tocilizumab probably decreases death slightly.
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.81 (CI 95% 0.7 — 0.93) Based on data from 4,248 patients in 4 studies. [3] (Randomized controlled)	159 per 1000	129 per 1000 Difference: **30 fewer** per 1000 (CI 95% 48 fewer — 11 fewer)	**High**	Tocilizumab decreases the need for invasive mechanical ventilation.
Respiratory failure or ARDS Within 14 days of commencing treatment 9 Critical	Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from 130 patients in 1 studies. [4] (Randomized controlled)	284 per 1000	142 per 1000 Difference: **142 fewer** per 1000 (CI 95% 213 fewer — 9 more)	**Low** Due to very serious imprecision [5]	We are uncertain whether tocilizumab increases or decreases respiratory failure or ARDS (28 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.89 (CI 95% 0.75 — 1.05) Based on data from 2,309 patients in 8 studies. [6] (Randomized controlled)	162 per 1000	144 per 1000 Difference: **18 fewer** per 1000 (CI 95% 41 fewer — 8 more)	**Moderate** Due to serious imprecision [7]	Tocilizumab probably has little impact on serious adverse events (396 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events End of follow-up 6 Important	Relative risk 1.06 (CI 95% 0.86 — 1.3) Based on data from 1,562 patients in 7 studies. [8] (Randomized controlled)	466 per 1000	494 per 1000 Difference: **28 more** per 1000 (CI 95% 65 fewer — 140 more)	**Moderate** Due to serious imprecision [9]	Tocilizumab probably has little impact on adverse events.
Septic shock End of follow-up 6 Important	Relative risk 0.59 (CI 95% 0.26 — 1.35) Based on data from 815 patients in 2 studies. [10] (Randomized controlled)	37 per 1000	22 per 1000 Difference: **15 fewer** per 1000 (CI 95% 27 fewer — 13 more)	**Moderate** Due to serious imprecision [11]	Tocilizumab probably has little impact on septic shock (22 events).
Admission to ICU End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.54 — 1.23) Based on data from 699 patients in 4 studies. [12] (Randomized controlled)	423 per 1000	347 per 1000 Difference: **76 fewer** per 1000 (CI 95% 195 fewer — 97 more)	**Moderate** Due to serious imprecision [13]	Tocilizumab probably decreases admission to ICU.
Discharge from hospital End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.99 — 1.16) Based on data from 4,611 patients in 4 studies. [14] (Randomized controlled)	506 per 1000	541 per 1000 Difference: **35 more** per 1000 (CI 95% 5 fewer — 81 more)	**Moderate** Due to serious imprecision [15]	Tocilizumab probably increases discharge from hospital.
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.92 — 1.27) Based on data from 65 patients in 1 studies. [16] (Randomized controlled)	871 per 1000	941 per 1000 Difference: **70 more** per 1000 (CI 95% 70 fewer — 235 more)	**Low** Due to very serious imprecision [17]	We are uncertain whether tocilizumab increases or decreases clinical recovery.
Clinical improvement Within 14 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.12) Based on data from 242 patients in 1 studies. [18] (Randomized controlled)	889 per 1000	916 per 1000 Difference: **27 more** per 1000 (CI 95% 53 fewer — 107 more)	**Low** Due to very serious imprecision [19]	We are uncertain whether tocilizumab increases or decreases clinical improvement.
Clinical progression Within 14 days of commencing treatment 6 Important	Relative risk 1.08 (CI 95% 0.72 — 1.62) Based on data from 365 patients in 2 studies. [20] (Randomized controlled)	215 per 1000	232 per 1000 Difference: **17 more** per 1000 (CI 95% 60 fewer — 133 more)	**Moderate** Due to serious imprecision [21]	Tocilizumab probably has little impact on clinical progression.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Time to deterioration Days 6 Important	Hazard Ratio 1.11 (CI 95% 0.59 — 2.1) Based on data from 45 patients in 1 studies. (Randomized controlled)			**Low** Due to very serious imprecision [22]	We are uncertain whether tocilizumab increases or decreases time to discharge.
Duration of mechanical ventilation Days 6 Important	Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from: 19 patients in 1 studies. [23] (Randomized controlled)	27.9 (Median)	15 (Median) Difference: 12.9 fewer CI 95%	**Low** Due to very serious imprecision [24]	We are uncertain whether tocilizumab decreases duration of mechanical ventilation.
Time to improvement Days 6 Important	Based on data from: 219 patients in 1 studies. [25] (Randomized controlled)	5 (Median)	6 (Median) Difference: 1 more CI 95%	**Low** Due to very serious imprecision [26]	We are uncertain whether tocilizumab increases or decreases time to improvement.
Duration of hospital stay (mean) Days 6 Important	Based on data from: 129 patients in 1 studies. [27] (Randomized controlled)	14.7 (Mean)	11.3 (Mean) Difference: MD 3.4 lower (CI 95% 6.2 lower — 0.6 lower)	**Low** Due to very serious imprecision [28]	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 patients in 1 studies. (Randomized controlled)	28 (Median)	20 (Median)	**Moderate** Due to serious imprecision [29]	Tocilizumab probably decreases duration of hospital stay.

1. Systematic review [92] with included studies: RECOVERY [total], Soin 2021, Salvarini 2020, Salama 2020, Rosas 2020, Hermine 2020, Veiga 2021, Stone 2020, REMAP-CAP tocilizumab. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [92] with included studies: Stone 2020, Rosas 2020, Soin 2021, RECOVERY [total]. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [68] with included studies: Hermine 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
6. Systematic review [92] with included studies: Veiga 2021, Salama 2020, Soin 2021, Wang 2020, Stone 2020, REMAP-CAP tocilizumab, Hermine 2020, Rosas 2020. **Baseline/comparator:** Control arm of reference used for

intervention.
7. **Imprecision: Serious.** Wide confidence intervals.
8. Systematic review [92] with included studies: Soin 2021, Rosas 2020, Salama 2020, Wang 2020, Hermine 2020, Stone 2020, Veiga 2021. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Imprecision: Serious.** Wide confidence intervals.
10. Systematic review [71] with included studies: Rosas 2020, Salama 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Imprecision: Serious.** due to few events.
12. Systematic review [92] with included studies: Salvarini 2020, Hermine 2020, Rosas 2020, Soin 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Imprecision: Serious.** Wide confidence intervals.
14. Systematic review [83] with included studies: Stone 2020, RECOVERY [total], Hermine 2020, Salvarini 2020. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Imprecision: Serious.** Wide confidence intervals.
16. Systematic review [68] with included studies: Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
17. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
18. Systematic review [68] with included studies: Stone 2020. **Baseline/comparator:** Control arm of reference used for intervention.
19. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study, Low number of patients.
20. Systematic review [71] with included studies: Stone 2020, Salvarini 2020. **Baseline/comparator:** Control arm of reference used for intervention.
21. **Imprecision: Serious.** Wide confidence intervals.
22. **Imprecision: Very serious.** Low number of patients, Only data from one study.
23. Systematic review [68] . **Baseline/comparator:** Control arm of reference used for intervention.
24. **Imprecision: Very serious.** Low number of patients, Only data from one study.
25. Systematic review [68] . **Baseline/comparator:** Control arm of reference used for intervention.
26. **Imprecision: Very serious.** Low number of patients, Only data from one study.
27. Systematic review [81] with included studies: Veiga 2021. **Baseline/comparator:** Control arm of reference used for intervention.
28. **Imprecision: Very serious.** Low number of patients, Only data from one study.
29. **Imprecision: Serious.** Only data from one study.

6.5.2. Tocilizumab for pregnant or breastfeeding women

Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 for 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, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved. 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.

*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.*

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

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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 *[89]*.

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 *[94]*.

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 *[97]*. The Australian Immunisation Handbook specifies that BCG can be administered up to 12 months of age *[98]*.

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 *[95]*. 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 *[99][100]*. 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 — Moderate

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 — 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 — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

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 — 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

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, and while there is 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. 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 *[69][70][72][73][82][86][87][88][91]*. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate to critical COVID-19 *[91]*. 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 *[86]*. 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 *[87]*, which included 108 patients with critical illness.

To determine whether differences in observed effect on mortality 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. *[82]*, 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

Disease severity	Number of patients	References
Moderate–Severe	952	*[69][70][72][73][88]*
Moderate–Critical	4683	*[82][87][91]*
Critical	755	*[86]*

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

Study	Tocilizumab	Control
RECOVERY	Median (IQR): 143 (107–203)	Median (IQR): 144 (106–205)
REMAP-CAP	Median (IQR): 150 (85–221)	Median (IQR): 130 (71–208)
Hermine 2020	Median (IQR): 120 (75–220)	Median (IQR): 127 (84–171)
Rosas 2021	Mean (SD): 168 (101)	Mean (SD): 173 (114)
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Salvarini 2020	Median (IQR): 105 (50–146)	Median (IQR): 65 (32–118)
Stone 2020	Median (IQR): 116 (67–191)	Median (IQR): 94 (58–142)
Veiga 2021	Mean (SD): 160 (104)	Mean (SD): 193 (283)

What are the main results?
Tocilizumab probably decreases mortality slightly (26 fewer deaths 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 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 (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 & 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 adverse effects related to tocilizumab are generally mild and include headache, dizziness, infections and injection site reactions *[67]*. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab.

Children and adolescents
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.

Pregnant and breastfeeding women
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [All patients] Day 21-28 after commencing treatment 9 Critical	Relative risk 0.91 (CI 95% 0.8 — 1.03) Based on data from 6,302 patients in 8 studies. [1] (Randomized controlled)	294 per 1000	268 per 1000 Difference: **26 fewer** per 1000 (CI 95% 59 fewer — 9 more)	**Low** Due to serious inconsistency and serious indirectness [2]	Tocilizumab may decrease death.
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.8 (CI 95% 0.69 — 0.92) Based on data from 4,069 patients in 3 studies. [3] (Randomized controlled)	159 per 1000	127 per 1000 Difference: **32 fewer** per 1000 (CI 95% 49 fewer — 13 fewer)	**Moderate** Due to serious indirectness [4]	Tocilizumab probably decreases need for invasive mechanical ventilation
Respiratory failure or ARDS Within 14 days of commencing treatment 9 Critical	Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from 130 patients in 1 studies. [5] (Randomized controlled)	284 per 1000	142 per 1000 Difference: **142 fewer** per 1000 (CI 95% 213 fewer — 9 more)	**Very low** Due to very serious imprecision and serious indirectness [6]	We are uncertain whether tocilizumab increases or decreases respiratory failure or ARDS (28 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.88 (CI 95% 0.74 — 1.05) Based on data from 2,129 patients in 7 studies. [7] (Randomized controlled)	161 per 1000	142 per 1000 Difference: **19 fewer** per 1000 (CI 95% 42 fewer — 8 more)	**Low** Due to serious imprecision and serious indirectness [8]	Tocilizumab may make little or no difference to serious adverse events (366 events).
Adverse events End of follow-up 6 Important	Relative risk 1.03 (CI 95% 0.82 — 1.28) Based on data from 1,382 patients in 6 studies. [9] (Randomized controlled)	504 per 1000	519 per 1000 Difference: **15 more** per 1000 (CI 95% 91 fewer — 141 more)	**Low** Due to serious imprecision and serious indirectness [10]	Tocilizumab may make little or no difference to adverse events.
Septic shock End of follow-up	Relative risk 0.59 (CI 95% 0.26 — 1.35) Based on data from 815 patients in 2 studies. [11]	37 per 1000	22 per 1000	**Low** Due to serious imprecision and serious	Tocilizumab may have little impact on septic shock (22 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	(Randomized controlled)	Difference: **15 fewer** per 1000 (CI 95% 27 fewer — 13 more)		indirectness [12]	
Admission to ICU End of follow-up 6 Important	Relative risk 0.68 (CI 95% 0.51 — 0.9) Based on data from 520 patients in 3 studies. [13] (Randomized controlled)	**300** per 1000	**204** per 1000 Difference: **96 fewer** per 1000 (CI 95% 147 fewer — 30 fewer)	**Low** Due to serious imprecision and serious indirectness [14]	Tocilizumab may decrease admission to ICU (135 events).
Discharge from hospital End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.99 — 1.16) Based on data from 4,611 patients in 4 studies. [15] (Randomized controlled)	**506** per 1000	**541** per 1000 Difference: **35 more** per 1000 (CI 95% 5 fewer — 81 more)	**Low** Due to serious imprecision and serious indirectness [16]	Tocilizumab may increase discharge from hospital.
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.92 — 1.27) Based on data from 65 patients in 1 studies. [17] (Randomized controlled)	**871** per 1000	**941** per 1000 Difference: **70 more** per 1000 (CI 95% 70 fewer — 235 more)	**Very low** Due to very serious imprecision, very serious indirectness and serious indirectness [18]	We are uncertain whether tocilizumab increases or decreases clinical recovery.
Clinical improvement Within 14 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.12) Based on data from 242 patients in 1 studies. [19] (Randomized controlled)	**889** per 1000	**916** per 1000 Difference: **27 more** per 1000 (CI 95% 53 fewer — 107 more)	**Very low** Due to very serious imprecision and serious indirectness [20]	We are uncertain whether tocilizumab increases or decreases clinical improvement.
Clinical progression Within 14 days of commencing treatment 6 Important	Relative risk 1.08 (CI 95% 0.72 — 1.62) Based on data from 365 patients in 2 studies. [21] (Randomized controlled)	**215** per 1000	**232** per 1000 Difference: **17 more** per 1000 (CI 95% 60 fewer — 133 more)	**Low** Due to serious imprecision and serious indirectness [22]	Tocilizumab may have little or no impact on clinical progression.
Time to deterioration Days 6 Important	Hazard Ratio 1.11 (CI 95% 0.59 — 2.1) Based on data from 45 patients in 1 studies. (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [23]	We are uncertain whether tocilizumab increases or decreases time to discharge.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Duration of mechanical ventilation Days 6 Important	Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from: 19 patients in 1 studies. [24] (Randomized controlled)	27.9 (Median)	15 (Median) Difference: 12.9 fewer CI 95%	Very low Due to very serious imprecision and serious indirectness [25]	We are uncertain whether tocilizumab decreases duration of mechanical ventilation.
Time to improvement Days 6 Important	Based on data from: 219 patients in 1 studies. [26] (Randomized controlled)	5 (Median)	6 (Median) Difference: 1 more CI 95%	Very low Due to very serious imprecision and serious indirectness [27]	We are uncertain whether tocilizumab increases or decreases time to improvement.
Duration of hospital stay (mean) Days 6 Important	Based on data from: 129 patients in 1 studies. [28] (Randomized controlled)	14.7 (Mean)	11.3 (Mean) Difference: MD 3.4 lower (CI 95% 6.2 lower — 0.6 lower)	Low Due to very serious imprecision [29]	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 patients in 1 studies. (Randomized controlled)	28 (Median)	20 (Median)	Low Due to serious imprecision and serious indirectness [30]	Tocilizumab may decrease duration of hospital stay.

1. Systematic review [83] with included studies: Stone 2020, Veiga 2021, REMAP-CAP tocilizumab, Hermine 2020, Rosas 2020, Salvarini 2020, Salama 2020, RECOVERY [total]. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: Serious. Indirectness: Serious.** Differences between the population of interest and those studied.
3. Systematic review [83] with included studies: RECOVERY [total], Rosas 2020, Stone 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Indirectness: Serious.** Differences between the population of interest and those studied.
5. Systematic review [68] with included studies: Hermine 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
7. Systematic review [81] with included studies: REMAP-CAP tocilizumab, Salama 2020, Stone 2020, Veiga 2021, Rosas 2020, Hermine 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.
9. Systematic review [81] with included studies: Salama 2020, Veiga 2021, Stone 2020, Wang 2020, Rosas 2020, Hermine 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.**

Wide confidence intervals.
11. Systematic review [71] with included studies: Salama 2020, Rosas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** due to few events.
13. Systematic review [71] with included studies: Hermine 2020, Salvarini 2020, Rosas 2020. **Baseline/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.
15. Systematic review [83] with included studies: Salvarini 2020, Stone 2020, Hermine 2020, RECOVERY [total]. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.
17. Systematic review [68] with included studies: Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
19. Systematic review [68] with included studies: Stone 2020. **Baseline/comparator:** Control arm of reference 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.
21. Systematic review [71] with included studies: Salvarini 2020, Stone 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [68] . **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 [68] . **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.
28. Systematic review [81] with included studies: Veiga 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.5.3. Tocilizumab for children or 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.

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 and adolescents. (The Taskforce notes that RECOVERY is recruiting children and adolescents with PIMS-TS for their trial of tocilizumab [90].) Tocilizumab should be administered as a single intravenous infusion over 60 minutes, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved. 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 [89]*
- *< 30 kg: 12 mg/kg*
- *≥ 30 kg: 8 mg/kg (max 800 mg)*

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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 *[85]*.

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 Low

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 Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

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 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

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.

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 *[69][70][72][73][82][86][87][88][91]*. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate to critical COVID-19 *[91]*. 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 *[86]*. 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 *[87]*, which included 108 patients with critical illness.

To determine whether differences in observed effect on mortality 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:

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- 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%).

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Study characteristics
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Pregnant and breastfeeding women
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [All patients] Day 21-28 after commencing treatment 9 Critical	Relative risk 0.91 (CI 95% 0.8 — 1.03) Based on data from 6,302 patients in 8 studies. [1] (Randomized controlled)	294 per 1000	268 per 1000 Difference: **26 fewer** per 1000 (CI 95% 59 fewer — 9 more)	**Low** Due to serious inconsistency and serious indirectness [2]	Tocilizumab may decrease death.
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.8 (CI 95% 0.69 — 0.92) Based on data from 4,069 patients in 3 studies. [3] (Randomized controlled)	159 per 1000	127 per 1000 Difference: **32 fewer** per 1000 (CI 95% 49 fewer — 13 fewer)	**Moderate** Due to serious indirectness [4]	Tocilizumab probably decreases need for invasive mechanical ventilation
Respiratory failure or ARDS Within 14 days of commencing treatment 9 Critical	Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from 130 patients in 1 studies. [5] (Randomized controlled)	284 per 1000	142 per 1000 Difference: **142 fewer** per 1000 (CI 95% 213 fewer — 9 more)	**Very low** Due to very serious imprecision and serious indirectness [6]	We are uncertain whether tocilizumab increases or decreases respiratory failure or ARDS (28 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.88 (CI 95% 0.74 — 1.05) Based on data from 2,129 patients in 7 studies. [7] (Randomized controlled)	161 per 1000	142 per 1000 Difference: **19 fewer** per 1000 (CI 95% 42 fewer — 8 more)	**Low** Due to serious imprecision and serious indirectness [8]	Tocilizumab may make little or no difference to serious adverse events (366 events).
Adverse events End of follow-up 6 Important	Relative risk 1.03 (CI 95% 0.82 — 1.28) Based on data from 1,382 patients in 6 studies. [9] (Randomized controlled)	504 per 1000	519 per 1000 Difference: **15 more** per 1000 (CI 95% 91 fewer — 141 more)	**Low** Due to serious imprecision and serious indirectness [10]	Tocilizumab may make little or no difference to adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Septic shock End of follow-up 6 Important	Relative risk 0.59 (CI 95% 0.26 — 1.35) Based on data from 815 patients in 2 studies. [11] (Randomized controlled)	37 per 1000	22 per 1000 Difference: **15 fewer** per 1000 (CI 95% 27 fewer — 13 more)	**Low** Due to serious imprecision and serious indirectness [12]	Tocilizumab may have little impact on septic shock (22 events).
Admission to ICU End of follow-up 6 Important	Relative risk 0.68 (CI 95% 0.51 — 0.9) Based on data from 520 patients in 3 studies. [13] (Randomized controlled)	300 per 1000	204 per 1000 Difference: **96 fewer** per 1000 (CI 95% 147 fewer — 30 fewer)	**Low** Due to serious imprecision and serious indirectness [14]	Tocilizumab may decrease admission to ICU (135 events).
Discharge from hospital End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.99 — 1.16) Based on data from 4,611 patients in 4 studies. [15] (Randomized controlled)	506 per 1000	541 per 1000 Difference: **35 more** per 1000 (CI 95% 5 fewer — 81 more)	**Low** Due to serious imprecision and serious indirectness [16]	Tocilizumab may increase discharge from hospital.
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.92 — 1.27) Based on data from 65 patients in 1 studies. [17] (Randomized controlled)	871 per 1000	941 per 1000 Difference: **70 more** per 1000 (CI 95% 70 fewer — 235 more)	**Very low** Due to very serious imprecision, very serious indirectness and serious indirectness [18]	We are uncertain whether tocilizumab increases or decreases clinical recovery.
Clinical improvement Within 14 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.12) Based on data from 242 patients in 1 studies. [19] (Randomized controlled)	889 per 1000	916 per 1000 Difference: **27 more** per 1000 (CI 95% 53 fewer — 107 more)	**Very low** Due to very serious imprecision and serious indirectness [20]	We are uncertain whether tocilizumab increases or decreases clinical improvement.
Clinical progression Within 14 days of commencing treatment 6 Important	Relative risk 1.08 (CI 95% 0.72 — 1.62) Based on data from 365 patients in 2 studies. [21] (Randomized controlled)	215 per 1000	232 per 1000 Difference: **17 more** per 1000 (CI 95% 60 fewer — 133 more)	**Low** Due to serious imprecision and serious indirectness [22]	Tocilizumab may have little or no impact on clinical progression.
Time to deterioration Days	Hazard Ratio 1.11 (CI 95% 0.59 — 2.1) Based on data from 45 patients in 1 studies.			**Very low** Due to very serious imprecision and	We are uncertain whether tocilizumab increases or decreases time to discharge.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	(Randomized controlled)			serious indirectness [23]	
Duration of mechanical ventilation Days 6 Important	Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from: 19 patients in 1 studies. [24] (Randomized controlled)	27.9 (Median)	15 (Median) Difference: 12.9 fewer CI 95%	**Very low** Due to very serious imprecision and serious indirectness [25]	We are uncertain whether tocilizumab decreases duration of mechanical ventilation.
Time to improvement Days 6 Important	Based on data from: 219 patients in 1 studies. [26] (Randomized controlled)	5 (Median)	6 (Median) Difference: 1 more CI 95%	**Very low** Due to very serious imprecision and serious indirectness [27]	We are uncertain whether tocilizumab increases or decreases time to improvement.
Duration of hospital stay (mean) Days 6 Important	Based on data from: 129 patients in 1 studies. [28] (Randomized controlled)	14.7 (Mean)	11.3 (Mean) Difference: MD 3.4 lower (CI 95% 6.2 lower — 0.6 lower)	**Low** Due to very serious imprecision [29]	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 patients in 1 studies. (Randomized controlled)	28 (Median)	20 (Median)	**Low** Due to serious imprecision and serious indirectness [30]	Tocilizumab may decrease duration of hospital stay.

1. Systematic review [83] with included studies: Stone 2020, Veiga 2021, REMAP-CAP tocilizumab, Hermine 2020, Rosas 2020, Salvarini 2020, Salama 2020, RECOVERY [total]. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: Serious. Indirectness: Serious.** Differences between the population of interest and those studied.
3. Systematic review [83] with included studies: RECOVERY [total], Rosas 2020, Stone 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Indirectness: Serious.** Differences between the population of interest and those studied.
5. Systematic review [68] with included studies: Hermine 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
7. Systematic review [81] with included studies: REMAP-CAP tocilizumab, Salama 2020, Stone 2020, Veiga 2021, Rosas 2020, Hermine 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide

confidence intervals.
9. Systematic review [81] with included studies: Salama 2020, Veiga 2021, Stone 2020, Wang 2020, Rosas 2020, Hermine 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.
11. Systematic review [71] with included studies: Salama 2020, Rosas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** due to few events.
13. Systematic review [71] with included studies: Hermine 2020, Salvarini 2020, Rosas 2020. **Baseline/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.
15. Systematic review [83] with included studies: Salvarini 2020, Stone 2020, Hermine 2020, RECOVERY [total]. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.
17. Systematic review [68] with included studies: Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
19. Systematic review [68] with included studies: Stone 2020. **Baseline/comparator:** Control arm of reference 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.
21. Systematic review [71] with included studies: Salvarini 2020, Stone 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [68] . **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 [68] . **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.
28. Systematic review [81] with included studies: Veiga 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.6. 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.

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 *[104]*.

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

Low

General adult population
Certainty of the evidence is high for the critical outcome of mortality (day 28). Certainty is moderate for patients 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.

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 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 No important issues with the recommended alternative

As azithromycin is not recommended there are no resource considerations.

Equity No important issues with the recommended alternative

As azithromycin is not recommended there are no equity considerations.

Acceptability No important issues with the recommended alternative

As azithromycin is not recommended there are no acceptability considerations.

Feasibility No important issues with the recommended alternative

As azithromycin is not recommended there are no feasibility considerations.

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

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 *[102][103][107][110][143]*. The vast majority of data are from the RECOVERY trial, which included 7763 adults hospitalised with moderate-to-critical COVID-19 *[107]*. One trial compared azithromycin with standard care in 1388 adult outpatients with mild COVID-19 *[110]*, two trials compared azithromycin plus hydroxychloroquine with hydroxychloroquine alone in 397 adults hospitalised with severe or critical COVID-19 *[102]* and 331 with moderate COVID-19 *[143]*, and one trial compared azithromycin plus hydroxychloroquine and lopinavir-ritonavir with hydroxychloroquine and lopinavir-ritonavir alone in 111 adults hospitalised with severe COVID-19 *[103]*.

We have found one new study comparing azithromycin with standard care (Hinks et al. medRxiv doi: 10.1101/2021.04.21.21255807). This study is currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

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 probably 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), 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 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 outcome of mortality. Certainty is moderate for number of patients 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 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 & 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, 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 *[104]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.92 — 1.1) Based on data from 9,595 patients in 4 studies. [1] (Randomized controlled)	172 per 1000	174 per 1000 Difference: **2 more** per 1000 (CI 95% 14 fewer — 17 more)	**High**	Azithromycin has no impact on death.
Mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.94 (CI 95% 0.79 — 1.14) Based on data from 8,433 patients in 2 studies. [2] (Randomized controlled)	60 per 1000	56 per 1000 Difference: **4 fewer** per 1000 (CI 95% 13 fewer — 8 more)	**High**	Azithromycin has little or no impact on mechanical ventilation or ECMO.
Supplemental oxygen [3] Within 28 days of commencing treatment 6 Important	Relative risk 0.84 (CI 95% 0.38 — 1.85) Based on data from 1,122 patients in 1 studies. [4] (Randomized controlled)	24 per 1000	20 per 1000 Difference: **4 fewer** per 1000 (CI 95% 15 fewer — 20 more)	**Low** Due to very serious imprecision [5]	Azithromycin may have little or no difference on need for supplemental oxygen (25 events).
Serious adverse events End of treatment 6 Important	Relative risk 1.13 (CI 95% 0.9 — 1.42) Based on data from 877 patients in 2 studies. [6] (Randomized controlled)	194 per 1000	219 per 1000 Difference: **25 more** per 1000 (CI 95% 19 fewer — 81 more)	**Moderate** Due to serious imprecision [7]	Azithromycin probably increases number of patients experiencing serious adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events End of treatment 6 Important	Relative risk 1.17 (CI 95% 0.91 — 1.5) Based on data from 438 patients in 1 studies. [8] (Randomized controlled)	337 per 1000	394 per 1000 Difference: 57 more per 1000 (CI 95% 30 fewer — 169 more)	**Low** Due to very serious imprecision [9]	Azithromycin may increase number of patients experiencing adverse events slightly (161 events).
ICU admission End of follow-up 6 Important	Relative risk 0.48 (CI 95% 0.17 — 1.35) Based on data from 1,231 patients in 2 studies. [10] (Randomized controlled)	18 per 1000	9 per 1000 Difference: 9 fewer per 1000 (CI 95% 15 fewer — 6 more)	**Low** Due to very serious imprecision [11]	We are uncertain whether azithromycin increases or decreases ICU admission (17 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.88 — 1.05) Based on data from 1,129 patients in 1 studies. [12] (Randomized controlled)	658 per 1000	632 per 1000 Difference: 26 fewer per 1000 (CI 95% 79 fewer — 33 more)	**Low** Due to very serious imprecision [13]	We are uncertain whether azithromycin increases or decreases clinical recovery (731 events).
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.92 (CI 95% 0.71 — 1.19) Based on data from 8,161 patients in 2 studies. [14] (Randomized controlled)	586 per 1000	539 per 1000 Difference: 47 fewer per 1000 (CI 95% 170 fewer — 111 more)	**Moderate** Due to serious imprecision [15]	Azithromycin probably decreases discharge from hospital slightly (4765 events).
Duration of hospital stay Mean 6 Important	Based on data from: 442 patients in 2 studies. [16] (Randomized controlled)	Difference: MD 0.41 lower (CI 95% 2.42 lower — 1.59 higher)		**Low** Due to serious inconsistency and imprecision [17]	Azithromycin may have little impact on duration of hospital stay.
Duration of hospital stay [18] Median 6 Important	Lower better Based on data from: 7,764 patients in 1 studies. (Randomized controlled)	13 (Median)	12 (Median) CI 95%	**Moderate** Due to serious imprecision [19]	Azithromycin probably makes little difference to duration of hospital stay.

1. Systematic review [108] with included studies: Furtado 2020, PRINCIPLE 2021, Sekhavati 2020, Horby 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [108] with included studies: Horby 2020, PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
3. The number of people who required supplemental oxygen who were not already receiving supplemental oxygen at baseline
4. Systematic review [108] with included studies: PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used

for intervention.
5. **Imprecision: Very serious.** Only data from one study, due to few events.
6. Systematic review [101] with included studies: Cavalcanti 2020, Furtado 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: Serious.** Wide confidence intervals.
8. Systematic review [101] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals.
10. Systematic review [108] with included studies: PRINCIPLE 2021, Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Imprecision: Very serious.** due to few events.
12. Systematic review [108] with included studies: PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
14. Systematic review [106] with included studies: Furtado 2020, Horby 2020. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Imprecision: Serious.** Wide confidence intervals.
16. Systematic review [101] with included studies: Cavalcanti 2020, Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
17. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Imprecision: Serious.** Wide confidence intervals.
18. No IQR or 95% CI reported for Horby (2020)
19. **Imprecision: Serious.** Only data from one study.

6.7. 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.

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 High

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). Certainty is very low for duration of hospital stay due to serious risk of bias (patients and personnel not blinded and the trial was stopped early) and serious imprecision (only one study with low patient numbers).

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 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 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 No important issues with the recommended alternative

As colchicine is not recommended there are no resource considerations.

Equity No important issues with the recommended alternative

As colchicine is not recommended there are no equity considerations.

Acceptability No important issues with the recommended alternative

As colchicine is not recommended there are no acceptability considerations.

Feasibility No important issues with the recommended alternative

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

Population: Colchicine for COVID-19
Intervention: Colchicine
Comparator: Standard care

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 *[488]*. An additional four randomised trials were included—three that compared colchicine with standard care in 240 adults hospitalised with COVID-19 *[216][218][220]* and one (COLCORONA trial) that compared colchicine to placebo in 4488 non-hospitalised adults with confirmed COVID-19 *[494]*.

We have found one new study comparing colchicine with standard care (Mareev et al. doi: 10.18087/cardio.2021.2.n1560). This study is currently under review and, although will not change the recommendation, will be incorporated in a future version of the guideline.

Publication status
Three studies are only available as preprints and have therefore not been peer reviewed (Lopes et al. posted to medRxiv on 11 August 2020 *[218]*, Salehzadeh et al. posted to Res Sq on 21 September 2020 *[220]* and Horby et al. (RECOVERY) posted to medRxiv on 18 May 2021 *[488]*).

The final results of Lopes et al. *[218]* 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.

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. For the three smaller studies, median age ranged from 48 to 65 years and ~50% were women. Pregnant and breastfeeding women were ineligible.

What are the main results?
Colchicine has no impact on mortality (0 fewer deaths 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 duration of hospital stay or the likelihood of experiencing a serious adverse event. However, colchicine probably increases adverse events (147 more per 1000 patients; 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). Certainty is very low for duration of hospital stay due to serious risk of bias (patients and personnel not blinded and the trial was stopped early) and serious imprecision (only one study with low patient numbers).

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 colchicine include diarrhoea and stomach cramps. Colchicine overdose can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock *[215]*. There are several known and potential interactions with other drugs *[215]*.

Children and adolescents
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.

Pregnant and breastfeeding women
Colchicine should be avoided in pregnancy and during breastfeeding, and in children under 2 years of age.

Older people living with frailty or cognitive impairment
Caution should be taken when prescribing colchicine to elderly patients who may be more susceptible to cumulative toxicity.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Colchicine	Certainty of the Evidence (Quality of evidence)	Plain text summary
All-cause mortality Within 21–28 days of commencing treatment	Relative risk 1 (CI 95% 0.93 — 1.07) Based on data from 15,968 patients in 4 studies. [1] (Randomized controlled)	149 per 1000	149 per 1000 Difference: **0 fewer** per 1000 (CI 95% 10 fewer — 10 more)	**High**	Colchicine does not impact death.
Mechanical ventilation Within 21–28 days of commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.91 — 1.13) Based on data from 15,404 patients in 3 studies. [2] (Randomized controlled)	80 per 1000	81 per 1000 Difference: **1 more** per 1000 (CI 95% 7 fewer — 10 more)	**High**	Colchicine has little or no impact on mechanical ventilation.
Serious adverse events End of follow-up 6 Important	Relative risk 0.78 (CI 95% 0.61 — 1) Based on data from 4,517 patients in 2 studies. [3] (Randomized controlled)	61 per 1000	48 per 1000 Difference: **13 fewer** per 1000 (CI 95% 24 fewer — 0 fewer)	**Moderate** Due to serious imprecision [4]	Colchicine probably has little impact on serious adverse events (247 events).
Adverse events End of follow-up 6 Important	Relative risk 1.93 (CI 95% 1.18 — 3.16) Based on data from 4,517 patients in 2 studies. [5] (Randomized controlled)	158 per 1000	305 per 1000 Difference: **147 more** per 1000 (CI 95% 28 more — 341 more)	**Moderate** Due to serious imprecision [6]	Colchicine probably increases adverse events (934 events).
Discontinuation due to adverse events During treatment 6 Important	Based on data from 140 patients in 2 studies. [7] (Randomized controlled)			**Low** Due to very serious imprecision [8]	There were too few who discontinued due to adverse events to determine whether colchicine makes a difference (2 events).
ICU admission Within 21 days of commencing treatment 6 Important	Based on data from 35 patients in 1 studies. [9] (Randomized controlled)			**Low** Due to very serious imprecision [10]	There were too few who were admitted to ICU to determine whether colchicine makes a difference (2 events).
Clinical progression Increase of 2	Relative risk 0.13 (CI 95% 0.02 — 1.02) Based on data from 105 patients in 1 studies. [11]	140 per 1000	18 per 1000	**Low** Due to very serious	There were too few who experienced clinical deterioration to determine whether

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
grades on 7-grade scale; 21 days after commencing treatment 6 Important	(Randomized controlled)	Difference: **122 fewer** per 1000 (CI 95% 137 fewer — 3 more)		imprecision [12]	colchicine makes a difference (8 events).
Discharge from hospital End of treatment 6 Important	Relative risk 0.99 (CI 95% 0.97 — 1.01) Based on data from 11,375 patients in 2 studies. [13] (Randomized controlled)	**704** per 1000	**697** per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer — 7 more)	**High**	Colchicine has little or no impact on discharge from hospital.
Duration of hospital stay Days 6 Important	Lower better Based on data from: 100 patients in 1 studies. (Randomized controlled)	**8.12** (Mean)	**6.28** (Mean) Difference: **1.84 lower** CI 95%	**Very low** Due to very serious risk of bias and very serious imprecision [14]	We are uncertain whether colchicine increase or decreases duration of hospital stay.

1. Systematic review [223] with included studies: RECOVERY 2021, Tardif 2021, Deftereos 2020, Lopes 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [224] with included studies: RECOVERY 2021, Tardif 2021, Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [221] with included studies: Deftereos 2020, Tardif 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** SAEs only occurred in one study.
5. Systematic review [221] with included studies: Deftereos 2020, Tardif 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [221] with included studies: Deftereos 2020, Lopes 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Low number of patients, due to few events.
9. Systematic review [221] with included studies: Lopes 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
11. Systematic review [221] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Low number of patients, Only data from one study.
13. Systematic review [223] with included studies: Lopes 2020, RECOVERY 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: Very 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, Selective outcome reporting, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: Very serious.** Low number of patients, Only data from one study.

6.8. Convalescent plasma

Not recommended

Do not use convalescent plasma 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 convalescent plasma may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include convalescent plasma.

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) *[112]*.

Certainty of the Evidence

Moderate

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 *[113]*. Three studies did not report specific NAb titers of included patients *[118][122][124]*. The remaining studies detected NAb in 76% *[119]*, 49% *[116]*, 80% *[492]* and 54% *[121]* 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 *[125]*.

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 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 No important issues with the recommended alternative

As convalescent plasma is not recommended there are no resource considerations.

Equity No important issues with the recommended alternative

As convalescent plasma is not recommended there are no equity considerations.

Acceptability No important issues with the recommended alternative

As convalescent plasma is not recommended there are no acceptability considerations.

Feasibility No important issues with the recommended alternative

As convalescent plasma is not recommended there are no feasibility considerations.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Convalescent plasma
Comparator: Control

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 nine randomised trials that compared convalescent plasma with standard care in over 12,800 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 *[125]*. The other studies included 160 adults with mild COVID-19 *[122]*, 631 adults with moderate COVID-19 *[116][119][492]* and 525 adults with severe COVID-19 *[113][118][121][124]*.

We have found seven new studies comparing convalescent plasma with standard care (Ray et al. medRxiv doi: 10.1101/2020.11.25.20237883, Salman et al. Egypt J Anaesth doi: 10.1080/11101849.2020.1842087, O'Donnell et al. J Clin Invest doi: 10.1172/JCI150646, Pouladzadeh et al. Intern Emerg Med doi: 10.1007/s11739-021-02734-8, Faqihi et al. Int J Antimicrob doi: 10.1016/j.ijantimicag.2021.106334, Bennett-Guerrero et al. Crit Care Med doi: 10.1097/CCM.0000000000005066 and Koerper et al. medRxiv doi: 10.1101/2021.05.10.21256192). These studies are currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

Publication status
One study is only available as a preprint (posted to medRxiv on 29 September 2020) and has therefore not been peer reviewed *[116]*.

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 (16 fewer per 1000 patients; RR 0.93, CI 95% 0.79 to 1.10; 12,872 patients in 9 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 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 *[113]*. Three studies did not report specific NAb titers of included patients *[118][122][124]*. The remaining studies detected NAb in 76% *[119]*, 49% *[116]*, 80% *[492]* and 54% *[121]* 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 *[125]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.93 (CI 95% 0.79 — 1.1) Based on data from 12,872 patients in 9 studies. [1] (Randomized controlled)	235 per 1000	219 per 1000 Difference: **16 fewer** per 1000 (CI 95% 49 fewer — 24 more)	**Moderate** Due to serious imprecision [2]	Convalescent plasma probably has little impact on death.
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 patients in 4 studies. [3] (Randomized controlled)	124 per 1000	122 per 1000 Difference: **2 fewer** per 1000 (CI 95% 14 fewer — 10 more)	**High**	Convalescent plasma makes little or no difference to invasive mechanical ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 patients in 1 studies. [4] (Randomized controlled)	239 per 1000	232 per 1000 Difference: 7 fewer per 1000 (CI 95% 26 fewer — 12 more)	**Moderate** Due to serious imprecision [5]	Convalescent plasma probably has little or no impact on non-invasive ventilation.
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 patients in 1 studies. [6] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [7]	We are uncertain whether convalescent plasma increases or decreases respiratory failure or ARDS.
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.24 (CI 95% 0.81 — 1.9) Based on data from 414 patients in 2 studies. [8] (Randomized controlled)	176 per 1000	218 per 1000 Difference: 42 more per 1000 (CI 95% 33 fewer — 158 more)	**Low** Due to serious risk of bias and imprecision [9]	Convalescent plasma may increase serious adverse events slightly (86 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.47 (CI 95% 0.38 — 5.74) Based on data from 370 patients in 2 studies. [10] (Randomized controlled)	537 per 1000	789 per 1000 Difference: 252 more per 1000 (CI 95% 333 fewer — 2,545 more)	**Low** Due to serious risk of bias and imprecision [11]	Convalescent plasma may increase adverse events (222 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.75 (CI 95% 0.36 — 1.59) Based on data from 493 patients in 2 studies. [12] (Randomized controlled)	373 per 1000	280 per 1000 Difference: 93 fewer per 1000 (CI 95% 239 fewer — 220 more)	**Low** Due to serious risk of bias and imprecision [13]	Convalescent plasma may decrease ICU admission slightly (194 events).
Clinical deterioration (progression to severe/critical) [14] Within 28 days of commencing treatment 6 Important	Relative risk 0.71 (CI 95% 0.18 — 2.78) Based on data from 545 patients in 2 studies. [15] (Randomized controlled)	74 per 1000	53 per 1000 Difference: 21 fewer per 1000 (CI 95% 61 fewer — 132 more)	**Low** Due to serious risk of bias and imprecision [16]	Convalescent plasma may have little impact on clinical deterioration (progression to severe/ critical) at day 28 (37 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Clinical improvement Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.84 — 1.18) Based on data from 435 patients in 2 studies. [17] (Randomized controlled)	673 per 1000	666 per 1000 Difference: 7 fewer per 1000 (CI 95% 108 fewer — 121 more)	**Low** Due to serious risk of bias and imprecision [18]	Convalescent plasma may make little or no difference to clinical improvement at day 28 (287 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.9 (CI 95% 0.76 — 1.06) Based on data from 333 patients in 1 studies. [19] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [20]	We are uncertain whether convalescent plasma worsens clinical recovery (223 events).
Hospital discharge Within 28 days of commencing treatment 6 Important	Relative risk 1.01 (CI 95% 0.96 — 1.06) Based on data from 12,073 patients in 4 studies. [21] (Randomized controlled)	668 per 1000	675 per 1000 Difference: 7 more per 1000 (CI 95% 27 fewer — 40 more)	**High**	Convalescent plasma has little or no impact on hospital discharge.
Resolution of dyspnoea End of treatment 6 Important	Relative risk 1.21 (CI 95% 0.87 — 1.68) Based on data from 797 patients in 2 studies. [22] (Randomized controlled)	371 per 1000	449 per 1000 Difference: 78 more per 1000 (CI 95% 48 fewer — 252 more)	**Low** Due to serious risk of bias and imprecision [23]	Convalescent plasma may increase resolution of dyspnoea slightly (285 events).
Viral nucleic acid negative 72 hours after commencing treatment 6 Important	Relative risk 2.33 (CI 95% 1.54 — 3.52) Based on data from 87 patients in 1 studies. [24] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [25]	Convalescent plasma may increase number of patients who are viral nucleic acid negative at 72 hours.
Time to improvement Days 6 Important	Based on data from: 382 patients in 2 studies. (Randomized controlled)	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).		**Low** Due to serious risk of bias and imprecision [26]	We are uncertain whether convalescent plasma increases or decreases time to improvement.
Time to	Based on data from: 797 patients in 2 studies.	Agarwal 2020 (n=464) and Simonovich 2020 (n=333) both reported time to		**Low** Due to serious	Convalescent plasma probably has little impact

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
discharge from hospital Days 6 Important	(Randomized controlled)	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).		risk of bias and imprecision [27]	on time to discharge from hospital.

1. Systematic review [123] with included studies: RECOVERY 2021, Gharbharan 2020, Agarwal 2020, Libster 2020, Li 2020, AlQahtani 2020, Avendano-Sola 2020, Simonovich 2020, Rasheed 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [123] with included studies: Libster 2020, Agarwal 2020, Simonovich 2020, RECOVERY 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [123] with included studies: RECOVERY 2021. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Imprecision: Serious.** Only data from one study.
6. Systematic review [120] with included studies: Libster 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. **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.
8. Systematic review [120] with included studies: Avendano-Sola 2020, Simonovich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **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.
10. Systematic review [120] with included studies: AlQahtani 2020, Simonovich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **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.
12. Systematic review [120] with included studies: Libster 2020, Simonovich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **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.
14. Measured by the number of patients who progressed from moderate to either severe or critical illness
15. Systematic review [111] with included studies: Avendano-Sola 2020, Agarwal 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Risk of Bias: Serious.** due to the high proportion of patients in the standard care arm possessing neutralising antibodies at baseline.. **Imprecision: Serious.** due to low event numbers.
17. Systematic review [120] with included studies: Li 2020, Simonovich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **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.
19. Systematic review [120] with included studies: Simonovich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **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.** Wide confidence intervals, Only data from one study.
21. Systematic review [123] with included studies: Simonovich 2020, RECOVERY 2021, Li 2020, Avendano-Sola 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. Systematic review [120] with included studies: Agarwal 2020, Simonovich 2020. **Baseline/comparator:** Control arm of reference used for intervention.

23. **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.
24. Systematic review [111] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
25. **Risk of Bias: Serious.** due to the high proportion of patients in the standard care arm possessing neutralising antibodies at baseline.. **Imprecision: Very serious.** Low number of patients, Only data from one study.
26. **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.
27. **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.

6.9. 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.

Evidence To Decision

Benefits and harms — Important 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 — High

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 — We expect few to want the intervention

The Consumer Panel believes that as there is substantial evidence demonstrating well-known harms of hydroxychloroquine,

informed patients would not choose this treatment.

Resources No important issues with the recommended alternative

As hydroxychloroquine is not recommended there are no resource considerations.

Equity No important issues with the recommended alternative

As hydroxychloroquine is not recommended there are no equity considerations.

Acceptability No important issues with the recommended alternative

As hydroxychloroquine is not recommended there are no acceptability considerations.

Feasibility No important issues with the recommended alternative

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

Population: Patients with COVID-19
Intervention: Hydroxychloroquine
Comparator: Standard care

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 23 randomised trials that compared hydroxychloroquine with standard care in over 10,800 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 *[149][51]*.

Publication status
Five studies, which contribute 410 patients to the results, are only available as preprints and have therefore not been peer reviewed *[130][136][282][484][486]*.

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 *[155]*. The proportion of women ranged from 20 to 72% with the exception of one study in which only 1.5% of participants were female *[160]*. 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	Number of patients	References
Mild	1405	*[137][138][159][185][486]*
Mild-Moderate	916	*[143][154][155][160]*
Moderate	192	*[129][130][136][282]*
Mild-Moderate-Severe	2676	*[51][133][145][153]*
Moderate-Severe	4881	*[146][148][149]*
Severe	612	*[484][487][491]*

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 mortality, 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 & 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 hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiomyopathy *[134]*. There are several known and potential interactions with other drugs *[134]*. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms *[134]*.

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, with no increase in fetal malformations *[139][140]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[139][140][141]*. While this evidence is reassuring, further research is needed.

Children and adolescents
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of follow-up 9 Critical	Relative risk 1.06 (CI 95% 0.97 — 1.16) Based on data from 10,382 patients in 19 studies. [1] (Randomized controlled)	**168** per 1000	**178** per 1000 Difference: **10 more** per 1000 (CI 95% 5 fewer — 27 more)	**High**	Hydroxychloroquine does not decrease death.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Invasive mechanical ventilation or ECMO End of follow-up 9 Critical	Relative risk 1.08 (CI 95% 0.91 — 1.28) Based on data from 5,701 patients in 8 studies. [2] (Randomized controlled)	85 per 1000	92 per 1000 Difference: **7 more** per 1000 (CI 95% 8 fewer — 24 more)	**High**	Hydroxychloroquine has no impact on the need for invasive mechanical ventilation or ECMO.
Patients requiring ventilation [3] Within 28 days of commencing treatment 6 Important	Relative risk 1.09 (CI 95% 0.79 — 1.49) Based on data from 1,686 patients in 1 studies. [4] (Randomized controlled)	80 per 1000	87 per 1000 Difference: **7 more** per 1000 (CI 95% 17 fewer — 39 more)	**Moderate** Due to serious imprecision [5]	Hydroxychloroquine probably has little impact on number of patients requiring ventilation (141 events).
Serious adverse events End of follow-up 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.37) Based on data from 2,721 patients in 11 studies. [6]	68 per 1000	74 per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer — 25 more)	**Moderate** Due to serious risk of bias	Hydroxychloroquine probably has little impact on serious adverse events
Adverse events End of follow-up 6 Important	Relative risk 1.67 (CI 95% 1.21 — 2.3) Based on data from 2,077 patients in 11 studies. [7]	322 per 1000	538 per 1000 Difference: **216 more** per 1000 (CI 95% 68 more — 419 more)	**Moderate** Due to serious risk of bias	Hydroxychloroquine probably increases adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 2.13 (CI 95% 0.65 — 6.95) Based on data from 398 patients in 2 studies. [8]	20 per 1000	43 per 1000 Difference: **23 more** per 1000 (CI 95% 7 fewer — 119 more)	**Low** Due to very serious imprecision	We are uncertain whether hydroxychloroquine decreases or increases treatment discontinuation due to adverse events (12 events).
Clinical improvement Within 28 days after commencing treatment 6 Important	Relative risk 1.05 (CI 95% 0.91 — 1.2) Based on data from 247 patients in 1 studies. [9] (Randomized controlled)	756 per 1000	794 per 1000 Difference: **38 more** per 1000 (CI 95% 68 fewer — 151 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether hydroxychloroquine improves or worsens clinical improvement (191 events).
Clinical deterioration Within 28 days	Relative risk 0.81 (CI 95% 0.35 — 1.89) Based on data from 247 patients in 1 studies. [11]	89 per 1000	72 per 1000	**Low** Due to very serious imprecision [12]	We are uncertain whether hydroxychloroquine improves or worsens

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
after commencing treatment 6 Important	(Randomized controlled)	Difference: **17 fewer** per 1000 (CI 95% 58 fewer — 79 more)			clinical deterioration (20 events).
Virological clearance (negative PCR) Day 6-14 of treatment 6 Important	Relative risk 1.02 (CI 95% 0.93 — 1.11) Based on data from 750 patients in 5 studies. [13]	410 per 1000	418 per 1000 Difference: **8 more** per 1000 (CI 95% 29 fewer — 45 more)	**Low** Due to very serious imprecision	Hydroxychloroquine may have little impact on virological clearance (negative PCR).
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.96 — 1.01) Based on data from 7,365 patients in 5 studies. [14]	694 per 1000	680 per 1000 Difference: **14 fewer** per 1000 (CI 95% 28 fewer — 7 more)	**High**	Hydroxychloroquine has little impact on discharge from hospital.
Hospitalisation End of follow up 6 Important	Relative risk 0.68 (CI 95% 0.41 — 1.13) Based on data from 1,345 patients in 5 studies. [15]	55 per 1000	37 per 1000 Difference: **18 fewer** per 1000 (CI 95% 32 fewer — 7 more)	**Low** Due to serious imprecision and serious risk of bias	We are uncertain whether hydroxychloroquine decreases or increases hospitalisation (62 events).
Duration of hospital stay Days 6 Important	Based on data from: 128 patients in 1 studies. [16] (Randomized controlled)	6.8 (Mean)	9.75 (Mean) Difference: **MD 2.95 higher** (CI 95% 0.07 higher — 5.83 higher)	**Low** Due to very serious imprecision [17]	We are uncertain whether hydroxychloroquine increases or decreases duration of hospital stay.

1. Systematic review [156] with included studies: Skipper 2020, Omrani 2020, Pan 2020, Abd-Elsalam 2020, Ader 2021, Gonzalez 2021, Cavalcanti 2020, Ulrich 2020, Self 2020, Hernandez Cardenas 2021, Horby 2020, Chen L 2020, Dubee 2020, Amaravadi 2021, Chen J 2020, Ra Neto 2021, Reis 2021, Johnston 2021, Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [156] with included studies: Self 2020, Ulrich 2020, Mitja 2020, Ra Neto 2021, Dubee 2020, Horby 2020, Abd-Elsalam 2020, Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. Includes non-invasive ventilation, invasive ventilation, mechanical ventilation, ECMO
4. Systematic review [147] with included studies: Pan 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Imprecision: Serious.** Only data from one study.
6. Systematic review [156] with included studies: Lyngbakken 2020, Cavalcanti 2020, Chen L 2020, Chen Z 2020, Ader 2021, Tang 2020, Self 2020, Skipper 2020, Mitja 2020, Omrani 2020, Dubee 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [156] with included studies: Amaravadi 2021, Cavalcanti 2020, Chen J 2020, Ader 2021, Ulrich 2020, Skipper 2020, Tang 2020, Dubee 2020, Mitja 2020, Chen L 2020, Chen Z 2020. **Baseline/comparator:** Control arm of

reference used for intervention.
8. Systematic review [156] with included studies: Dubee 2020, Johnston 2021. **Baseline/comparator:** Control arm of reference used for intervention.
9. Systematic review [151] with included studies: Dubee 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals.
11. Systematic review [151] with included studies: Dubee 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals, Only data from one study.
13. Systematic review [156] with included studies: Tang 2020, Johnston 2021, Omrani 2020, Chen J 2020, Dubee 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. Systematic review [156] with included studies: Self 2020, Horby 2020, Pan 2020, Dubee 2020, Gonzalez 2021. **Baseline/comparator:** Control arm of reference used for intervention.
15. Systematic review [156] with included studies: Reis 2021, Amaravadi 2021, Johnston 2021, Skipper 2020, Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [147] with included studies: Ulrich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
17. **Imprecision: Very serious.** Low number of patients, Only data from one study.

6.10. Hydroxychloroquine plus azithromycin

Not recommended

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.

Evidence To Decision

Benefits and harms Important 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 Low

General adult population
Certainty of the evidence is low for the critical outcomes of mortality at day 15 and the need for invasive mechanical 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.

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 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 No important issues with the recommended alternative

As hydroxychloroquine plus azithromycin is not recommended there are no resource considerations.

Equity No important issues with the recommended alternative

As hydroxychloroquine plus azithromycin is not recommended there are no equity considerations.

Acceptability No important issues with the recommended alternative

As hydroxychloroquine plus azithromycin is not recommended there are no acceptability considerations.

Feasibility No important issues with the recommended alternative

As hydroxychloroquine plus azithromycin is not recommended there are no feasibility considerations.

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.

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) *[143]* and two included 464 adult outpatients with mild COVID-19 *[159][160]*.

We have found one new study comparing hydroxychloroquine plus azithromycin with placebo (Sivapalan et al. doi: 10.1183/13993003.00752-2021). This study is currently under review and, although will not change the recommendation, will be incorporated in a future version of the guideline.

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 *[134]*.

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 *[104]*.

In addition to the known harms associated with hydroxychloroquine and azithromycin, there are concerns regarding the safety of combination treatment using these two therapeutics.

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, with no increase in fetal malformations *[139][140]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[139][140][141]*. 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).

Children and adolescents
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) *[104]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** HCQ+AZM	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 15 days of commencing treatment 9 Critical	Relative risk 0.6 (CI 95% 0.15 — 2.49) Based on data from 345 patients in 1 studies. [1] (Randomized controlled)	29 per 1000	17 per 1000 Difference: **12 fewer** per 1000 (CI 95% 25 fewer — 43 more)	**Low** Due to very serious imprecision [2]	There were too few who died to determine whether hydroxychloroquine plus azithromycin makes a difference (8 events).
All-cause mortality End of follow-up 9 Critical	Based on data from 459 patients in 2 studies. [3] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether Hydroxychloroquine plus azithromycin increases or decreases all-cause mortality (0 events)
Invasive mechanical ventilation Within 15 days of commencing treatment 9 Critical	Relative risk 1.59 (CI 95% 0.8 — 3.18) Based on data from 345 patients in 1 studies. [5] (Randomized controlled)	69 per 1000	110 per 1000 Difference: **41 more** per 1000 (CI 95% 14 fewer — 150 more)	**Low** Due to very serious imprecision [6]	We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases the need for invasive mechanical ventilation (31 events).
Adverse events End of follow-up 6 Important	Relative risk 2.38 (CI 95% 1.05 — 5.37) Based on data from 576 patients in 2 studies. [7] (Randomized controlled)	173 per 1000	412 per 1000 Difference: **239 more** per 1000 (CI 95% 9 more — 756 more)	**Low** Due to serious risk of bias and serious imprecision [8]	Hydroxychloroquine plus azithromycin may increase adverse events (158 events)
Serious adverse events End of follow-up 6 Important	Relative risk 1.85 (CI 95% 0.36 — 9.43) Based on data from 715 patients in 2 studies. [9] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [10]	There were too few who experienced a serious adverse event to determine whether hydroxychloroquine plus azithromycin makes a difference (7 events).
Discharge from hospital Within 15 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.86 — 1.08) Based on data from 345 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [12]	Hydroxychloroquine plus azithromycin may have little impact on discharge from hospital (266 events).
Hospitalisation End of follow-up	Relative risk 0.77 (CI 95% 0.09 — 6.83) Based on data from 459 patients in 2 studies. [13]	13 per 1000	10 per 1000	**Low** Due to very serious imprecision [14]	Hydroxychloroquine plus azithromycin may have little or no difference on hospitalisation (5 events)

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** HCQ+AZM	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	(Randomized controlled)	Difference: **3 fewer** per 1000 (CI 95% 12 fewer — 76 more)			
Virological clearance (negative PCR) End of follow-up 6 Important	Relative risk 0.64 (CI 95% 0.43 — 0.96) Based on data from 292 patients in 1 studies. [15] (Randomized controlled)	**315** per 1000	**202** per 1000 Difference: **113 fewer** per 1000 (CI 95% 180 fewer — 13 fewer)	**Low** Due to very serious imprecision [16]	Hydroxychloroquine plus azithromycin may decrease virological clearance slightly (75 events)
Duration of hospital stay Days 6 Important	Based on data from: 345 patients in 1 studies. [17] (Randomized controlled)	**9.5** (Mean)	**10.3** (Mean) Difference: **MD 0.8 higher** (CI 95% 0.85 lower — 2.45 higher)	**Very low** Due to serious risk of bias and very serious imprecision [18]	We are uncertain if hydroxychloroquine plus azithromycin increases duration of hospital stay.

1. Systematic review [157] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** due to few events, Only data from one study.
3. Systematic review [158] with included studies: Omrani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
5. Systematic review [157] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** due to few events, Only data from one study.
7. Systematic review [158] with included studies: Johnston 2021, Cavalcanti 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Wide confidence intervals.
9. Systematic review [158] with included studies: Cavalcanti 2020, Omrani 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Very serious.** due to few events.
11. Systematic review [157] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [158] with included studies: Omrani 2020, Johnston 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, due to few events.
15. Systematic review [158] with included studies: Omrani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
17. Systematic review [157] with included studies: Cavalcanti 2020. **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.** Only data from one study, Wide confidence intervals.

6.11. Interferon β-1a

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.

Evidence To Decision

Benefits and harms — Important 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 — High

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 — 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 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 Important issues, or potential issues not investigated

As interferon β-1a is not recommended there are no resource considerations.

Equity Important issues, or potential issues not investigated

As interferon β-1a is not recommended there are no equity considerations.

Acceptability Important issues, or potential issues not investigated

As interferon β-1a is not recommended there are no acceptability considerations.

Feasibility Important issues, or potential issues not investigated

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
Intervention: Interferon β-1a
Comparator: Standard care

Summary

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 *[51]*. The second, smaller trial randomised 81 adults hospitalised with severe COVID-19 *[164]*.

We have found one new study comparing interferon β-1a with standard care (Darazam et al. Sci Rep doi: 10.1038/s41598-021-86859-y). This study is currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

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 *[161][162]*.

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 *[163]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1a	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 1.07 (CI 95% 0.91 — 1.27) Based on data from 4,181 patients in 2 studies. [1] (Randomized controlled)	112 per 1000	120 per 1000 Difference: 8 more per 1000 (CI 95% 10 fewer — 30 more)	**High**	Interferon β-1a does not decrease death.
Patients requiring ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.99 (CI 95% 0.83 — 1.17) Based on data from 3,912 patients in 2 studies. [2] (Randomized controlled)	116 per 1000	115 per 1000 Difference: 1 fewer per 1000 (CI 95% 20 fewer — 20 more)	**High**	Interferon β-1a has no impact on number of patients requiring ventilation.
Septic shock Within 28 days of commencing treatment	Relative risk 1.67 (CI 95% 0.7 — 3.99) Based on data from 91 patients in 1 studies. [3]			**Very low** Due to serious risk of bias and very serious	We are uncertain whether interferon β-1a improves or worsens septic shock (17 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1a	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	(Randomized controlled)			imprecision [4]	
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.95 (CI 95% 0.92 — 0.99) Based on data from 4,181 patients in 2 studies. [5] (Randomized controlled)	778 per 1000	739 per 1000 Difference: **39 fewer** per 1000 (CI 95% 62 fewer — 8 fewer)	**High**	Interferon β-1a has no impact on number of patients discharged from hospital.
Duration of hospital stay Mean days to discharge 6 Important	Based on data from: 81 patients in 1 studies. [6] (Randomized controlled)	12.3 (Mean)	14.8 (Mean) Difference: **MD 2.55 higher** (CI 95% 0.92 lower — 6.02 higher)	**Very low** Due to serious risk of bias and very serious imprecision [7]	We are uncertain whether interferon β-1a increases or decreases duration of hospital stay.

1. Systematic review [166] with included studies: Davoudi-Monfared 2020, Solidarity 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [167] with included studies: Solidarity 2020, Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [166] with included studies: Davoudi-Monfared 2020. **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, 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.
5. Systematic review [166] with included studies: Davoudi-Monfared 2020, Solidarity 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [166] with included studies: Davoudi-Monfared 2020. **Baseline/comparator:** 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.

6.12. Interferon β-1a plus lopinavir-ritonavir

Not recommended

Do not use intravenous interferon β-1a plus lopinavir-ritonavir 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 intravenous interferon β-1a nor lopinavir-ritonavir as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

Evidence To Decision

Benefits and harms

Important 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

Very low

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 outcomes 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 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

No important issues with the recommended alternative

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no resource considerations.

Equity No important issues with the recommended alternative

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no equity considerations.

Acceptability No important issues with the recommended alternative

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no acceptability considerations.

Feasibility No important issues with the recommended alternative

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 *[491]*.

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.

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.
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1a plus lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 1.19 (CI 95% 0.57 — 2.49) Based on data from 293 patients in 1 studies. [1] (Randomized controlled)	81 per 1000	96 per 1000 Difference: **15 more** per 1000 (CI 95% 35 fewer — 121 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether interferon β-1a plus lopinavir-ritonavir increases or decreases all-cause mortality (26 events)
Serious adverse events End of follow-up 6 Important	Relative risk 1.41 (CI 95% 1.09 — 1.81) Based on data from 292 patients in 1 studies. [3] (Randomized controlled)	385 per 1000	543 per 1000 Difference: **158 more** per 1000 (CI 95% 35 more — 312 more)	**Very low** Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether interferon β-1a plus lopinavir-ritonavir increases serious adverse events (135 events).
Adverse events End of follow-up 6 Important	Relative risk 1.15 (CI 95% 1.01 — 1.3) Based on data from 292 patients in 1 studies. [5] (Randomized controlled)	709 per 1000	815 per 1000 Difference: **106 more** per 1000 (CI 95% 7 more — 213 more)	**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).

1. Systematic review [170] with included studies: Ader 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **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.**
3. Systematic review [172] with included studies: Ader 2021. **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, 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. **Publication bias: No serious.**
5. Systematic review [170] with included studies: Ader 2021. **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, 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, Wide confidence intervals. **Publication bias: No serious.**

6.13. Lopinavir-ritonavir

Not recommended

Do not use lopinavir-ritonavir 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 lopinavir-ritonavir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include lopinavir-ritonavir.

Evidence To Decision

Benefits and harms Important 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 *[131][132][174]*. 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 Moderate

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 — 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 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.

Resources — Important issues, or potential issues not investigated

As lopinavir-ritonavir is not recommended there are no resource considerations.

Equity — Important issues, or potential issues not investigated

As lopinavir-ritonavir is not recommended there are no equity considerations.

Acceptability — Important issues, or potential issues not investigated

As lopinavir-ritonavir is not recommended there are no acceptability considerations.

Feasibility — Important issues, or potential issues not investigated

As lopinavir-ritonavir is not recommended there are no feasibility considerations.

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 *[51][131][132][174][181][185][491]*. The vast majority of data come from the RECOVERY and WHO SOLIDARITY trials, which included 5040 *[181]* and 2771 patients *[51]* 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 *[174][185]*.

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 *[173]*.

Children and adolescents
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.

Pregnant and breastfeeding women
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 *[175][176][177][179][180]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of treatment 9 Critical	Relative risk 1.02 (CI 95% 0.93 — 1.12) Based on data from 8,825 patients in 6 studies. [1]	180 per 1000	184 per 1000 Difference: **4 more** per 1000 (CI 95% 13 fewer — 22 more)	**High**	Lopinavir/ritonavir has no impact on mortality.
Invasive mechanical ventilation or ECMO End of treatment 9 Critical	Relative risk 1.15 (CI 95% 0.95 — 1.38) Based on data from 5,074 patients in 3 studies. [2] (Randomized controlled)	84 per 1000	97 per 1000 Difference: **13 more** per 1000 (CI 95% 4 fewer — 32 more)	**High**	Lopinavir-ritonavir has no impact on patients requiring invasive mechanical ventilation or ECMO.
Non-invasive or invasive ventilation Within 28 days after commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.8 — 1.29) Based on data from 2,545 patients in 1 studies. [3] (Randomized controlled)	95 per 1000	97 per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer — 28 more)	**Moderate** Only one study [4]	Lopinavir/ritonavir probably has no impact on patients requiring non-invasive or invasive ventilation.
Respiratory failure or ARDS End of treatment 6 Important	Relative risk 0.7 (CI 95% 0.49 — 1) Based on data from 540 patients in 3 studies. [5]	231 per 1000	162 per 1000 Difference: **69 fewer** per 1000 (CI 95% 118 fewer — 0 fewer)	**Low** Due to serious inconsistency and serious imprecision	Lopinavir-ritonavir may decrease respiratory failure or ARDS (104 events).
Serious adverse events End of treatment 6 Important	Relative risk 1.1 (CI 95% 0.66 — 1.82) Based on data from 966 patients in 4 studies. [6] (Randomized controlled)	213 per 1000	234 per 1000 Difference: **21 more** per 1000 (CI 95% 72 fewer — 175 more)	**Low** Due to serious risk of bias and serious imprecision [7]	Lopinavir-ritonavir may have little or no difference on serious adverse events (217 events).
Adverse events End of treatment 6 Important	Relative risk 1.32 (CI 95% 0.93 — 1.86) Based on data from 1,031 patients in 5 studies. [8] (Randomized controlled)	396 per 1000	523 per 1000 Difference: **127 more** per 1000 (CI 95% 28 fewer — 341 more)	**Low** Due to serious risk of bias and serious imprecision [9]	Lopinavir-ritonavir may increase adverse events.
Clinical improvement Day 14 after treatment	Relative risk 1.15 (CI 95% 0.92 — 1.42) Based on data from 534 patients in 3 studies. [10]	324 per 1000	373 per 1000 Difference: **49 more** per 1000 (CI 95% 26 fewer — 136 more)	**Low** Due to serious risk of bias and serious imprecision [11]	Lopinavir-ritonavir may increase clinical improvement slightly.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important **Discharge from hospital** 28 Days after commencing treatment 6 Important	Relative risk 1 (CI 95% 0.98 — 1.03) Based on data from 8,104 patients in 3 studies. [12]	742 per 1000	742 per 1000 Difference: **0 fewer** per 1000 (CI 95% 15 fewer — 22 more)	**High**	Lopinavir/ritonavir has no impact on discharge from hospital at 28 days.
Hospitalisation End of follow-up 6 Important	Relative risk 1.24 (CI 95% 0.6 — 2.56) Based on data from 471 patients in 1 studies. [13] (Randomized controlled)	53 per 1000	66 per 1000 Difference: **13 more** per 1000 (CI 95% 21 fewer — 83 more)	**Low** Due to very serious imprecision [14]	We are uncertain whether lopinavir-ritonavir increases or decreases hospitalisation.
Time to discharge from hospital Days 6 Important	Lower better Based on data from: 5,040 patients in 1 studies. (Randomized controlled)	11 (Median)	11 (Median) CI 95%	**Low** Due to serious risk of bias and only one study [15]	Lopinavir-ritonavir may have little impact on time to discharge from hospital.

1. Systematic review [184] with included studies: Pan 2020, Reis 2021, Cao 2020, Ader 2021, Li 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [182] with included studies: Cao 2020, Li 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [182] with included studies: Pan 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Only data from one study.
5. Systematic review [184] with included studies: Ader 2021, Cao 2020, Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [184] with included studies: Ader 2021, Li 2020, Reis 2021, Cao 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
8. Systematic review [184] with included studies: Ader 2021, Reis 2021, Cao 2020, Li 2020, Zheng 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
10. Systematic review [184] with included studies: Ader 2021, Cao 2020, Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
12. Systematic review [184] with included studies: RECOVERY, Ader 2021, Pan 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. Systematic review [184] with included studies: Reis 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14. 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 we have sufficient evidence to make recommendations in support of using or not using some treatments (baricitinib, corticosteroids, remdesivir, sarilumab, tocilizumab, azithromycin, convalescent plasma, hydroxychloroquine, interferon β-1a and lopinavir-ritonavir), for many other 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 the 'Disease-modifying treatments' section above.

6.14.1. Angiotensin 2 receptor agonist (C21)

Not recommended

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

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.

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 Very low

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 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.

Resources 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, 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 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 *[489]*.

Publication status
The study is only available as a preprint (posted to medRxiv on 28 January 2021) and has therefore not been peer reviewed.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** C21	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Day 14 9 Critical	Relative risk 0.36 (CI 95% 0.04 — 3.35) Based on data from 106 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious imprecision and serious publication bias [2]	We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases mortality (4 deaths).
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.27 (CI 95% 0.03 — 2.33) Based on data from 106 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision and serious publication bias [4]	We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases invasive mechanical ventilation (5 events).
Supplemental oxygen End of follow-up 6 Important	Relative risk 0.1 (CI 95% 0.01 — 0.73) Based on data from 106 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to very serious imprecision and serious publication bias [6]	We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases supplemental oxygen (12 events).

1. Systematic review [189] with included studies: Tornling 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [189] with included studies: Tornling 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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].
5. Systematic review [189] with included studies: Tornling 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.2. Anakinra

Not recommended

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.

Evidence To Decision

Benefits and harms — Important 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 *[187]*. 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 — Low

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 — 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
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 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, 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 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 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 *[188]*.

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 decease 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 thrombocytopaenia *[187]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Anakinra	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.93 (CI 95% 0.47 — 1.83) Based on data from 114 patients in 1 studies. [1] (Randomized controlled)	236 per 1000	219 per 1000 Difference: 17 fewer per 1000 (CI 95% 125 fewer — 196 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether anakinra impacts death (26 events).
All-cause mortality or mechanical ventilation [composite] Within 14 days of commencing treatment 9 Critical	Relative risk 0.98 (CI 95% 0.59 — 1.63) Based on data from 114 patients in 1 studies. [3] (Randomized controlled)	345 per 1000	338 per 1000 Difference: 7 fewer per 1000 (CI 95% 141 fewer — 217 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether anakinra impacts the composite outcome of death or mechanical ventilation (39 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Anakinra	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Respiratory failure or ARDS Within 28 days of commencing treatment 6 Important	Relative risk 0.79 (CI 95% 0.39 — 1.61) Based on data from 114 patients in 1 studies. [5] (Randomized controlled)	236 per 1000	186 per 1000 Difference: **50 fewer** per 1000 (CI 95% 144 fewer — 144 more)	**Low** Due to very serious imprecision [6]	We are uncertain whether anakinra increases or decreases respiratory failure or ARDS (24 events).
Sepsis Within 28 days of commencing treatment 6 Important	Relative risk 2.33 (CI 95% 0.78 — 7) Based on data from 114 patients in 1 studies. [7] (Randomized controlled)	73 per 1000	170 per 1000 Difference: **97 more** per 1000 (CI 95% 16 fewer — 438 more)	**Very low** Due to serious risk of bias and very serious imprecision [8]	We are uncertain whether anakinra increases or decreases sepsis (14 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.18 (CI 95% 0.78 — 1.76) Based on data from 114 patients in 1 studies. [9] (Randomized controlled)	418 per 1000	493 per 1000 Difference: **75 more** per 1000 (CI 95% 92 fewer — 318 more)	**Very low** Due to serious risk of bias and very serious imprecision [10]	We are uncertain whether anakinra increases or decreases adverse events (52 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 0.77 — 1.85) Based on data from 114 patients in 1 studies. [11] (Randomized controlled)	382 per 1000	458 per 1000 Difference: **76 more** per 1000 (CI 95% 88 fewer — 325 more)	**Very low** Due to serious risk of bias and very serious imprecision [12]	We are uncertain whether anakinra increases or decreases serious adverse events (48 events).
Hospital discharge Within 28 days of commencing treatment 6 Important	Relative risk 0.93 (CI 95% 0.69 — 1.26) Based on data from 114 patients in 1 studies. [13] (Randomized controlled)	618 per 1000	575 per 1000 Difference: **43 fewer** per 1000 (CI 95% 192 fewer — 161 more)	**Very low** Due to serious risk of bias and very serious imprecision [14]	We are uncertain whether anakinra increases or decreases hospital discharge (68 events).

1. Systematic review [186] with included studies: CORIMUNO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [186] with included studies: CORIMUNO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
5. Systematic review [186] with included studies: CORIMUNO-19 2020. **Baseline/comparator:** Control arm of

reference used for intervention.
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.
7. Systematic review [186] with included studies: CORIMUNO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: 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.
9. Systematic review [186] with included studies: CORIMUNO-19 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study, Low number of patients.
11. Systematic review [186] with included studies: CORIMUNO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, 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.
13. Systematic review [186] with included studies: CORIMUNO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, 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.

6.14.3. Aprepitant

Not recommended

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.

Evidence To Decision

Benefits and harms Important 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 Very low

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 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
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 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, 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 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 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 *[190]*.

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 *[191]*. There are several known and potential interactions with other drugs, including hormonal contraceptives *[191]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Aprepitant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 5 days of commencing treatment 9 Critical	Relative risk 0.8 (CI 95% 0.06 — 10.89) Based on data from 18 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious risk of bias, very serious imprecision and serious indirectness [2]	There were too few who died to determine whether aprepitant makes a difference (2 events).
Invasive mechanical ventilation Within 5 days of commencing treatment 9 Critical					No studies were found that looked at patients requiring invasive mechanical ventilation.
Adverse events Within 5 days of commencing treatment 6 Important					No studies were found that looked at adverse events.
Serious adverse events Within 5 days of commencing treatment 6 Important					No studies were found that looked at serious adverse events.
Discharge from hospital Within 5 days of commencing treatment	Relative risk 0.8 (CI 95% 0.06 — 10.89) Based on data from 18 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious risk of bias, very serious imprecision and serious	There were too few who were discharged from hospital (2 events) to determine whether aprepitant makes a difference.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Aprepitant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important				indirectness [4]	

1. Systematic review [192] with included studies: Mehboob 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 time frame in studies were insufficient. **Imprecision: Very serious.** Low number of patients, Only data from one study, due to few events.
3. Systematic review [192] with included studies: Mehboob 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 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 *[190]*.

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 *[191]*. There are several known and potential interactions with other drugs including hormonal contraceptives *[191]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Aprepitant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 5 days of commencing treatment 9 Critical	Relative risk 0.8 (CI 95% 0.06 — 10.89) Based on data from 18 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious risk of bias, very serious imprecision and serious indirectness [2]	There were too few who died to determine whether aprepitant makes a difference 2 events).
Invasive mechanical ventilation Within 5 days of commencing treatment 9 Critical					No studies were found that looked at patients requiring invasive mechanical ventilation.
Adverse events Within 5 days of commencing treatment 6 Important					No studies were found that looked at adverse events.
Serious adverse events Within 5 days of commencing treatment 6 Important					No studies were found that looked at serious adverse events.
Discharge from hospital Within 5 days of commencing treatment	Relative risk 0.8 (CI 95% 0.06 — 10.89) Based on data from 18 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious risk of bias, very serious imprecision and serious	There were too few who were discharged from hospital to determine whether aprepitant makes a difference (2 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Aprepitant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important				indirectness [4]	

1. Systematic review [192] with included studies: Mehboob 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [192] with included studies: Mehboob 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.4. Baloxavir marboxil

Not recommended

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

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.

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 Very low

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 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
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 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, 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 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 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 *[196]*.

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 *[195]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baloxavir marboxil	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality During treatment (14 days) 9 Critical	Based on data from 20 patients in 1 studies. [1]				There were no deaths in the study.
Respiratory support and ARDS During treatment (14 days) 9 Critical	Odds Ratio 2.25 (CI 95% 0.38 — 13.47) Based on data from 20 patients in 1 studies. [2] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [3]	We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (10 events).
Invasive mechanical ventilation or ECMO During treatment (14 days) 9 Critical	Odds Ratio 3.32 (CI 95% 0.12 — 91.6) Based on data from 20 patients in 1 studies. [4] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [5]	There were too few who required invasive mechanical ventilation or ECMO to determine whether baloxavir marboxil makes a difference (1 event).
Serious adverse events During treatment (14 days) 9 Critical	[6]				Data for number of patients experiencing one or more events were not reported.
Adverse events During treatment (14 days) 6 Important	[7]				Data for number of patients experiencing one or more events were not reported.
Clinical improvement End of treatment (14 days)	Odds Ratio 1.5 (CI 95% 0.26 — 8.82) Based on data from 20 patients in 1 studies. [8] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [9]	We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (11 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baloxavir marboxil	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important					

1. Systematic review [193] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [193] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Risk of Bias: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study.
4. Systematic review [193] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Risk of Bias: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study.
6. Systematic review [193] with included studies: [194]. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [193] with included studies: [194]. **Baseline/comparator:** Control arm of reference used for intervention.
8. Systematic review [193] with included studies: Lou 2020. **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
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 *[196]*.

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 *[195]*.

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	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baloxavir marboxil	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality During treatment (14 days) 9 Critical	Based on data from 20 patients in 1 studies. [1]				There were no deaths in the study.
Respiratory support and ARDS During treatment (14 days) 9 Critical	Odds Ratio 2.25 (CI 95% 0.38 — 13.47) Based on data from 20 patients in 1 studies. [2] (Randomized controlled)			**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [3]	We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (10 events).
Invasive mechanical ventilation or ECMO During treatment (14 days) 9 Critical	Odds Ratio 3.32 (CI 95% 0.12 — 91.6) Based on data from 20 patients in 1 studies. [4] (Randomized controlled)			**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [5]	There were too few who required mechanical ventilation or ECMO (1 event) to determine whether baloxavir marboxil makes a difference.
Serious adverse events During treatment (14 days) 9 Critical	[6]				Data for number of patients experiencing one or more events were not reported.
Adverse events					Data for number of patients experiencing

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baloxavir marboxil	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
During treatment (14 days) 6 Important	[7]				one or more events were not reported.
Clinical improvement End of treatment (14 days) 6 Important	Odds Ratio 1.5 (CI 95% 0.26 — 8.82) Based on data from 20 patients in 1 studies. [8] (Randomized controlled)			**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [9]	We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (11 events).

1. Systematic review [193] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [193] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Risk of Bias: Serious. Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study.
4. Systematic review [193] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Risk of Bias: Serious. Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study.
6. Systematic review [193] with included studies: [194]. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [193] with included studies: [194]. **Baseline/comparator:** Control arm of reference used for intervention.
8. Systematic review [193] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Risk of Bias: Serious. Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study.

6.14.5. Bamlanivimab

Not recommended

Do not use bamlanivimab 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 bamlanivimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

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

Very low

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

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
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.

Resources

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, 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 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 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: Bamlanivimab for COVID-19
Intervention: Bamlanivimab
Comparator: Standard care

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 *[200]*, and ACTIV-3/TICO compared bamlanivimab with placebo in 314 patients with moderate to severe illness *[201]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Bamlanivimab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 1.67 (CI 95% 0.57 — 4.86) Based on data from 779 patients in 2 studies. [1] (Randomized controlled)	16 per 1000	27 per 1000 Difference: **11 more** per 1000 (CI 95% 7 fewer — 62 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether bamlanivimab impacts death (19 events).
Serious adverse events Within 30 days of commencing treatment 6 Important	Based on data from 465 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision [4]	No patients experienced a serious adverse event.
Adverse events Within 30 days of commencing treatment 6 Important	Relative risk 0.9 (CI 95% 0.65 — 1.25) Based on data from 465 patients in 1 studies. [5] (Randomized controlled)	269 per 1000	242 per 1000 Difference: **27 fewer** per 1000 (CI 95% 94 fewer — 67 more)	**Low** Due to very serious imprecision [6]	We are uncertain whether bamlanivimab increases or decreases adverse events (117 events).
Hospitalisation Within 30 days of commencing treatment	Relative risk 0.28 (CI 95% 0.1 — 0.82) Based on data from 465 patients in 1 studies. [7] (Randomized controlled)	58 per 1000	16 per 1000 Difference: **42 fewer** per 1000	**Low** Due to very serious imprecision [8]	We are uncertain whether bamlanivimab increases or decreases hospitalisation (14 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Bamlanivimab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important		(CI 95% 52 fewer — 10 fewer)			
Discharge from hospital Within 30 days of commencing treatment 6 Important	Relative risk 0.97 (CI 95% 0.9 — 1.05) Based on data from 314 patients in 1 studies. [9] (Randomized controlled)	901 per 1000	874 per 1000 Difference: **27 fewer** per 1000 (CI 95% 90 fewer — 45 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether bamlanivimab increases or decreases discharge from hospital (279 events).
Virological clearance (negative PCR) End of follow-up 6 Important	Relative risk 0.85 (CI 95% 0.67 — 1.08) Based on data from 431 patients in 1 studies. [11] (Randomized controlled)	459 per 1000	390 per 1000 Difference: **69 fewer** per 1000 (CI 95% 151 fewer — 37 more)	**Low** Due to very serious imprecision [12]	We are uncertain whether bamlanivimab increases or decreases negative PCR (177 events).
Clinical recovery Within 30 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 — 1.2) Based on data from 168 patients in 1 studies. [13] (Randomized controlled)	790 per 1000	814 per 1000 Difference: **24 more** per 1000 (CI 95% 87 fewer — 158 more)	**Low** Due to very serious imprecision [14]	We are uncertain whether bamlanivimab improves or worsens clinical recovery (135 events).
Clinical improvement Within 30 days of commencing treatment 6 Important	Relative risk 1.11 (CI 95% 0.93 — 1.33) Based on data from 253 patients in 1 studies. [15] (Randomized controlled)	632 per 1000	702 per 1000 Difference: **70 more** per 1000 (CI 95% 44 fewer — 209 more)	**Low** Due to very serious imprecision [16]	We are uncertain whether bamlanivimab improves or worsens clinical improvement (167 events).

1. Systematic review [199] with included studies: Lundgren 2020, Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Wide confidence intervals, due to few events.
3. Systematic review [199] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Only data from one study, due to few events.
5. Systematic review [199] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
7. Systematic review [199] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.

9. Systematic review [199] with included studies: Lundgren 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
11. Systematic review [199] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Wide confidence intervals.
13. Systematic review [199] with included studies: Lundgren 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
15. Systematic review [199] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Imprecision: Very serious.** Low number of patients, Only data from one study, Wide confidence intervals.

6.14.6. Bamlanivimab plus etesevimab

Not recommended

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

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.

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 Low

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 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
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 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, 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 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 one randomised trial that compared bamlanivimab plus etesevimab with placebo in 248 adults with mild COVID-19 *[200]*.

Study characteristics
Median age of participants was 45 years and 53% 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 no deaths in the study and too few who experienced a serious adverse event to determine whether bamlanivimab plus etesevimab makes a difference. We are uncertain if bamlanivimab plus etesevimab increases or decreases adverse events, hospitalisation, 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).

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 16 March 2021, there are no reliable safety data to inform treatment.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Bam+etesevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of treatment 9 Critical	Based on data from 268 patients in 1 studies. [1]				There were no deaths.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Bam+etesevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Serious adverse events End of follow-up 6 Important	Based on data from 268 patients in 1 studies. [2]				There were too few who experienced a serious adverse event to determine whether bamlanivimab plus etesevimab makes a difference (2 events).
Adverse events End of follow-up 6 Important	Relative risk 0.63 (CI 95% 0.39 — 1.02) Based on data from 268 patients in 1 studies. [3] (Randomized controlled)	269 per 1000	169 per 1000 Difference: **100 fewer** per 1000 (CI 95% 164 fewer — 5 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether bamlanivimab plus etesevimab increases or decreases adverse events (61 events).
Hospitalisation Within 29 days of commencing treatment 6 Important	Relative risk 0.15 (CI 95% 0.02 — 1.21) Based on data from 261 patients in 1 studies. [5] (Randomized controlled)	59 per 1000	9 per 1000 Difference: **50 fewer** per 1000 (CI 95% 58 fewer — 12 more)	**Low** Due to very serious imprecision [6]	We are uncertain whether bamlanivimab plus etesevimab increases or decreases hospitalisation (10 events).
Clinical improvement Within 22 days of commencing treatment 6 Important	Relative risk 1.13 (CI 95% 0.96 — 1.34) Based on data from 261 patients in 1 studies. [7] (Randomized controlled)	632 per 1000	714 per 1000 Difference: **82 more** per 1000 (CI 95% 25 fewer — 215 more)	**Low** Due to very serious imprecision [8]	We are uncertain whether bamlanivimab plus etesevimab improves or worsens clinical improvement (174 events).
Clinical recovery Within 22 days of commencing treatment 6 Important	Relative risk 1.19 (CI 95% 0.99 — 1.43) Based on data from 261 patients in 1 studies. [9] (Randomized controlled)	579 per 1000	689 per 1000 Difference: **110 more** per 1000 (CI 95% 6 fewer — 249 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether bamlanivimab plus etesevimab improves or worsens clinical recovery (163 events).
Negative PCR Day 22 6 Important	Relative risk 1 (CI 95% 0.72 — 1.38) Based on data from 261 patients in 1 studies. [11] (Randomized controlled)	368 per 1000	368 per 1000 Difference: **0 fewer** per 1000 (CI 95% 103 fewer — 140 more)	**Low** Due to very serious imprecision [12]	We are uncertain whether bamlanivimab plus etesevimab increases or decreases negative PCR (96 events).

1. Systematic review [202] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [202] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [202] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used

for intervention.
4. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals.
5. Systematic review [202] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Low number of patients, Only data from one study, Wide confidence intervals, due to few events.
7. Systematic review [202] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
9. Systematic review [202] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
11. Systematic review [202] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.

6.14.7. Bromhexine hydrochloride

Not recommended

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

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.

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 Very low

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 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
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 bromhexine hydrochloride during pregnancy and breastfeeding are unknown in the context of COVID-19.

Resources 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

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 *[204][205][209]*.

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 *[204]*; 32 mg three times a day *[205]*; 8 mg four times a day *[209]*). 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 *[273]*.

Pregnant and breastfeeding women
Bromhexine hydrochloride is considered safe in pregnancy *[273]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Bromhexine hydrochloride	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of follow-up 9 Critical	Relative risk 0.5 (CI 95% 0.1 — 2.47) Based on data from 196 patients in 3 studies. [1] (Randomized controlled)	154 per 1000 Difference: 60 fewer per 1000 (CI 95% 120 fewer — 105 more)	94 per 1000	**Very low** Due to serious risk of bias and very serious imprecision [2]	There were too few who died to determine whether bromhexine hydrochloride makes a difference (9 deaths).
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.61 (CI 95% 0.22 — 1.68) Based on data from 178 patients in 2 studies. [3]			**Low** Due to serious risk of bias and serious imprecision [4]	There were too few who required invasive mechanical ventilation to determine whether bromhexine hydrochloride makes a difference (20 events).
Serious adverse events End of follow-up 6 Important	Based on data from 178 patients in 2 studies. [5]			**Very low** Due to very serious risk of bias and very serious imprecision	No patients experienced a serious adverse event.
Adverse events End of follow-up 6 Important	Relative risk 0.38 (CI 95% 0.12 — 1.16) Based on data from 118 patients in 2 studies. [6]			**Very low** Due to very serious risk of bias and very serious imprecision	There were too few adverse events to determine whether bromhexine hydrochloride makes a difference (7 events).
Discontinuation due to adverse events End of follow-up 6 Important	Based on data from 18 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [8]	No patients discontinued treatment due to adverse events.
ICU admission End of follow-up 6 Important	Relative risk 0.18 (CI 95% 0.04 — 0.77) Based on data from 96 patients in 2 studies. [9] (Randomized controlled)			**Very low** Due to very serious risk of bias and serious imprecision [10]	There were too few who required ICU admission to determine whether bromhexine hydrochloride makes a difference (13 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Bromhexine hydrochloride	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Virological clearance (negative PCR) End of follow-up 6 Important	Relative risk 1 (CI 95% 0.79 — 1.26) Based on data from 18 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [12]	We are uncertain whether bromhexine hydrochloride increases or decreases virological clearance.
Discharge from hospital End of follow-up 6 Important	Relative risk 2.5 (CI 95% 0.78 — 7.97) Based on data from 18 patients in 1 studies. [13] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [14]	We are uncertain whether bromhexine hydrochloride increases discharge from hospital.

1. Systematic review [206] with included studies: Tolouian 2021, Li 2020, Ansarin 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **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.** due to few events, Wide confidence intervals.
3. Systematic review [207] with included studies: Tolouian 2021, Ansarin 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [208] with included studies: Ansarin 2020, Tolouian 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [206] with included studies: Tolouian 2021, Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [203] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: Very 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, Low number of patients. **Publication bias: No serious.**
9. Systematic review [203] with included studies: Li 2020, Ansarin 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**
11. Systematic review [203] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: Very 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, Low number of patients, Only data from one study. **Publication bias: No serious.**
13. Systematic review [203] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: Very 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, Low number of patients, Only data from one study. **Publication bias: No serious.**

6.14.8. Budesonide

Not recommended

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

Budesonide 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 budesonide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

Based on available evidence, it is unclear if budesonide is safe for the treatment of COVID-19. Common side effects and harms associated with budesonide include 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.

Certainty of the Evidence — Very low

Certainty of the evidence is very low for all outcomes due to very serious imprecision (low patient numbers, reliance on a single study), serious risk of bias (lack of blinding of participants and assessors) and serious publication bias (commercial funding).

For children & adolescents, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included study).

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
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 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, 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 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 budesonide 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 budesonide 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 budesonide to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Budesonide

Comparator: Standard care

Summary

There remains significant uncertainty whether budesonide 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 budesonide with standard care in 146 adults in the community with mild COVID-19 *[212]*.

We have found one new study comparing budesonide with standard care (PRINCIPLE trial medRxiv doi: 10.1101/2021.04.10.21254672). 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 ~45 years and 58% were women. Ninety-four per cent had laboratory-confirmed COVID-19.

What are the main results?
Hospitalisation was infrequent, with 13 events reported. Mean time to recovery was 8 days in the budesonide group and 11 days in the standard care group.

Our confidence in the results
Certainty of the evidence is very low for all outcomes due to very serious imprecision (low patient numbers, reliance on a single study), serious risk of bias (lack of blinding of participants and assessors) and serious publication bias (commercial funding).

For children & 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.

Pregnant and breastfeeding women
Budesonide is safe to use in pregnancy and during breastfeeding but has not been tested in this population to treat COVID-19.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Budesonide	Certainty of the Evidence (Quality of evidence)	Plain text summary
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.18 (CI 95% 0.04 — 0.79) Based on data from 146 patients in 1 studies. [1] (Randomized controlled)			Very low Due to serious risk of bias and very serious imprecision [2]	We are uncertain whether budesonide increases or decreases hospitalisation (13 events).
Time to recovery Days 6 Important	Lower better Based on data from: 146 patients in 1 studies. (Randomized controlled)	11 (Mean)	8 (Mean) Difference: MD 3 lower CI 95%	Very low Due to serious risk of bias and very serious imprecision [3]	We are uncertain whether budesonide increases or decreases time to recovery.

1. Systematic review [211] with included studies: Ramakrishnan 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** Only data from one study, Low number of patients. **Publication bias: No serious.**
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. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: No serious.** Mostly commercially funded studies, Mostly commercially funded studies.

6.14.9. Camostat mesilate

Not recommended

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.

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 an 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 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.

Resources 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, 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 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

Population: Patients with COVID-19
Intervention: Camostat mesilate
Comparator: Placebo

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 *[490]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Camostat mesilate	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Day 28 9 Critical	Relative risk 0.99 (CI 95% 0.31 — 3.18) Based on data from 205 patients in 1 studies. [1] (Randomized controlled)	59 per 1000	58 per 1000 Difference: **1 fewer** per 1000 41 fewer — 129 more	**Low** Due to very serious imprecision [2]	We are uncertain whether camostat mesilate increases or decreases mortality (12 deaths).
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 2.15 (CI 95% 0.63 — 7.29) Based on data from 205 patients in 1 studies. [3] (Randomized controlled)	44 per 1000	95 per 1000 Difference: **51 more** per 1000 16 fewer — 277 more	**Low** Due to very serious imprecision [4]	We are uncertain whether camostat mesilate increases or decreases invasive mechanical ventilation (16 events).
Supplemental oxygen End of follow-up 6 Important	Relative risk 0.98 (CI 95% 0.84 — 1.16) Based on data from 205 patients in 1 studies. [5] (Randomized controlled)	765 per 1000	750 per 1000 Difference: **15 fewer** per 1000 122 fewer — 122 more	**Low** Due to very serious imprecision [6]	We are uncertain whether camostat mesilate increases or decreases supplemental oxygen (155 events).
Serious adverse events End of follow-up 6 Important	Relative risk 1.68 (CI 95% 0.8 — 3.49) Based on data from 205 patients in 1 studies. [7] (Randomized controlled)	118 per 1000	198 per 1000 Difference: **80 more** per 1000 24 fewer — 294 more	**Low** Due to very serious imprecision [8]	We are uncertain whether camostat mesilate increases serious adverse events (38 events).
Adverse events End of follow-up 6 Important	Relative risk 0.86 (CI 95% 0.55 — 1.33) Based on data from 205 patients in 1 studies. [9] (Randomized controlled)	324 per 1000	279 per 1000 Difference: **45 fewer** per 1000 146 fewer — 107 more	**Low** Due to very serious imprecision [10]	We are uncertain whether camostat mesilate increases adverse events (60 events).
ICU admission End of follow-up 6 Important	Relative risk 0.87 (CI 95% 0.38 — 1.97) Based on data from 205 patients in 1 studies. [11] (Randomized controlled)	118 per 1000	103 per 1000 Difference: **15 fewer** per 1000 73 fewer — 114 more	**Low** Due to very serious imprecision [12]	We are uncertain whether camostat mesilate increases or decreases ICU admission (22 events).

1. Systematic review [213] with included studies: Gunst 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [213] with included studies: Gunst 2021. **Baseline/comparator:** Control arm of reference used for intervention.

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.
5. Systematic review [213] with included studies: Gunst 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
7. Systematic review [213] with included studies: Gunst 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
9. Systematic review [213] with included studies: Gunst 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
11. Systematic review [213] with included studies: Gunst 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.10. Chloroquine

Not recommended

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

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.

Evidence To Decision

Benefits and harms

Important 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 *[214]*. For people requiring palliative care, the benefits for symptom management are uncertain.

Certainty of the Evidence Very low

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 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
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 Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

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.

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 Important issues, or potential issues not investigated

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 Intervention is likely difficult to implement

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

Population: Patients 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 *[136]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Chloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days after commencing treatment 9 Critical	Based on data from 30 patients in 1 studies. [1] (Randomized controlled)			[2]	There were no deaths.
Progression to severe or critical disease Within 28 days after commencing treatment 6 Important	Based on data from 30 patients in 1 studies. [3] (Randomized controlled)			[4]	No patients progressed to severe or critical disease.
Adverse events Within 28 days after commencing treatment 6 Important	Relative risk 2.67 (CI 95% 0.68 — 10.46) Based on data from 30 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [6]	We are uncertain whether chloroquine increases or decreases adverse events (10 events).
Serious adverse events Within 28 days	Based on data from 30			[7]	There were no serious adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Chloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
after commencing treatment 6 Important	patients in 1 studies. (Randomized controlled)				
Time to clinical recovery Median time to clinical recovery (Days) 6 Important	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)	7.5 (Median) CI 95%	5.5 (Median)	**Very low** Due to serious risk of bias and very serious imprecision [8]	We are uncertain whether chloroquine increases or decreases time to clinical recovery.
Time to termination of oxygen therapy Median time from randomisation to termination of oxygen therapy (Days) 6 Important	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)	8 (Median) CI 95%	8.5 (Median)	**Very low** Due to serious risk of bias and very serious imprecision [9]	We are uncertain whether chloroquine increases or decreases time to termination of oxygen therapy.

1. Systematic review [135] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [135] with included studies: Chen L 2020. **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, 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.
5. Systematic review [135] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

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 *[136]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Chloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days after commencing treatment 9 Critical	Based on data from 30 patients in 1 studies. [1] (Randomized controlled)			[2]	There were no deaths.
Progression to severe or critical disease Within 28 days after commencing treatment 6 Important	Based on data from 30 patients in 1 studies. [3] (Randomized controlled)			[4]	No patients progressed to severe or critical disease.
Adverse events Within 28 days after commencing treatment 6 Important	Relative risk 2.67 (CI 95% 0.68 — 10.46) Based on data from 30 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [6]	We are uncertain whether chloroquine increases or decreases adverse events (10 events).
Serious adverse events Within 28 days after commencing treatment 6 Important	Based on data from 30 patients in 1 studies. (Randomized controlled)			[7]	There were no serious adverse events.
Time to clinical recovery Median time to clinical recovery (Days) 6 Important	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)	7.5 (Median) CI 95%	5.5 (Median)	**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [8]	We are uncertain whether chloroquine increases or decreases time to clinical recovery.
Time to termination of oxygen therapy	Measured by: Median time to termination of oxygen therapy; chloroquine: 8.5 days	8 (Median)	8.5 (Median)	**Very low** Due to serious risk of bias, serious	We are uncertain whether chloroquine increases or decreases time to termination of

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Chloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Median time from randomisation to termination of oxygen therapy (Days) 6 Important	(IQR 0-9.25); control: 8 days (IQR 3.25-14) Lower better (Randomized controlled)	CI 95%		indirectness and very serious imprecision [9]	oxygen therapy.

1. Systematic review [135] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [135] with included studies: Chen L 2020. **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, 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.
5. Systematic review [135] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.11. Combined metabolic cofactor supplementation (CMCS)

Not recommended

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

Combined metabolic cofactor supplementation (CMCS) 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 CMCS to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

Evidence To Decision

Benefits and harms

General adult population
As the safety profile for combined metabolic cofactor supplementation 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 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 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 combined metabolic cofactor supplementation (CMCS) 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 CMCS 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 CMCS to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Combined metabolic cofactor supplementation
Comparator: Control

Summary

There remains significant uncertainty whether combined metabolic cofactor supplementation (CMCS) is 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 CMCS with placebo in 93 non-hospitalised adults with mild or moderate COVID-19 *[226]*.

Publication status
The study is only available as a preprint (posted to medRxiv on 5 October 2020) and has therefore not been peer reviewed.

Study characteristics
Mean age of participants was 33 years and 60% were women. Patients in the intervention group received CMCS twice a day for 14 days as follows: L-carnitine tartrate, 7.46 g/day; N-acetylcysteine, 5.1 g/day; nicotinamide riboside 2 g/day; and serine 24.7 g/day as water-soluble powders containing the entire CMCS 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 CMCS makes a difference (2 events). It is unclear whether CMCS 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 *[300]*.

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 *[273]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** CMCS	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality Within 14 days of commencing treatment 9 Critical					Data for number of patients who died were not reported.
Serious adverse events End of follow-up 9 Critical					Data for number of patients experiencing one or more serious adverse events were not reported.
Adverse events End of follow-up 6 Important	Relative risk 1.6 (CI 95% 0.08 — 32.08) Based on data from 93 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [2]	Too few experienced adverse events to determine whether CMCS makes a difference (2 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** CMCS	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Clinical recovery End of follow-up 6 Important	Relative risk 1.13 (CI 95% 0.95 — 1.33) Based on data from 93 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether CMCS increases or decreases clinical recovery (88 events).
Time to recovery End of follow-up 6 Important	Hazard Ratio 2.68 (CI 95% 1.57 — 4.59) Based on data from 93 patients in 1 studies. (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [5]	We are uncertain whether CMCS decreases time to recovery.

1. Systematic review [225] with included studies: Altay 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: No serious.**
3. Systematic review [225] with included studies: Altay 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**

6.14.12. CT-P59 monoclonal antibody

Not recommended

Do not use the monoclonal antibody CT-P59 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 CT-P59 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

Evidence To Decision

Benefits and harms

Based on the available evidence, it is unclear if CT-P59 is safer or more effective than standard care for the treatment of

COVID-19. The safety profile for CT-P59 is incompletely characterised in humans and it is not approved for use in Australia.

Certainty of the Evidence Very low

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 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
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 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, 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 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 CT-P59 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 CT-P59 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 CT-P59 to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: CT-P59 monoclonal antibody
Comparator: Standard care

Summary

There remains significant uncertainty whether 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 CT-P59 with standard care in 327 adult outpatients with mild or moderate COVID-19 *[228]*.

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 CT-P59 group (27%) compared with the placebo group (31%). By day 28 clinical recovery was higher with CT-P59 (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, CT-P59 is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. The safety profile for CT-P59 is incompletely characterised in humans.

Pregnant and breastfeeding women
There are additional concerns regarding harms, as CT-P59 has not been sufficiently tested in this population.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** CT-P59 monoclonal antibody	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Day 28 9 Critical	Based on data from 307 patients in 1 studies. [1]			[2]	There were no deaths.
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 1.52 (CI 95% 0.06 — 37.04) Based on data from 307 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision and serious publication bias [4]	There were too few who required invasive mechanical ventilation to determine whether CT-P59 makes a difference (1 event).
Supplemental oxygen End of follow-up 6 Important	Relative risk 0.45 (CI 95% 0.18 — 1.13) Based on data from 307 patients in 1 studies. [5] (Randomized controlled)	**87** per 1000	**39** per 1000 Difference: **48 fewer** per 1000 (CI 95% 71 fewer — 11 more)	**Very low** Due to very serious imprecision and serious publication bias [6]	We are uncertain whether CT-P59 increases or decreases requirement for supplemental oxygen (17 events).
ICU admission End of follow-up 6 Important	Based on data from 307 patients in 1 studies. [7] (Randomized controlled)			[8]	There were no admissions to ICU.
Adverse events End of follow-up 6 Important	Relative risk 0.87 (CI 95% 0.61 — 1.25) Based on data from 325 patients in 1 studies. [9] (Randomized controlled)	**309** per 1000	**269** per 1000 Difference: **40 fewer** per 1000 (CI 95% 121 fewer — 77 more)	**Very low** Due to very serious imprecision and serious publication bias [10]	We are uncertain whether CT-P59 increases adverse events (92 events).
Hospitalisation End of follow-up 6 Important	Relative risk 0.5 (CI 95% 0.21 — 1.23) Based on data from 307 patients in 1 studies. [11] (Randomized controlled)	**87** per 1000	**44** per 1000 Difference: **44 fewer** per 1000 (CI 95% 69 fewer — 20 more)	**Very low** Due to very serious imprecision and serious publication bias [12]	We are uncertain whether CT-P59 increases or decreases hospitalisation (18 events).
Clinical recovery End of follow-up 6 Important	Relative risk 1.21 (CI 95% 1.06 — 1.39) Based on data from 285 patients in 1 studies. [13] (Randomized controlled)	**714** per 1000	**864** per 1000 Difference: **150 more** per 1000 (CI 95% 43 more — 278 more)	**Very low** Due to very serious imprecision and serious publication bias [14]	We are uncertain whether CT-P59 improves or worsens clinical recovery (232 events).

1. Systematic review [227] with included studies: JoongSikEom 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [227] with included studies: JoongSikEom 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** Wide confidence intervals, Only data from one study, Low number of patients. **Publication bias: Serious.** Mostly commercially funded studies.
5. Systematic review [227] with included studies: JoongSikEom 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
7. Systematic review [227] with included studies: JoongSikEom 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
9. Systematic review [227] with included studies: JoongSikEom 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
11. Systematic review [227] with included studies: JoongSikEom 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **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.
13. Systematic review [227] with included studies: JoongSikEom 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **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.

6.14.13. Darunavir-cobicistat

Not recommended

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.

Evidence To Decision

Benefits and harms Important 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 Very low

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.

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
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 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, 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 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 *[232]*.

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).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Darunavir-cobicistat	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 14 days after commencing treatment 9 Critical	Based on data from 30 patients in 1 studies. [1] (Randomized controlled)			2	There were no deaths in the study.
Progression to critical illness 14 days after commencing treatment 9 Critical	Based on data from 30 patients in 1 studies. [3] (Randomized controlled)			4	There were too few who experienced progression to critical illness to determine whether darunavir-cobicistat makes a difference (1 event).
Adverse events Within 14 days of commencing treatment 6 Important	Odds Ratio 1.31 (CI 95% 0.31 — 5.48) Based on data from 30 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [6]	We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (15 events).
Viral clearance Day 7 of treatment 6 Important	Relative risk 0.78 (CI 95% 0.39 — 1.54) Based on data from 30 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [8]	We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 7 (16 events).
Viral clearance Day 5 of treatment 6 Important	Odds Ratio 1.45 (CI 95% 0.26 — 8.01) Based on data from 30 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [10]	We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 5 (5 events).
Viral clearance Day 3 of	Odds Ratio 1 (CI 95% 0.17 — 5.98)			**Very low** Due to serious	We are uncertain whether darunavir-

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Darunavir-cobicistat	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
treatment 6 Important	Based on data from 30 patients in 1 studies. [11] (Randomized controlled)			risk of bias and very serious imprecision [12]	cobicistat increases or decreases viral clearance at day 3 (6 events).

1. Systematic review [229] with included studies: Chen J 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
3. Systematic review [229] with included studies: Chen J 2020. **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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
5. Primary study[232]. **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. **Publication bias: No serious.**
7. Systematic review [229] with included studies: Chen J 2020. **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: No serious. Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [229] with included studies: Chen J 2020. **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: No serious. Indirectness: No serious. Imprecision: Very serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
11. Systematic review [229] with included studies: Chen J 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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

Population: Special populations with 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 *[232]*.

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 *[233]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Darunavir-cobicistat	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 14 days after commencing treatment 9 Critical	Based on data from 30 patients in 1 studies. [1] (Randomized controlled)			2	There were no deaths in the study.
Progression to critical illness 14 days after commencing treatment 9 Critical	Based on data from 30 patients in 1 studies. [3] (Randomized controlled)			4	There were too few who experienced progression to critical illness to determine whether darunavir-cobicistat makes a difference (1 event).
Adverse events Within 14 days of commencing treatment 6 Important	Odds Ratio 1.31 (CI 95% 0.31 — 5.48) Based on data from 30 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [6]	We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (15 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Darunavir-cobicistat	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Viral clearance Day 7 of treatment 6 Important	Relative risk 0.78 (CI 95% 0.39 — 1.54) Based on data from 30 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [8]	We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 7 (16 events).
Viral clearance Day 5 of treatment 6 Important	Odds Ratio 1.45 (CI 95% 0.26 — 8.01) Based on data from 30 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [10]	We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 5 (5 events).
Viral clearance Day 3 of treatment 6 Important	Odds Ratio 1 (CI 95% 0.17 — 5.98) Based on data from 30 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to serious risk of bias, serious indirectness and very serious imprecision [12]	We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 3 (6 events).

1. Systematic review [229] with included studies: Chen J 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study, due to no events. **Publication bias: No serious.**
3. Systematic review [229] with included studies: Chen J 2020. **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. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
5. Primary study[232]. **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: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
7. Systematic review [229] with included studies: Chen J 2020. **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: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [229] with included studies: Chen J 2020. **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: No serious. Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
11. Systematic review [229] with included studies: Chen J 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for

performance bias. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**

6.14.14. Dutasteride

Not recommended

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.

Evidence To Decision

Benefits and harms — Important harms

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 — Very low

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.

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
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 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, 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 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.

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 *[236]*.

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 absencethese populations in the included studies.

Additional information
Dutasteride is contraindicated in children as its use not been studied in this population *[235]*.

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 *[235]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard Care	**Intervention** Dutasteride	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Hospitalisation End of Follow-up 9 Critical	Based on data from 87 patients in 1 studies. [1]			2	No patients required hospitalisation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard Care	**Intervention** Dutasteride	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Time to recovery Remission of all symptoms 6 Important	Based on data from: 87 patients in 1 studies. [3]	9.2 (Mean)	16.3 (Mean) CI 95%	Very low Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether dutasteride increases or decreases time to recovery.

1. Systematic review [234] with included studies: Cadegiani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 [234] . **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.**

6.14.15. Enisamium

Not recommended

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

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.

Evidence To Decision

Benefits and harms

General adult population
As the safety profile for enisamium 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 Very low

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 — 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
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 — 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, 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 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.

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 *[237]*.

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.

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Enisamium	Certainty of the Evidence (Quality of evidence)	Plain text summary
Time to recovery Days 6 Important	Lower better Based on data from: 373 patients in 1 studies. (Randomized controlled)	13.9 (Mean) CI 95%	11.1 (Mean)	Very low Due to very serious risk of bias and serious imprecision [1]	We are uncertain whether enisamium increases or decreases time to recovery.

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.

6.14.16. Favipiravir

Not recommended

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.

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 Very low

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 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
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 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.

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 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 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 *[196][238][242][243]*.

We have found one new study comparing favipiravir with standard care (Balykova et al. Infectious Diseases [Russian] doi: 10.33029/2305-3496-2020-9-3-16-29). 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 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Favipiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.34 (CI 95% 0.01 — 8.27) Based on data from 316 patients in 2 studies. [1] (Randomized controlled)	8 per 1000	3 per 1000 Difference: **5 fewer** per 1000 (CI 95% 8 fewer — 58 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether favipiravir impacts death (1 event).
All-cause mortality End of follow-up 9 Critical	Relative risk 2.56 (CI 95% 0.13 — 50.95) Based on data from 79 patients in 2 studies. [3] (Randomized controlled)			**Low** Due to very serious imprecision [4]	There were too few who died to determine whether favipiravir makes a difference (2 events).
Respiratory failure or ARDS End of follow-up 9 Critical	Relative risk 1.11 (CI 95% 0.39 — 3.19) Based on data from 19 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [6]	There were too few who experienced respiratory failure or ARDS to determine whether favipiravir makes a difference (8 events).
Invasive mechanical ventilation or ECMO End of follow-up 9 Critical	Based on data from 19 patients in 1 studies. [7] (Randomized controlled)			8	No patients required mechanical ventilation.
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.38 (CI 95% 0.24 — 8.08) Based on data from 371 patients in 3 studies. [9]	7 per 1000	10 per 1000 Difference: **3 more** per 1000 (CI 95% 5 fewer — 50 more)	**Low** Due to serious risk of bias and serious imprecision [10]	We are uncertain whether favipiravir increases serious adverse events (5 events).
Adverse events Within 28 days of commencing treatment	Relative risk 1.92 (CI 95% 0.83 — 4.43) Based on data from 371 patients in 3 studies. [11] (Randomized controlled)	293 per 1000	563 per 1000 Difference: **270 more** per 1000	**Low** Due to serious risk of bias and serious imprecision [12]	We are uncertain whether favipiravir increases adverse events (165 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Favipiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		(CI 95% 50 fewer — 1,005 more)			
Discontinuation due to adverse events End of treatment	Relative risk 1.24 (CI 95% 0.25 — 6.25) Based on data from 376 patients in 3 studies. [13] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [14]	We are uncertain whether favipiravir increases discontinuation due to adverse events.
Clinical improvement End of follow-up 6 Important	Relative risk 1.11 (CI 95% 0.47 — 2.6) Based on data from 19 patients in 1 studies. [15] (Observational (non-randomized))			**Very low** Due to serious risk of bias and very serious imprecision [16]	We are uncertain whether favipiravir improves clinical improvement (10 events).
Discharge from hospital End of follow-up	Relative risk 1.05 (CI 95% 0.97 — 1.13) Based on data from 188 patients in 2 studies. [17] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [18]	We are uncertain whether favipiravir increases discharge from hospital.
Negative PCR End of follow-up 6 Important	Relative risk 1.09 (CI 95% 1.01 — 1.18) Based on data from 315 patients in 2 studies. [19] (Randomized controlled)	809 per 1000	882 per 1000 Difference: **73 more** per 1000 (CI 95% 8 more — 146 more)	**Low** Due to serious risk of bias and very serious imprecision [20]	We are uncertain whether favipiravir increases negative PCR.

1. Systematic review [241] with included studies: ?, Ruzhentsova 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [239] with included studies: Lou 2020, Ivashchenko 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Only data from one study, few events.
5. Systematic review [239] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
7. Systematic review [239] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [241] with included studies: Ivashchenko 2020, ?, Ruzhentsova 2020. **Baseline/comparator:** Control arm of reference used for intervention.

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.
11. Systematic review [241] with included studies: ?, Ruzhentsova 2020, Ivashchenko 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [241] with included studies: , Ruzhentsova 2020, Ivashchenko 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, Wide confidence intervals.
15. Systematic review [239] with included studies: Lou 2020. **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 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.
17. Systematic review [241] with included studies: Ruzhentsova 2020, . **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.** Wide confidence intervals, Low number of patients.
19. Systematic review [241] with included studies: Ruzhentsova 2020, ?. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients.

6.14.17. Fluvoxamine

Not recommended

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.

Evidence To Decision

Benefits and harms Important 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 *[246]*.

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 *[246]*. Caution should be taken when prescribing fluvoxamine to children, adolescents or elderly patients.

Certainty of the Evidence Low

General adult population
Certainty of the evidence for each outcome is low due to very serious imprecision (reliance on a single study, low patient or event numbers, 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
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
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 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.

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 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 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: Fluvoxamine for 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 a single randomised trial that compared fluvoxamine with placebo in 152 adult outpatients with mild COVID-19 *[245]*.

Study characteristics
Median age of participants was ~46 years and 72% were women. Pregnant women were ineligible.

What are the main results?
No patients died in either arm. There were too few who required mechanical ventilation (one event) to determine whether fluvoxamine makes a difference. We are uncertain whether fluvoxamine increases or decreases incidence of adverse or serious adverse events, patients requiring hospitalisation or clinical deterioration.

Our confidence in the results
Certainty of the evidence for all outcomes is low due to very serious imprecision (reliance on a single study and either wide confidence intervals or few events).

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 *[246]*. 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 patients
According to the Therapeutic Goods Administration, the use of fluvoxamine in pregnant women, particularly in late pregnancy, has been demonstrated to increase the risk of persistent pulmonary hypertension in the newborn *[246]*. 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 *[246]*.

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) *[246]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Fluvoxamine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 15 days of commencing treatment 9 Critical	Based on data from 152 patients in 1 studies. [1]				There were no deaths.
Mechanical ventilation Within 45 days of commencing treatment 6 Important	Based on data from 152 patients in 1 studies. [2] (Randomized controlled)			**Low** Due to very serious imprecision [3]	There were too few who required mechanical ventilation to determine whether fluvoxamine makes a difference (1 event).
Serious adverse events Within 15 days of commencing treatment 6 Important	Relative risk 0.18 (CI 95% 0.02 — 1.5) Based on data from 152 patients in 1 studies. [4] (Randomized controlled)	**69** per 1000	**12** per 1000 Difference: **57 fewer** per 1000 (CI 95% 68 fewer — 35 more)	**Low** Due to very serious imprecision [5]	We are uncertain whether fluvoxamine increases or decreases number of patients who experience one or more serious adverse events (6 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Fluvoxamine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events Within 15 days of commencing treatment 6 Important	Relative risk 1.65 (CI 95% 0.64 — 4.23) Based on data from 152 patients in 1 studies. [6] (Randomized controlled)	83 per 1000	137 per 1000 Difference: **54 more** per 1000 (CI 95% 30 fewer — 268 more)	**Low** Due to very serious imprecision [7]	We are uncertain whether fluvoxamine increases or decreases number of patients who experience one or more adverse events (17 events).
Clinical deterioration Within 15 days of commencing treatment 6 Important	Relative risk 0.07 (CI 95% 0 — 1.21) Based on data from 152 patients in 1 studies. [8] (Randomized controlled)	83 per 1000	6 per 1000 Difference: **77 fewer** per 1000 (CI 95% 83 fewer — 17 more)	**Low** Due to very serious imprecision [9]	We are uncertain whether fluvoxamine improves or worsens clinical deterioration (6 events).
Hospitalisation Within 45 days of commencing treatment 6 Important	Relative risk 0.1 (CI 95% 0.01 — 1.83) Based on data from 152 patients in 1 studies. [10] (Randomized controlled)	56 per 1000	6 per 1000 Difference: **50 fewer** per 1000 (CI 95% 55 fewer — 46 more)	**Low** Due to very serious imprecision [11]	We are uncertain whether fluvoxamine increases or decreases hospitalisation (4 events).

1. Systematic review [244] with included studies: Lenze 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [244] with included studies: Lenze 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision: Very serious.** due to few events, Only data from one study.
4. Systematic review [244] with included studies: Lenze 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study, due to few events.
6. Systematic review [244] with included studies: Lenze 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study, due to few events.
8. Systematic review [244] with included studies: Lenze 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals, due to few events, Only data from one study.
10. Systematic review [244] with included studies: Lenze 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Imprecision: Very serious.** Only data from one study, due to few events.

6.14.18. Human umbilical cord mesenchymal stem cells

Not recommended

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.

Evidence To Decision

Benefits and harms — Important 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) *[247]*.

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 *[247]*.

Certainty of the Evidence — Very low

General adult population
Certainty of the evidence is low for 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 — 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

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 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. There is very limited capacity to produce stem cell-related products, which would limit implementation of this treatment if effective.

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
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 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. 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

Population: Patients with COVID-19
Intervention: Human umbilical cord mesenchymal stem cells (hUC-MSC)
Comparator: Standard care

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 three randomised trials that compared hUC-MSC therapy with standard care in 141 adults hospitalised with severe COVID-19 *[248][252]* and 24 adults with mild to severe disease *[251]*.

We have found one new study comparing hUC-MSC therapy with standard care (Dilogo et al. Stem Cells Transl Med doi: https://doi.org/10.1002/sctm.21-0046. 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 and 44% were women. Standard care across the studies included supplemental oxygen (non-invasive or invasive ventilation), antiviral agents (abidor/oseltamivir), antibiotic agents and glucocorticoid therapy. Pregnant and breastfeeding women were ineligible in two studies *[251][252]*; in one study their eligibility was unclear *[248]*.

Patients in the intervention groups received either: 2 x 10^6 cells/kg on day 0 *[248]*, 100 x 10^6 cells on days 0 and 3 *[251]*, or 4 x 10^7 cells on days 0, 3 and 6 *[252]*.

What are the main results?
For the critical outcomes of death, mechanical ventilation and serious adverse events, there were too few events to determine whether hUC-MSC therapy makes a difference (12 deaths, four requiring ventilation and 10 serious adverse events). hU-MSC therapy may decrease adverse events slightly (77 events). 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 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 *[247]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** hU-MSC	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.29 (CI 95% 0.09 — 1) Based on data from 165 patients in 3 studies. [1] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [2]	There were too few who died to determine whether hU-MSC makes a difference (12 deaths).
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.26 (CI 95% 0.01 — 4.43) Based on data from 41 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [4]	There were too few who required invasive mechanical ventilation to determine whether hU-MSC makes a difference (4 patients).
Serious adverse events End of follow-up 9 Critical	Relative risk 0.25 (CI 95% 0.07 — 0.94) Based on data from 24 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to very serious imprecision [6]	There were too few who experienced serious adverse events to determine whether hU-MSC makes a difference (10 events).
Adverse events End of follow-up 6 Important	Relative risk 0.86 (CI 95% 0.65 — 1.12) Based on data from 124 patients in 2 studies. [7] (Randomized controlled)	**681** per 1000	**586** per 1000 Difference: **95 fewer** per 1000 (CI 95% 238 fewer — 82 more)	**Low** Due to very serious imprecision [8]	hU-MSC may decrease adverse events slightly (77 events).
Hospital discharge End of follow-up 6 Important	Relative risk 2.42 (CI 95% 0.85 — 6.85) Based on data from 41 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [10]	We are uncertain whether hU-MSC increases hospital discharge.
Clinical improvement End of follow-up 6 Important	Relative risk 1.13 (CI 95% 0.94 — 1.36) Based on data from 41 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [12]	We are uncertain whether hU-MSC increases clinical improvement.
Duration of hospital stay End of follow-up 6 Important	Based on data from: 41 patients in 1 studies. [13] (Randomized controlled)	Median duration of hospital stay was 20 days (IQR 16 to 24) with hU-MSC therapy vs 24 days (IQR 20 to 27) with standard care.		**Very low** Due to very serious risk of bias and very serious imprecision [14]	We are uncertain whether hU-MSC decreases duration of hospital stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** hU-MSC	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Time to clinical improvement [15] End of follow-up 6 Important	Based on data from: 41 patients in 1 studies. [16] (Randomized controlled)	Median time to clinical improvement was 9 days (IQR 6 to 13) with hU-MSC therapy vs 14 days (IQR 10 to 21) with standard care.		**Very low** Due to very serious risk of bias and very serious imprecision [17]	We are uncertain whether hU-MSC decreases time to clinical improvement.

1. Systematic review [250] with included studies: Shi 2020, Shu 2020, Lanzoni 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 (in 1 of 3 studies). **Inconsistency: No serious. Imprecision: Very serious.** Wide confidence intervals, due to few events, Low number of patients. **Publication bias: No serious.**
3. Systematic review [250] with included studies: Shu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
5. Systematic review [250] with included studies: Lanzoni 2020. **Baseline/comparator:** Systematic review [250] with included studies: Lanzoni 2020.
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.**
7. Systematic review [250] with included studies: Lanzoni 2020, Shi 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Wide confidence intervals, due to few events, Low number of patients. **Publication bias: No serious.**
9. Systematic review [250] with included studies: Shu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, Wide confidence intervals. **Publication bias: No serious.**
11. Systematic review [250] with included studies: Shu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, Selective outcome reporting. **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.**
13. Primary study **Supporting references:** [248],
14. **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, Selective outcome reporting. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** Wide confidence intervals, Only data from one study, Low number of patients.
15. 2-point change on a 7-point ordinal scale
16. Primary study **Supporting references:** [248],
17. **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, Selective outcome reporting. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** Wide confidence intervals, Only data from one study, Low number of patients.

6.14.19. Interferon β-1a (inhaled)

Not recommended

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.

Evidence To Decision

Benefits and harms Important 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 Very low

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 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
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 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 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 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 *[254]*.

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 *[161][162]*.

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 *[163]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Inhaled interferon β-1a	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.15 (CI 95% 0.01 — 2.8) Based on data from 98 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious imprecision [2]	There were too few who died to determine whether inhaled interferon β-1a makes a difference (3 deaths).
Invasive mechanical ventilation or death [composite] Within 28 days of commencing treatment 9 Critical	Relative risk 0.63 (CI 95% 0.16 — 2.47) Based on data from 98 patients in 1 studies. [3] (Randomized controlled)	**100** per 1000	**63** per 1000 Difference: **37 fewer** per 1000 (CI 95% 84 fewer — 147 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether inhaled interferon β-1a decreases invasive mechanical ventilation or death [composite] (8 events)
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 0.85 — 1.44) Based on data from 98 patients in 1 studies. [5] (Randomized controlled)	**660** per 1000	**726** per 1000 Difference: **66 more** per 1000 (CI 95% 99 fewer — 290 more)	**Low** Due to very serious imprecision [6]	We are uncertain whether inhaled interferon β-1a increases discharge from hospital at day 28 (68 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.49 (CI 95% 0.22 — 1.09) Based on data from 98 patients in 1 studies. [7] (Randomized controlled)	**300** per 1000	**147** per 1000 Difference: **153 fewer** per 1000 (CI 95% 234 fewer — 27 more)	**Low** Due to very serious imprecision [8]	We are uncertain whether inhaled interferon β-1a increases or decreases serious adverse events (22 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Inhaled interferon β-1a	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.9 (CI 95% 0.64 — 1.27) Based on data from 98 patients in 1 studies. [9] (Randomized controlled)	600 per 1000	540 per 1000 Difference: **60 fewer** per 1000 (CI 95% 216 fewer — 162 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether inhaled interferon β-1a increases or decreases adverse events (56 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 1.99 (CI 95% 1.08 — 3.67) Based on data from 98 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [12]	We are uncertain whether inhaled interferon β-1a increases or decreases clinical recovery.
Clinical improvement Within 28 days of commencing treatment 6 Important	Relative risk 1.43 (CI 95% 1.01 — 2.02) Based on data from 98 patients in 1 studies. [13] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [14]	We are uncertain whether inhaled interferon β-1a increases or decreases clinical improvement.

1. Systematic review [253] with included studies: Monk 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
3. Systematic review [253] with included studies: Monk 2020. **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.
5. Systematic review [253] with included studies: Monk 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients.
7. Systematic review [253] with included studies: Monk 2020. **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.
9. Systematic review [253] with included studies: Monk 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals, Only data from one study.
11. Systematic review [253] with included studies: Monk 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [253] with included studies: Monk 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.20. Interferon β-1b

Not recommended

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

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.

Evidence To Decision

Benefits and harms — Important 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 — Very low

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 — 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
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 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 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 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 *[255]*.

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 *[258]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1b	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.33 (CI 95% 0.04 — 3.04) Based on data from 66 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious imprecision [2]	There were too few events to determine whether interferon β-1b increases or decreases death at 14 days (4 events).
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.33 (CI 95% 0.07 — 1.53) Based on data from 66 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision [4]	There were too few events to determine whether interferon β-1b increases or decreases death at 28 days (8 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1b	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Respiratory failure or ARDS Within 28 days after commencing treatment 9 Critical	Relative risk 0.33 (CI 95% 0.07 — 1.53) Based on data from 66 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to very serious imprecision [6]	There were too few events to determine whether interferon β-1b increases or decreases respiratory failure or ARDS (8 events).
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 0.25 (CI 95% 0.03 — 2.12) Based on data from 66 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision [8]	There were too few events to determine whether interferon β-1b increases or decreases septic shock (5 events).
Adverse events 6 Important	[9]				Data for adverse events were not reported.
Serious adverse events 6 Important	[10]				Data for serious adverse events were not reported.
Discharge from hospital Within 14 days of commencing treatment 6 Important	Relative risk 1.44 (CI 95% 1.01 — 2.07) Based on data from 66 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to very serious imprecision and serious risk of bias [12]	We are uncertain if interferon β-1b increases discharge from hospital within 14 days (44 events).
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.15 (CI 95% 0.96 — 1.38) Based on data from 66 patients in 1 studies. [13] (Randomized controlled)			**Very low** Due to very serious imprecision and serious risk of bias [14]	We are uncertain if interferon β-1b makes any difference to discharge from hospital within 28 days (58 events).
Clinical deterioration (admission to ICU) Within 28 days of	Relative risk 0.64 (CI 95% 0.4 — 1.01) Based on data from 66 patients in 1 studies. [15] (Randomized controlled)			**Very low** Due to very serious imprecision and serious risk of	We are uncertain if interferon β-1b decreases clinical deterioration (based on admission to ICU; 36

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1b	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
commencing treatment 6 Important				bias [16]	events).
Time to discharge from hospital Days 6 Important	Based on data from: 66 patients in 1 studies. [17] (Randomized controlled)	**13** (Median) CI 95%	**11** (Median)	**Very low** Due to very serious imprecision and serious risk of bias [18]	We are uncertain whether interferon β-1b increases or decreases time to discharge from hospital.

1. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Low number of patients, Only data from one study, due to few events.
3. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Only data from one study, due to few events.
5. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Low number of patients, due to few events, Only data from one study.
7. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Low number of patients, Only data from one study, due to few events.
9. Systematic review [257] . **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [257] . **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.** Low number of patients, Only data from one study.
13. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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. **Imprecision: Very serious.** Low number of patients, Only data from one study.
15. Systematic review [256] with included studies: Rahmani 2020. **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 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.
17. Primary study[255]. **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 *[255]*.

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 *[258]*.

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 *[163]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1b	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 14 days of commencing	Relative risk 0.33 (CI 95% 0.04 — 3.04) Based on data from 66 patients in 1 studies. [1]			**Very low** Due to very serious imprecision and	We are uncertain whether interferon β-1b increases or decreases death at 14 days (4

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1b	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
treatment 9 Critical	(Randomized controlled)			serious indirectness [2]	events).
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.33 (CI 95% 0.07 — 1.53) Based on data from 66 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [4]	We are uncertain whether interferon β-1b increases or decreases death at 28 days (8 events).
Respiratory failure or ARDS Within 28 days after commencing treatment 9 Critical	Relative risk 0.33 (CI 95% 0.07 — 1.53) Based on data from 66 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [6]	We are uncertain whether interferon β-1b increases or decreases respiratory failure or ARDS (8 events).
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 0.25 (CI 95% 0.03 — 2.12) Based on data from 66 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [8]	We are uncertain whether interferon β-1b increases or decreases septic shock (5 events).
Adverse events 6 Important	[9]				Data for adverse events were not reported.
Serious adverse events 6 Important	[10]				Data for serious adverse events were not reported.
Discharge from hospital Within 14 days of commencing treatment 6 Important	Relative risk 1.44 (CI 95% 1.01 — 2.07) Based on data from 66 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to very serious imprecision, serious risk of bias and serious indirectness [12]	We are uncertain whether interferon β-1b may increases discharge from hospital within 14 days (44 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1b	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.15 (CI 95% 0.96 — 1.38) Based on data from 66 patients in 1 studies. [13] (Randomized controlled)			**Very low** Due to very serious imprecision, serious risk of bias and serious indirectness [14]	We are uncertain whether interferon β-1b has any impact on discharge from hospital within 28 days (58 events).
Clinical deterioration (admission to ICU) Within 28 days of commencing treatment 6 Important	Relative risk 0.64 (CI 95% 0.4 — 1.01) Based on data from 66 patients in 1 studies. [15] (Randomized controlled)			**Very low** Due to very serious imprecision, serious risk of bias and serious indirectness [16]	We are uncertain whether interferon β-1b has any impact on on clinical deterioration (based on admission to ICU; 36 events).
Time to discharge from hospital Days 6 Important	Based on data from: 66 patients in 1 studies. [17] (Randomized controlled)	**13** (Median)	**11** (Median) CI 95%	**Very low** Due to very serious imprecision, serious risk of bias and serious indirectness [18]	We are uncertain whether interferon β-1b increases or decreases time to discharge from hospital.

1. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **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.
5. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, due to few events, Only data from one study.
7. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **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.
9. Systematic review [257] . **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [257] . **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low

number of patients, Only data from one study.
13. Systematic review [257] with included studies: Rahmani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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: Very serious.** Low number of patients, Only data from one study.
15. Systematic review [256] with included studies: Rahmani 2020. **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 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.
17. Primary study[255]. **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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, Only data from one study.

6.14.21. Interferon gamma

Not recommended

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.

Evidence To Decision

Benefits and harms Important 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 Very low

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 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
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 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, 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 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 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

Population:	Patients with COVID-19
Intervention:	Interferon gamma
Comparator:	Standard care

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 *[260]*.

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 *[261]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon gamma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 21 days after commencing treatment 9 Critical	Based on data from 63 patients in 1 studies. [1]				No patients died in the study.
Adverse events 21 days after commencing treatment 6 Important	Relative risk 1.21 (CI 95% 0.56 — 2.61) Based on data from 57 patients in 1 studies. [2] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [3]	We are uncertain whether interferon gamma increases or decreases adverse events (18 events).
Serious adverse events 21 days after commencing treatment	Based on data from 63 patients in 1 studies. [4]				No patients had serious adverse events.
Negative PCR (Day 3) 3 days after commencing treatment 6 Important	Relative risk 1.84 (CI 95% 1.04 — 3.25) Based on data from 59 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [6]	We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 3 (29 events).
Negative PCR (Day 5) 5 days after commencing treatment 6 Important	Relative risk 1.3 (CI 95% 1 — 1.68) Based on data from 47 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [8]	We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events).
Discharge from hospital 14 days after commencing treatment 6 Important	Relative risk 1.1 (CI 95% 0.97 — 1.24) Based on data from 63 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [10]	We are uncertain whether interferon gamma increases discharge from hospital (60 events).

1. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference 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.
4. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **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.
7. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **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.
9. Systematic review [259] with included studies: Moynelo 2020. **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, 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 gamma
Comparator: Standard care

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 *[260]*.

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), 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
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 *[261]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon gamma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 21 days after commencing treatment 9 Critical	Based on data from 63 patients in 1 studies. [1]				No patients died in the study.
Adverse events 21 days after commencing treatment 6 Important	Relative risk 1.21 (CI 95% 0.56 — 2.61) Based on data from 57 patients in 1 studies. [2] (Randomized controlled)			**Very low** Due to serious risk of bias, very serious imprecision and serious indirectness [3]	We are uncertain whether interferon gamma increases or decreases adverse events (18 events).
Serious adverse events 21 days after commencing treatment	Based on data from 63 patients in 1 studies. [4]				No patients had serious adverse events.
Negative PCR (Day 3) 3 days after commencing treatment 6 Important	Relative risk 1.84 (CI 95% 1.04 — 3.25) Based on data from 59 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias, very serious imprecision and serious indirectness [6]	We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 3 (29 events).
Negative PCR (Day 5) 5 days after commencing treatment	Relative risk 1.3 (CI 95% 1 — 1.68) Based on data from 47 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to serious risk of bias, very serious imprecision and serious	We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon gamma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important				indirectness [8]	
Discharge from hospital 14 days after commencing treatment 6 Important	Relative risk 1.1 (CI 95% 0.97 — 1.24) Based on data from 63 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to serious risk of bias, very serious imprecision and serious indirectness [10]	We are uncertain whether interferon gamma increases discharge from hospital (60 events).

1. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
4. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
7. Systematic review [259] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
9. Systematic review [259] with included studies: Moynelo 2020. **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, 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.

6.14.22. Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)

Not recommended

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.

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

Very low

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

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
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

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, 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 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

Population: Patients with COVID-19
Intervention: IFN-κ plus TFF2
Comparator: Standard care

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 *[263]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** IFN-κ plus TFF2	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 12 days of commencing treatment 9 Critical	Based on data from 80 patients in 1 studies. [1]				No patients died.
Serious adverse events Within 12 days of commencing treatment 6 Important	Based on data from 80 patients in 1 studies. [2]				No patients experienced a serious adverse event.
Clinical improvement [3] Within 12 days of commencing treatment 6 Important	Relative risk 1.21 (CI 95% 0.96 — 1.51) Based on data from 80 patients in 1 studies. [4] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [5]	We are uncertain whether IFN-κ plus TFF2 increases or decreases clinical improvement based on chest CT scan (64 events).
Time to discharge from hospital Days	Lower better Based on data from: 80 patients in 1 studies. (Randomized controlled)	20.1 (Mean)	15.5 (Mean) Difference: MD 4.55 lower CI 95%	**Very low** Due to serious risk of bias and very serious imprecision [6]	We are uncertain whether IFN-κ plus TFF2 increases or decreases time to discharge from hospital.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention IFN-κ plus TFF2	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important Time to negative PCR Days 6 Important	Lower better Based on data from: 80 patients in 1 studies.	7.4 (Mean)	3.8 (Mean) Difference: MD 3.6 lower CI 95%	Very low Due to very serious imprecision [7]	We are uncertain whether IFN-κ plus TFF2 increases or decreases time to negative PCR

1. Systematic review [262] with included studies: Fu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [262] with included studies: Fu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. Based on chest CT imaging; reduction in the size and density of lesions.
4. Systematic review [262] with included studies: Fu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. **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.
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.
7. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

6.14.23. Intravenous immunoglobulin

Not recommended

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

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.

Evidence To Decision

Benefits and harms Important 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 Very low

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 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
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 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 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 Important issues, or potential issues not investigated

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 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 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 *[265]*.

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 one new study comparing intravenous immunoglobulin with standard care (Raman et al. J Infect Dis doi: 10.1093/infdis/jiab098). 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 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 *[267]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Immunoglobulin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of treatment 9 Critical	Relative risk 0.47 (CI 95% 0.24 — 0.93) Based on data from 64 patients in 1 studies. [1]			**Very low** Due to very serious risk of bias and very serious imprecision [2]	We are uncertain whether immunoglobulin increases or decreases risk of death (25 events).
Duration of hospital stay During follow-up 6 Important	Based on data from: 59 patients in 1 studies. (Randomized controlled)	7 (Median)	9 (Median)	**Very low** Due to serious risk of bias and very serious imprecision [3]	We are uncertain whether immunoglobulin increases or decreases duration of hospital stay.

1. Systematic review [264] with included studies: Gharebaghi 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.24. Intravenous immunoglobulin plus methylprednisolone

Not recommended

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.

Evidence To Decision

Benefits and harms

Important 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.

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

Very low

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

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
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 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 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 Important issues, or potential issues not investigated

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 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 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 *[268]*.

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 *[267]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Immunoglobulin plus methylprednisolone	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 30 days after commencing treatment 9 Critical	Relative risk 0.33 (CI 95% 0.04 — 2.89) Based on data from 34 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious imprecision [2]	There were too few who died to determine whether combination immunoglobulin plus methylprednisolone makes a difference (4 events).
Invasive mechanical ventilation 30 days after commencing	Relative risk 0.29 (CI 95% 0.07 — 1.18) Based on data from 34 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision [4]	There were too few who experienced invasive mechanical ventilation to determine whether combination

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Immunoglobulin plus methylprednisolone	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
treatment 9 Critical					immunoglobulin plus methylprednisolone makes a difference (9 events).
Adverse events Within 30 days of commencing treatment 6 Important	Based on data from 34 patients in 1 studies. [5]				No patients experienced an adverse event.
Serious adverse events Within 30 days of commencing treatment 6 Important	6				No studies were found that looked at serious adverse events.

1. Systematic review [266] with included studies: Sakoulas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Low number of patients, Only data from one study, low events.
3. Systematic review [266] with included studies: Sakoulas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Only data from one study, few events.
5. Systematic review [266] with included studies: Sakoulas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [266] . **Baseline/comparator:** Control arm of reference used for intervention.

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 *[268]*.

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 *[267]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Immunoglobulin plus methylprednisolone	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 30 days after commencing treatment 9 Critical	Relative risk 0.33 (CI 95% 0.04 — 2.89) Based on data from 34 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [2]	There were too few who died to determine whether combination immunoglobulin plus methylprednisolone makes a difference (4 events).
Invasive mechanical ventilation 30 days after commencing treatment 9 Critical	Relative risk 0.29 (CI 95% 0.07 — 1.18) Based on data from 34 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [4]	There were too few who experienced invasive mechanical ventilation to determine whether combination immunoglobulin plus methylprednisolone makes a difference (9 events).
Adverse events Within 30 days of commencing treatment 6 Important	Based on data from 34 patients in 1 studies. [5]				No patients experienced an adverse event.
Serious adverse events Within 30 days of	[6]				No studies were found that looked at serious adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Immunoglobulin plus methylprednisolone	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
commencing treatment 6 Important					

1. Systematic review [266] with included studies: Sakoulas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study, low events.
3. Systematic review [266] with included studies: Sakoulas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study, few events.
5. Systematic review [266] with included studies: Sakoulas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [266] . **Baseline/comparator:** Control arm of reference used for intervention.

6.14.25. Ivermectin

Not recommended

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.

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.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

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 *[272]*.

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 to 12 years of age is similar to that observed in adults *[272]*.

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 *[273]*.

Certainty of the Evidence — Very low

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 seriuos 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 — 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
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 — 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, 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 13 randomised trials that compared ivermectin with standard care in over 1260 adults with COVID-19 *[269][270][271][276][277][278][279][281][282][283][285][288][287]*.

We have found four new studies comparing ivermectin with standard care (Shahbaznejad et al. Clin Ther doi: 10.1016/j.clinthera.2021.04.007, Samaha et al. Viruses doi: 10.3390/v13060989, Biber et al. medRxiv doi: 10.1101/2021.05.31.21258081 and Abd-Elsalam et al. J Med Virol doi: 10.1002/jmv.27122). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

Publication status
Six studies are only available as preprints and have therefore not been peer reviewed (Krolewiecki et al. posted to SSRN on 11 November 2020 *[271]*, Niaee et al. posted to Res Sq on 24 November 2020 *[270]*, Kirti et al. posted to medRxiv on 9 January 2021 *[278]*, Mohan et al. posted to Res Sq on 2 February 2021 *[281]*, Shah Bukhari et al. posted to medRxiv on 5 February 2021 *[283]* and Beltran-Gonzalez et al. posted to medRxiv on 23 February 2021 *[282]*).

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% *[281][283]*). 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 *[272]*.

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 *[273]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.34 (CI 95% 0.12 — 0.94) Based on data from 915 patients in 5 studies. [1] (Randomized controlled)	54 per 1000	18 per 1000 Difference: 36 fewer per 1000 (CI 95% 48 fewer — 3 fewer)	**Low** Due to serious risk of bias and serious imprecision [2]	We are uncertain whether ivermectin impacts death (31 events).
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.21 (CI 95% 0.03 — 1.72) Based on data from 264 patients in 2 studies. [3] (Randomized controlled)	46 per 1000	10 per 1000 Difference: 36 fewer per 1000 (CI 95% 45 fewer — 33 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether ivermectin increases or decreases need for invasive mechanical ventilation (6 events).
ICU admission End of follow-up 6 Important	Relative risk 0.53 (CI 95% 0.11 — 2.51) Based on data from 143 patients in 2 studies. [5] (Randomized controlled)	115 per 1000	61 per 1000 Difference: 54 fewer per 1000 (CI 95% 102 fewer — 174 more)	**Low** Due to serious risk of bias and serious imprecision [6]	We are uncertain whether ivermectin increases or decreases admission to icu (13 events)
Adverse events (end of follow up)	Relative risk 0.95 (CI 95% 0.86 — 1.05)	549	522	**Low** Due to serious	We are uncertain whether ivermectin

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	Based on data from 736 patients in 6 studies. [7] (Randomized controlled)	per 1000	per 1000 Difference: **27 fewer** per 1000 (CI 95% 77 fewer — 27 more)	risk of bias and serious imprecision [8]	increases or decreases adverse events
Serious adverse events End of follow-up 6 Important	Relative risk 1.12 (CI 95% 0.21 — 5.88) Based on data from 664 patients in 5 studies. [9] (Randomized controlled)	**7** per 1000	**8** per 1000 Difference: **1 more** per 1000 (CI 95% 6 fewer — 34 more)	**Low** Due to serious risk of bias and serious imprecision [10]	We are uncertain whether ivermectin increases or decreases serious adverse events (5 events).
Discontinuation due to adverse event End of treatment 6 Important	Relative risk 2.97 (CI 95% 1.1 — 8.02) Based on data from 398 patients in 1 studies. [11] (Randomized controlled)	**25** per 1000	**74** per 1000 Difference: **49 more** per 1000 (CI 95% 3 more — 176 more)	**Low** Due to very serious imprecision [12]	We are uncertain whether ivermectin increases or decreases discontinuation due to adverse event (20 events).
Discharge from hospital (end of follow-up) 6 Important	Relative risk 1.06 (CI 95% 0.99 — 1.12) Based on data from 342 patients in 4 studies. [13] (Randomized controlled)	**868** per 1000	**920** per 1000 Difference: **52 more** per 1000 (CI 95% 9 fewer — 104 more)	**Low** Due to serious risk of bias and serious imprecision [14]	Ivermectin may increase discharge from hospital slightly (302 events).
Supplemental oxygen End of follow-up 6 Important	Based on data from 45 patients in 1 studies. [15]				No participants required supplemental oxygen.
Clinical progression End of follow-up 6 Important	Based on data from 24 patients in 1 studies. [16]			17	No participants progressed to severe disease.
Clinical improvement [18] End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.94 — 1.22) Based on data from 125 patients in 1 studies. [19] (Randomized controlled)	**867** per 1000	**928** per 1000 Difference: **61 more** per 1000 (CI 95% 52 fewer — 191 more)	**Low** Due to very serious imprecision [20]	We are uncertain whether ivermectin increases clinical improvement (113 events).
Viral clearance 7–10 days after	Relative risk 1.35 (CI 95% 0.69 — 2.62)	**482**	**651**	**Very low** Due to very	We are uncertain whether ivermectin

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
treatment 6 Important	Based on data from 243 patients in 3 studies. [21] (Randomized controlled)	per 1000	per 1000 Difference: **169 more** per 1000 (CI 95% 149 fewer — 781 more)	serious risk of bias and serious imprecision [22]	increases viral clearance (137 events).
Clinical recovery Within 21 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.94 — 1.15) Based on data from 398 patients in 1 studies. [23] (Randomized controlled)	**788** per 1000	**820** per 1000 Difference: **32 more** per 1000 (CI 95% 47 fewer — 118 more)	**Low** Due to very serious imprecision [24]	We are uncertain whether ivermectin increases or decreases clinical recovery (320 events).
Time to clinical recovery [onset to resolution] [25] Days 6 Important	Lower better Based on data from: 62 patients in 1 studies. (Randomized controlled)	**11.5** (Mean)	**10.09** (Mean) Difference: **MD 1.41 lower** (CI 95% 3.63 lower — 0.86 lower)	**Very low** Due to very serious risk of bias and very serious imprecision [26]	We are uncertain whether ivermectin increases or decreases time to clinical recovery (from onset of illness).
Time to clinical recovery [randomisation to resolution] Days 6 Important	Lower better Based on data from: 62 patients in 1 studies. (Randomized controlled)	**6.3** (Mean)	**5.3** (Mean) Difference: **MD 1 lower** (CI 95% 2.81 lower — 0.77 higher)	**Very low** Due to very serious risk of bias and very serious imprecision [27]	We are uncertain whether ivermectin increases or decreases time to clinical recovery (from randomisation).
Time to recovery [28] Days 6 Important	Lower better Based on data from: 398 patients in 1 studies. (Randomized controlled)	**12** (Median)	**10** (Median) CI 95%	**Low** Due to very serious imprecision [29]	We are uncertain whether ivermectin increases or decreases time to recovery.
Duration of hospital stay (days)	Based on data from: 180 patients in 1 studies.	Niaee et al. reported duration of hospital stay across all arms. For placebo and standard care it was 7 days [7-9] and 8 days [6-11] respectively. For intervention arms 6 [5-7], 8 [6-9], 5 [4-7] and 7 [6-10]. Units are likely medians and interquartile ranges although the reporting is unclear.		**Very low** Due to very serious risk of bias and very serious imprecision [30]	We are uncertain whether ivermectin increases or decreases duration of hospital stay.

1. Systematic review [284] with included studies: Mohan 2021, Lopez 2021, Niaee 2020, Gonzalez 2021, Ravikirti 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **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.** due to few events.
3. Systematic review [280] with included studies: Mohan 2021, Ravikirti 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, due to few events.
5. Systematic review [286] with included studies: Pott-junior 2021, Ravikirti 2021. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Wide confidence intervals, Low number of patients.
7. Systematic review [286] with included studies: Pott-junior 2021, Krolewiecki 2020, Chaccour 2020, Mohan 2021, Shah Bukhari 2021, Lopez 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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Wide confidence intervals, Low number of patients.
9. Systematic review [284] with included studies: Lopez 2021, Krolewiecki 2020, Ahmed 2020, Mohan 2021, Chaccour 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection 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, Incomplete data and/or large loss to follow up. **Imprecision: Serious.** due to few events.
11. Systematic review [284] with included studies: Lopez 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study, due to few events.
13. Systematic review [286] with included studies: Gonzalez 2021, Kishoria 2020, Mohan 2021, Ravikirti 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **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.
15. Systematic review [275] with included studies: Ahmed 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [275] with included studies: Chaccour 2020. Defined as progression to severe disease. **Baseline/ comparator:** Control arm of reference used for intervention.
17. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, due to no events, Only data from one study.
18. Based on a decrease of two or more points on the WHO ordinal scale.
19. Systematic review [280] with included studies: Mohan 2021. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
21. Systematic review [280] with included studies: Mohan 2021, Podder 2020, Shah Bukhari 2021. **Baseline/ comparator:** Control arm of reference used for intervention.
22. **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, 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, Selective outcome reporting, Incomplete data and/or large loss to follow up. **Imprecision: Serious.** Wide confidence intervals.
23. Systematic review [284] with included studies: Lopez 2021. **Baseline/comparator:** Control arm of reference used for intervention.
24. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study, due to few events.
25. Measured as time to clinical recovery from onset of illness to complete resolution of symptoms
26. **Risk of Bias: Very serious. Imprecision: Very serious.** Low number of patients, Only data from one study, Wide confidence intervals.

27. **Risk of Bias: Very serious. Imprecision: Very serious.** Low number of patients, Only data from one study.
28. Defined as sustained resolution of symptoms
29. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
30. **Risk of Bias: Very serious.** Incomplete data and/or large loss to follow up. **Imprecision: Very serious.** Only data from one study.

6.14.26. Ivermectin plus doxycycline

Not recommended

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.

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 Very low

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 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.

Resources 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, 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 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 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

Population: Patients with COVID-19
Intervention: Ivermectin plus doxycycline

Comparator: Standard care

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 *[276][294]*.

We have found one new study comparing ivermectin plus doxycycline with placebo (Mahmud et al. J Int Med Res doi: 10.1177/03000605211013550). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

Publication status
One study provides data published only in ClinicalTrials.gov *[294]*.

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 *[272]*. Common side effects and harms associated with doxycycline are nausea, vomiting, diarrhoea, epigastric burning, tooth discolouration, enamel dysplasia and photosensitivity *[293]*.

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 *[273]*. 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 *[273]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin plus doxycycline	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Day 28 9 Critical	Relative risk 0.14 (CI 95% 0.01 — 2.7) Based on data from 363 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [2]	There were too few who died to determine whether ivermectin plus doxycycline makes a difference (3 deaths).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin plus doxycycline	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Serious adverse events End of treatment 6 Important	Relative risk 4.92 (CI 95% 0.24 — 101.74) Based on data from 411 patients in 2 studies. [3] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [4]	There were too few who experienced serious adverse events to determine whether ivermectin plus doxycycline makes a difference (2 events).
Adverse events End of treatment 6 Important	Relative risk 14.76 (CI 95% 0.85 — 256.46) Based on data from 363 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [6]	There were too few who experienced adverse events to determine whether ivermectin plus doxycycline makes a difference (7 events).
Virological clearance (negative PCR) End of treatment 6 Important	Relative risk 1.15 (CI 95% 1.06 — 1.26) Based on data from 363 patients in 1 studies. [7] (Randomized controlled)	**800** per 1000	**920** per 1000 Difference: **120 more** per 1000 (CI 95% 48 more — 208 more)	**Very low** Due to serious risk of bias and very serious imprecision [8]	We are uncertain whether ivermectin plus doxycycline increases or decreases virological clearance (negative PCR).
Clinical improvement End of treatment 6 Important	Relative risk 1.36 (CI 95% 1.12 — 1.67) Based on data from 363 patients in 1 studies. [9] (Randomized controlled)	**444** per 1000	**604** per 1000 Difference: **160 more** per 1000 (CI 95% 53 more — 297 more)	**Very low** Due to serious risk of bias and very serious imprecision [10]	We are uncertain whether ivermectin plus doxycycline increases or decreases clinical improvement.
Clinical deterioration End of treatment 6 Important	Relative risk 0.49 (CI 95% 0.28 — 0.86) Based on data from 363 patients in 1 studies. [11] (Randomized controlled)	**177** per 1000	**97** per 1000 Difference: **80 fewer** per 1000 (CI 95% 112 fewer — 22 fewer)	**Very low** Due to serious risk of bias and very serious imprecision [12]	We are uncertain whether ivermectin plus doxycycline improves or worsens clinical deterioration.

1. Systematic review [291] with included studies: Reaz 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
3. Systematic review [291] with included studies: Reaz 2020, Ahmed 2020. **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, 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.
5. Systematic review [291] with included studies: Reaz 2020. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of Bias: Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
7. Systematic review [291] with included studies: Reaz 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, Wide confidence intervals.
9. Systematic review [291] with included studies: Reaz 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals.
11. Systematic review [291] with included studies: Reaz 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals.

6.14.27. Lenzilumab

Not recommended

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.

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 Very low

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 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
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 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, 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 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 *[297]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Lenzilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Serious adverse events End of follow-up 6 Important	Relative risk 0.84 (CI 95% 0.63 — 1.11) Based on data from 512 patients in 1 studies. [1] (Randomized controlled)	296 per 1000	249 per 1000 Difference: **47 fewer** per 1000 (CI 95% 110 fewer — 33 more)	**Low** Due to very serious imprecision [2]	Lenzilumab may decrease serious adverse events slightly (139 events).
Adverse events End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.62 — 1.07) Based on data from 512 patients in 1 studies. [3] (Randomized controlled)	327 per 1000	268 per 1000 Difference: **59 fewer** per 1000 (CI 95% 124 fewer — 23 more)	**Low** Due to very serious imprecision [4]	Lenzilumab may decrease adverse events slightly (152 events).

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Lenzilumab	Certainty of the Evidence (Quality of evidence)	Plain text summary
Septic shock End of follow-up 6 Important	Relative risk 0.56 (CI 95% 0.19 — 1.63) Based on data from 512 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to very serious imprecision [6]	We are uncertain whether lenzilumab increases or decreases septic shock (14 events).
Time to recovery Median (Days) 6 Important	Lower better Based on data from: 479 patients in 1 studies. (Randomized controlled)	8 (Median)	8 (Median) CI 95%	**Low** Due to very serious imprecision [7]	Lenzilumab may make little or no difference to time to recovery.

1. Systematic review [296] with included studies: Temesgen 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
3. Systematic review [295] with included studies: Temesgen 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study.
5. Systematic review [295] with included studies: Temesgen 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.28. N-acetylcysteine

Not recommended

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

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.

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 *[300]*.

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 *[273]*.

Certainty of the Evidence Very low

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 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
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.

Resources 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, 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 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 *[299]*.

We have found one new study comparing N-acetylcysteine with standard care (Gaynitdinova et al. Pulmonology doi: 10.18093/0869-0189-2021-31-1-21-29). This study is 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 (totalling 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 *[300]*.

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 *[273]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** N-acetylcysteine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of follow-up 9 Critical	Relative risk 1.01 (CI 95% 0.43 — 2.4) Based on data from 135 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [2]	There were too few events to determine whether N-acetylcysteine made a difference regarding death (18 events).
Invasive mechanical ventilation [3] End of follow-up 9 Critical	Relative risk 1.16 (CI 95% 0.62 — 2.18) Based on data from 135 patients in 1 studies. [4] (Randomized controlled)	206 per 1000	239 per 1000 Difference: **33 more** per 1000 (CI 95% 78 fewer — 243 more)	**Low** Due to very serious imprecision [5]	N-acetylcysteine may make little or no difference to the need for invasive mechanical ventiliation (30 events).
ICU admission End of follow-up 6 Important	Relative risk 0.92 (CI 95% 0.63 — 1.33) Based on data from 135 patients in 1 studies. [6] (Randomized controlled)	471 per 1000	433 per 1000 Difference: **38 fewer** per 1000 (CI 95% 174 fewer — 155 more)	**Low** Due to very serious imprecision [7]	N-acetylcysteine may make little or no difference to ICU admission (61 events).
Hospital length of stay Days 6 Important	Lower better Based on data from: 135 patients in 1 studies. [8] (Randomized controlled)	10 (Median)	11 (Median) CI 95%	**Low** Due to very serious imprecision [9]	N-acetylcysteine may have little or no impact on hospital length of stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** N-acetylcysteine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
ICU length of stay Days 6 Important	Lower better Based on data from: 135 patients in 1 studies. [10] (Randomized controlled)	8 (Median)	9 (Median) CI 95%	Low Due to very serious imprecision [11]	N-acetylcysteine may have little or no impact on ICU length of stay

1. Systematic review [298] with included studies: de Alencar 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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
4. Systematic review [298] with included studies: de Alencar 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
6. Systematic review [298] with included studies: de Alencar 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
8. Systematic review [298] with included studies: de Alencar 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
10. Systematic review [298] with included studies: de Alencar 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**

6.14.29. Nitazoxanide

Not recommended

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.

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 Very low

General adult population
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 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
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 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, 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 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 *[302][304][305]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Nitazoxanide	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of treatment 9 Critical	Relative risk 1.46 (CI 95% 0.2 — 10.92) Based on data from 1,363 patients in 3 studies. [1]			**Very low** Due to serious risk of bias and very serious imprecision	We are uncertain whether nitazoxanide impacts death (4 events).
Serious adverse events End of follow up 6 Important	Relative risk 0.38 (CI 95% 0.1 — 1.5) Based on data from 1,327 patients in 2 studies. [2] (Randomized controlled)	12 per 1000 Difference: **7 fewer** per 1000 (CI 95% 11 fewer — 6 more)	5 per 1000	**Low** Due to serious risk of bias and serious imprecision [3]	We are uncertain whether nitazoxanide increases or decreases serious adverse events (11 events).
Adverse events End of follow-up 6 Important	Relative risk 0.92 (CI 95% 0.74 — 1.14) Based on data from 1,327 patients in 2 studies. [4] (Randomized controlled)	204 per 1000 Difference: **16 fewer** per 1000 (CI 95% 53 fewer — 29 more)	188 per 1000	**Low** Due to serious risk of bias and serious imprecision [5]	We are uncertain whether nitazoxanide increases or decreases adverse events (258 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Nitazoxanide	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Discontinuation due to an adverse event End of follow-up 6 Important	Relative risk 6.12 (CI 95% 0.74 — 50.4) Based on data from 392 patients in 1 studies. [6] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [7]	We are uncertain whether nitazoxanide increases or decreases discontinuation due to an adverse event (7 events).
Hospitalisation End of follow up 6 Important	Relative risk 0.21 (CI 95% 0.02 — 1.8) Based on data from 379 patients in 1 studies. [8]			**Very low** Due to serious risk of bias and very serious imprecision	We are uncertain whether nitazoxanide increases or decreases hospitalisation (6 events).
Clinical deterioration End of follow-up 6 Important	Relative risk 0.15 (CI 95% 0.02 — 1.22) Based on data from 379 patients in 1 studies. [9]			**Very low** Due to serious risk of bias and very serious imprecision	We are uncertain whether nitazoxanide increases or decreases clinical deterioration (8 events).
Clinical recovery End of follow-up 6 Important	Relative risk 0.94 (CI 95% 0.83 — 1.07) Based on data from 392 patients in 1 studies. [10] (Randomized controlled)	737 per 1000 Difference: **44 fewer** per 1000 (CI 95% 125 fewer — 52 more)	693 per 1000	**Very low** Due to serious risk of bias and very serious imprecision [11]	We are uncertain whether nitazoxanide increases or decreases clinical recovery (281 events).

1. Systematic review [303] with included studies: RoccoPRM 2021, Rossignol 2021, Silva 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [303] with included studies: Rossignol 2021, RoccoPRM 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
4. Systematic review [303] with included studies: RoccoPRM 2021, Rossignol 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
6. Systematic review [301] with included studies: RoccoPRM 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
8. Systematic review [303] with included studies: Rossignol 2021. **Baseline/comparator:** Control arm of reference used for intervention.
9. Systematic review [303] with included studies: Rossignol 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [301] with included studies: RoccoPRM 2021. **Baseline/comparator:** Control arm of reference used for intervention.

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.

6.14.30. Peginterferon lambda

We have found two new studies comparing peginterferon lambda with placebo (Jagannathan et al. medRxiv doi: 110.1101/2020.11.18.20234161 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.

Not recommended

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

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.

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 Low

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 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
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 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 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 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

Population: Patients with COVID-19
Intervention: Peginterferon lambda
Comparator: Standard care

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 *[308][309]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Peginterferon lambda	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Based on data from 60 patients in 1 studies. [1]				There were no deaths in the study that reported this outcome.
Serious adverse events Within 28 days of commencing treatment	Relative risk 1 (CI 95% 0.21 — 4.82) Based on data from 180 patients in 2 studies. [2] (Randomized controlled)	33 per 1000 Difference: **0 fewer** per 1000 (CI 95% 26 fewer — 126 more)	33 per 1000	**Low** Due to very serious imprecision [3]	We are uncertain whether peginterferon lambda increases or decreases serious adverse events (6 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Peginterferon lambda	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important					
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.21 (CI 95% 0.77 — 1.9) Based on data from 180 patients in 2 studies. [4] (Randomized controlled)	244 per 1000	295 per 1000 Difference: **51 more** per 1000 (CI 95% 56 fewer — 220 more)	**Low** Due to very serious imprecision [5]	We are uncertain whether peginterferon lambda increases or decreases adverse events (49 events).
Hospitalisation End of follow-up 6 Important	Relative risk 1 (CI 95% 0.21 — 4.82) Based on data from 180 patients in 2 studies. [6] (Randomized controlled)	33 per 1000	33 per 1000 Difference: **0 fewer** per 1000 (CI 95% 26 fewer — 126 more)	**Low** Due to very serious imprecision [7]	We are uncertain whether peginterferon lambda increases or decreases incidence of hospitalisation (6 events).
Time to clinical progression Days 6 Important	Based on data from: 120 patients in 1 studies. (Randomized controlled)	Jagannathan 2020 provided data for time to clinical progression (HR 1.38, 95% CI 0.52 to 3.63).		**Low** Due to very serious imprecision [8]	We are uncertain whether peginterferon lambda increases or decreases time to clinical progression.

1. Systematic review [306] with included studies: Feld 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [306] with included studies: Jagannathan 2020, Feld 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals, due to few events.
4. Systematic review [306] with included studies: Feld 2020, Jagannathan 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals.
6. Systematic review [306] with included studies: Feld 2020, Jagannathan 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.31. Recombinant human granulocyte colony-stimulating factor (rhG-CSF)

Not recommended

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.

Evidence To Decision

Benefits and harms — Important 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 thrombocytopaenia (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 — Very low

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 — 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
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 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 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 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.

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 *[310]*.

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).

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 *[311]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** rhG-CSF	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 21 days of commencing treatment 9 Critical	Relative risk 0.2 (CI 95% 0.04 — 0.89) Based on data from 200 patients in 1 studies. [1] (Randomized controlled)	100 per 1000	20 per 1000 Difference: **80 fewer** per 1000 (CI 95% 96 fewer — 11 fewer)	**Low** Due to very serious imprecision [2]	There were too few who died to determine whether rhG-CSF makes a difference (12 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** rhG-CSF	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Invasive mechanical ventilation Within 21 days of commencing treatment 9 Critical	Relative risk 0.14 (CI 95% 0.03 — 0.61) Based on data from 200 patients in 1 studies. [3] (Randomized controlled)	140 per 1000	20 per 1000 Difference: **120 fewer** per 1000 (CI 95% 136 fewer — 55 fewer)	**Low** Due to very serious imprecision [4]	There were too few who required invasive mechanical ventilation to determine whether rhG-CSF makes a difference (16 events).
Serious adverse events End of treatment 6 Important	Relative risk 0.72 (CI 95% 0.49 — 1.05) Based on data from 200 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [6]	We are uncertain whether rhG-CSF increases or decreases serious adverse events (71 events).
Adverse events End of treatment 6 Important	Relative risk 2.02 (CI 95% 1.62 — 2.5) Based on data from 200 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [8]	We are uncertain whether rhG-CSF increases adverse events (138 events).
Duration of hospital stay Days 6 Important	Based on data from: 200 patients in 1 studies. [9] (Randomized controlled)	14 (Median)	13 (Median) Difference: **1 fewer**	**Low** Due to serious risk of bias and serious imprecision [10]	RhG-CSF may have little impact on duration of hospital stay.

1. Systematic review [178] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 number of patients, Few events. **Publication bias: No serious.**
3. Systematic review [178] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: No serious.** Inadequate/lack of blinding of participants, personnel and outcome assessors. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** Low number of patients, only data from one study, few events. **Publication bias: No serious.**
5. Systematic review [178] with included studies: Cheng 2020. **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, 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, Wide confidence intervals, Only data from one study. **Publication bias: No serious.**
7. Systematic review [178] with included studies: Cheng 2020. **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, 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. **Publication bias: No serious.**
9. Systematic review [178] with included studies: Cheng 2020. **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, 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, Low number of patients. **Publication bias: No serious.**

Clinical Question/ PICO

Population:	Special populations 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 *[310]*.

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 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 *[311]*.

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 *[311]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** rhG-CSF	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 21 days of commencing treatment 9 Critical	Relative risk 0.2 (CI 95% 0.04 — 0.89) Based on data from 200 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [2]	There were too few who died to determine whether rhG-CSF makes a difference (12 events).
Invasive mechanical ventilation Within 21 days of commencing treatment 9 Critical	Relative risk 0.14 (CI 95% 0.03 — 0.61) Based on data from 200 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [4]	There were too few who required invasive mechanical ventilation to determine whether rhG-CSF makes a difference (16 events).
Serious adverse events End of treatment 6 Important	Relative risk 0.72 (CI 95% 0.49 — 1.05) Based on data from 200 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to very serious imprecision, serious risk of bias and serious indirectness [6]	We are uncertain whether rhG-CSF increases or decreases serious adverse events
Adverse events End of treatment 6 Important	Relative risk 2.02 (CI 95% 1.62 — 2.5) Based on data from 200 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision, serious risk of bias and serious indirectness [8]	We are uncertain whether rhG-CSF increases adverse events.
Duration of hospital stay Days 6 Important	Based on data from: 200 patients in 1 studies. [9] (Randomized controlled)	**14** (Median)	**13** (Median) Difference: **1 fewer**	**Very low** Due to serious risk of bias, serious imprecision and serious indirectness [10]	We are uncertain whether rhG-CSF increases or decreases duration of hospital stay.

1. Systematic review [178] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **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.**
3. Systematic review [178] with included studies: Cheng 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **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.**
5. Systematic review [178] with included studies: Cheng 2020. **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, 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.**
7. Systematic review [178] with included studies: Cheng 2020. **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, 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, Low number of patients, Only data from one study. **Publication bias: No serious.**
9. Systematic review [178] with included studies: Cheng 2020. **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, 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.**

6.14.32. REGN-COV2

Not recommended

Do not use REGN-COV2 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 REGN-COV2 for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

Evidence To Decision

Benefits and harms

General adult population
Although preliminary evidence suggests that compared with standard care REGN-COV2 does not result in more adverse or serious adverse events, it remains unclear if REGN-COV2 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 REGN-COV2 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 REGN-COV2 for pregnant or breastfeeding women.

Certainty of the Evidence Very low

General adult population
Certainty of the evidence for all outcomes is very low due to serious risk of bias (lack of blinding of study personnel), very serious imprecision (reliance on a single study and either wide confidence intervals or few events) and serious publication bias (commercially funded).

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
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 REGN-COV2 in pregnancy are unknown.

Resources 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, 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 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 REGN-COV2 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 REGN-COV2 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 REGN-COV2 to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: REGN-COV2
Comparator: Placebo

Summary

There remains significant uncertainty whether REGN-COV2 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 REGN-COV2 with placebo in 275 non-hospitalised adults with suspected COVID-19 *[314]*.

The phase III results of Weinreich et al. comparing two doses of REGN-COV with placebo in 4,057 outpatients were published in medRxiv on 21 May 2021 (doi: 10.1101/2021.05.19.21257469). These results are currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
Median age of participants was 44 years and 51% were women. In this three-arm trial, patients received a single dose of 2.4 g or 8 g REGN-COV2 on day one or placebo. Pregnant and breastfeeding women were ineligible.

What are the main results?
There were too few patients who experienced a serious adverse event (three SAEs) to determine whether REGN-COV2 makes a difference. No patients withdrew from the study due to adverse events.

Our confidence in the results
Certainty of the evidence is very low for both outcomes due to very serious risk of bias (lack of blinding of certain study personnel), very serious imprecision (low patient numbers, few events and wide confidence intervals) 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 18 January 2021, REGN-COV2 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 REGN-COV2.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGN-COV2	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Serious adverse events End of treatment 6 Important	Based on data from 269 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious imprecision, serious risk of bias and serious publication bias [2]	There were too few who experienced a serious adverse event to determine whether REGN-COV2 makes a difference (3 events).
Withdrawals due to adverse events End of treatment 6 Important	Based on data from 269 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision, serious risk of bias and serious publication bias [4]	No patients withdrew due to an adverse event.

1. Systematic review [313] with included studies: Weinreich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals, Low number of patients. **Publication bias: Serious.** Mostly commercially funded studies.
3. Systematic review [313] with included studies: Weinreich 2020. **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. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: Serious.** Mostly commercially funded studies.

6.14.33. Ruxolitinib

Not recommended

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

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.

Evidence To Decision

Benefits and harms — Important 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 thrombocytopaenia 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 — Very low

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 — 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
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.

Resources — 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, 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 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, 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 ruxolitinib to treat COVID-19 in these populations should be avoided until evidence becomes available.

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 *[317]*.

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 *[316]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 patients in 1 studies. [1] (Randomized controlled)	143 per 1000	21 per 1000 Difference: **122 fewer** per 1000 (CI 95% 141 fewer — 165 more)	**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 patients in 1 studies. [3] (Randomized controlled)			**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 of commencing treatment 9 Critical	Odds Ratio 0.19 (CI 95% 0.01 — 4.22) Based on data from 41 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [6]	There were too few who experienced septic shock to determine whether ruxolitinib makes a difference (2 events).
Clinical improvement At day 14 of treatment	Odds Ratio 2 (CI 95% 0.58 — 6.94) Based on data from 41 patients in 1 studies. [7]			**Very low** Due to serious risk of bias and very serious	We are uncertain whether ruxolitinib improves or worsens clinical improvement

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	(Randomized controlled)			imprecision [8]	(21 events).
Adverse events Within 28 days of commencing treatment 6 Important	Odds Ratio 1.35 (CI 95% 0.36 — 5.04) Based on data from 41 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [10]	We are uncertain whether ruxolitinib increases or decreases adverse events (13 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Odds Ratio 0.09 (CI 95% 0 — 1.89) Based on data from 41 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [12]	There were too few who experienced serious adverse events to determine whether ruxolitinib makes a difference (4 events).
Clinical deterioration At day 14 of treatment 6 Important	Odds Ratio 0.09 (CI 95% 0 — 1.89) Based on data from 41 patients in 1 studies. [13] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [14]	We are uncertain whether ruxolitinib improves or worsens clinical deterioration (4 events).
Time to improvement Median days to improvement 6 Important	Lower better [15] (Randomized controlled)	**15** (Median) CI 95%	**12** (Median)	**Very low** Due to serious risk of bias and very serious imprecision [16]	We are uncertain whether ruxolitinib decreases time to improvement.
Time to discharge Median days to discharge 6 Important	Lower better [17] (Randomized controlled)	**16** (Median) CI 95%	**17** (Median)	**Very low** Due to serious risk of bias and very serious imprecision [18]	We are uncertain whether ruxolitinib increases or decreases time to discharge.

1. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Low number of patients, Only data from one study.
3. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: Serious.** 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.
5. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: Serious.** 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.
7. Systematic review [315] 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. **Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: Serious.** 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.
11. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: Serious.** 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.
13. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: Serious.** 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.
15. Systematic reviewwith included studies: [317]. **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. **Imprecision: Very serious.** Low number of patients, Only data from one study.
17. Systematic reviewwith included studies: [317]. **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. **Imprecision: Very serious.** Low number of patients, Only data from one study.

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 *[317]*.

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 inderectness (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 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 *[316]*.

Children and adolescents
There is insufficient safety data on the use of ruxolitinib in children and adolescents for other indications.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to serious indirectness and 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 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to serious risk of bias and indirectness, 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 of commencing treatment 9 Critical	Odds Ratio 0.19 (CI 95% 0.01 — 4.22) Based on data from 41 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and indirectness, and very serious imprecision [6]	There were too few who experienced septic shock to determine whether ruxolitinib makes a difference (2 events).
Clinical improvement At day 14 of treatment 6 Important	Odds Ratio 2 (CI 95% 0.58 — 6.94) Based on data from 41 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to serious risk of bias and indirectness, and very serious imprecision [8]	We are uncertain whether ruxolitinib improves or worsens clinical improvement (21 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events Within 28 days of commencing treatment 6 Important	Odds Ratio 1.35 (CI 95% 0.36 — 5.04) Based on data from 41 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to serious risk of bias and indirectness, and very serious imprecision [10]	We are uncertain whether ruxolitinib increases or decreases adverse events (13 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Odds Ratio 0.09 (CI 95% 0 — 1.89) Based on data from 41 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to serious risk of bias and indirectness, and very serious imprecision [12]	There were too few who experienced serious adverse events to determine whether ruxolitinib makes a difference (4 events).
Clinical deterioration At day 14 of treatment 6 Important	Odds Ratio 0.09 (CI 95% 0 — 1.89) Based on data from 41 patients in 1 studies. [13] (Randomized controlled)			**Very low** Due to serious risk of bias and indirectness, and very serious imprecision [14]	We are uncertain whether ruxolitinib improves or worsens clinical deterioration (4 events).
Time to improvement Median days to improvement 6 Important	Lower better [15] (Randomized controlled)	15 (Median) CI 95%	12 (Median)	**Very low** Due to serious risk of bias and indirectness, and very serious imprecision [16]	We are uncertain whether ruxolitinib decreases time to improvement.
Time to discharge Median days to discharge 6 Important	Lower better [17] (Randomized controlled)	16 (Median) CI 95%	17 (Median)	**Very low** Due to serious risk of bias and indirectness, and very serious imprecision [18]	We are uncertain whether ruxolitinib increases or decreases time to discharge.

1. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Indirectness: Serious. Imprecision: Very serious.** Low number of patients, Only data from one study.
3. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
5. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **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 [315] 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.
9. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
11. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [315] with included studies: Cao Y 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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 reviewwith included studies: [317]. **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 reviewwith included studies: [317]. **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.

6.14.34. Sofosbuvir-daclatasvir

Not recommended

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

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.

Evidence To Decision

Benefits and harms Important 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 Low

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 — 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.

Resources — 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.

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.

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 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

Population: Patients with COVID-19
Intervention: Sofosbuvir-daclatasvir
Comparator: Standard care

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 *[324]* and 89 adults hospitalised with mild to severe COVID-19 *[329]*. A third study compared sofosbovir-daclatasvir plus hydroxychloroquine with hydroxychloroquine alone in 55 adult outpatients with confirmed COVID-19 *[331]*.

We have found one new study comparing sofosbuvir-daclatasvir with placebo (Mobarak et al. SSRN preprint doi: 10.2139/ssrn.3792895). 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 *[329]*) 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 recover per 1000 patients; RR 1.21 95% CI 1.04 to 1.41; 155 patients in 2 studies).

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 *[325]*, and known acute harms for daclatasvir include fatigue, diarrhoea, nausea and headache. There are several known and potential interactions with other drugs *[326]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sofosbuvir-daclatasvir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of	Relative risk 0.41 (CI 95% 0.08 — 2) Based on data from 89			**Very low** Due to very serious	We are uncertain whether sofosbuvir-daclatasvir increases or

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sofosbuvir-daclatasvir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
commencing treatment 9 Critical	patients in 1 studies. [1] (Randomized controlled)			imprecision [2]	decreases risk of dying (7 deaths).
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.6 (CI 95% 0.16 — 2.31) Based on data from 66 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision [4]	We are uncertain whether sofosbuvir-daclatasvir increases or decreases risk of dying (8 deaths).
Mechanical ventilation Within 14 days of commencing treatment 9 Critical	Relative risk 0.42 (CI 95% 0.16 — 1.13) Based on data from 155 patients in 2 studies. [5] (Randomized controlled)	**154** per 1000	**65** per 1000 Difference: **89 fewer** per 1000 (CI 95% 129 fewer — 20 more)	**Low** Due to very serious imprecision [6]	We are uncertain whether sofosbuvir-daclatasvir decreases mechanical ventilation (17 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.15 — 6.94) Based on data from 89 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision [8]	We are uncertain whether sofosbuvir-daclatasvir increases or decreases ICU admission (4 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.36 — 2.93) Based on data from 89 patients in 1 studies. [9] (Randomized controlled)	**133** per 1000	**136** per 1000 Difference: **3 more** per 1000 (CI 95% 85 fewer — 257 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether sofosbuvir-daclatasvir increases or decreases adverse events (12 events).
Clinical recovery Within 14 days of commencing treatment 6 Important	Relative risk 1.21 (CI 95% 1.04 — 1.41) Based on data from 155 patients in 2 studies. [11] (Randomized controlled)	**731** per 1000	**885** per 1000 Difference: **154 more** per 1000 (CI 95% 29 more — 300 more)	**Low** Due to very serious imprecision [12]	Sofosbuvir-daclatasvir may improve clinical recovery slightly (126 events).
Hospitalisation End of follow-up	Relative risk 0.26 (CI 95% 0.03 — 2.17) Based on data from 55	**143** per 1000	**37** per 1000	**Low** Due to very serious	We are uncertain whether sofosbuvir-daclatasvir decreases incidence of

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sofosbuvir-daclatasvir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	patients in 1 studies. [13] (Randomized controlled)	Difference: **106 fewer** per 1000 (CI 95% 139 fewer — 167 more)		imprecision [14]	hospitalisation (5 events).
Dyspnoea End of follow-up 6 Important	Relative risk 0.38 (CI 95% 0.14 — 1.04) Based on data from 55 patients in 1 studies. [15] (Randomized controlled)	**393** per 1000 Difference: **244 fewer** per 1000 (CI 95% 338 fewer — 16 more)	**149** per 1000	**Low** Due to very serious imprecision [16]	We are uncertain whether sofosbuvir-daclatasvir improves dyspnoea (15 events).
Time to hospital discharge Days 6 Important	Based on data from: 66 patients in 1 studies. (Randomized controlled)	In Sadeghi 2020 time to clinical recovery was lower in the sofosbuvir-daclatasvir group (median 6 days, IQR 4-10 days) than the control group (median 11 days, IQR 6-17 days).		**Low** Due to very serious imprecision [17]	We are uncertain whether sofosbuvir-daclatasvir increases or decreases time to hospital discharge.

1. Systematic review [328] with included studies: Yakoot 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
3. Systematic review [328] with included studies: Sadeghi 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals, Only data from one study.
5. Systematic review [328] with included studies: Sadeghi 2020, Yakoot 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals.
7. Systematic review [328] with included studies: Yakoot 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
9. Systematic review [328] with included studies: Yakoot 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
11. Systematic review [328] with included studies: Sadeghi 2020, Yakoot 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals.
13. Systematic review [330] with included studies: Roozbeh 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
15. Systematic review [330] with included studies: Roozbeh 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.35. Sulodexide

Not recommended

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.

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 Low

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 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.

Resources 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, 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 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 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
Intervention: 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 *[333]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sulodexide	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 21 days of commencing treatment 9 Critical	Relative risk 0.41 (CI 95% 0.11 — 1.55) Based on data from 243 patients in 1 studies. [1] (Randomized controlled)	59 per 1000	24 per 1000 Difference: 35 fewer per 1000 (CI 95% 53 fewer — 32 more)	Very low Due to very serious imprecision and serious risk of bias [2]	We are uncertain whether sulodexide impacts death (10 events).
Invasive mechanical ventilation Within 21 days of commencing treatment 9 Critical	Relative risk 0.48 (CI 95% 0.12 — 1.87) Based on data from 243 patients in 1 studies. [3] (Randomized controlled)	50 per 1000	24 per 1000 Difference: 26 fewer per 1000 (CI 95% 44 fewer — 44 more)	Very low Due to very serious imprecision and serious risk of bias [4]	We are uncertain whether sulodexide increases or decreases need for invasive mechanical ventilation (9 events).
Supplemental oxygen Within 21 days of commencing treatment 6 Important	Relative risk 0.71 (CI 95% 0.5 — 1) Based on data from 243 patients in 1 studies. [5] (Randomized controlled)	420 per 1000	298 per 1000 Difference: 122 fewer per 1000 (CI 95% 210 fewer — 0 fewer)	Very low Due to very serious imprecision and serious risk of bias [6]	We are uncertain whether sulodexide increases or decreases need for supplemental oxygen (87 events).
Hospitalisation Within 21 days of commencing	Relative risk 0.6 (CI 95% 0.38 — 0.97) Based on data from 243	294	176	Very low Due to very serious	We are uncertain whether sulodexide increases or decreases

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sulodexide	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
treatment 6 Important	patients in 1 studies. [7] (Randomized controlled)	per 1000	per 1000 Difference: **118 fewer** per 1000 (CI 95% 182 fewer — 9 fewer)	imprecision and serious risk of bias [8]	need for hospitalisation (57 events)
Adverse events Within 21 days of commencing treatment 6 Important	Relative risk 1.08 (CI 95% 0.93 — 1.26) Based on data from 243 patients in 1 studies. [9] (Randomized controlled)	**714** per 1000	**771** per 1000 Difference: **57 more** per 1000 (CI 95% 50 fewer — 186 more)	**Very low** Due to very serious imprecision and serious risk of bias [10]	We are uncertain whether sulodexide increases or decreases adverse events (181 events).
Discontinuation due to adverse events Within 21 days of commencing treatment 6 Important	Relative risk 1.28 (CI 95% 0.46 — 3.58) Based on data from 243 patients in 1 studies. [11] (Randomized controlled)	**50** per 1000	**64** per 1000 Difference: **14 more** per 1000 (CI 95% 27 fewer — 129 more)	**Very low** Due to very serious imprecision and serious risk of bias [12]	We are uncertain whether sulodexide increases or decreases discontinuation due to adverse events (14 events).
Duration of supplemental oxygen Days 6 Important	Based on data from: 243 patients in 1 studies. [13] (Randomized controlled)	**11.5** (Mean)	**9** (Mean) Difference: **MD 2.5 lower** (CI 95% 4.64 lower — 0.36 lower)	**Very low** Due to very serious imprecision and serious risk of bias [14]	We are uncertain whether sulodexide increases or decreases duration of supplemental oxygen.
Duration of hospitalisation Days 6 Important	Based on data from: 243 patients in 1 studies. [15] (Randomized controlled)	**7.8** (Mean)	**6.2** (Mean) Difference: **MD 1.6 lower** (CI 95% 2.68 lower — 0.52 lower)	**Very low** Due to very serious imprecision and serious risk of bias [16]	We are uncertain whether sulodexide increases or decreases duration of hospitalisation.

1. Systematic review [332] with included studies: Gonzalez Ochoa 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
3. Systematic review [332] with included studies: Gonzalez Ochoa 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
5. Systematic review [332] with included studies: Gonzalez Ochoa 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
7. Systematic review [332] with included studies: Gonzalez Ochoa 2020. **Baseline/comparator:** Control arm of

reference used for intervention.
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.
9. Systematic review [332] with included studies: Gonzalez Ochoa 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
11. Systematic review [332] with included studies: Gonzalez Ochoa 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [332] with included studies: Gonzalez Ochoa 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
15. Systematic review [332] with included studies: Gonzalez Ochoa 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.36. Telmisartan

Not recommended

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.

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 Low

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 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.

Resources 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, 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 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 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

Population: Patients 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 *[334]*.

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 invasvive 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 *[335]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Telmisartan	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 15 days after commencing treatment 9 Critical	Relative risk 0.95 (CI 95% 0.14 — 6.41) Based on data from 78 patients in 1 studies. [1] (Randomized controlled)	53 per 1000	50 per 1000 Difference: 3 fewer per 1000 (CI 95% 46 fewer — 287 more)	**Low** Due to very serious imprecision [2]	There were too few who had died by day 15 to determine whether telmisartan makes a difference (4 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Telmisartan	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 30 days after commencing treatment 9 Critical	Relative risk 0.48 (CI 95% 0.09 — 2.44) Based on data from 78 patients in 1 studies. [3] (Randomized controlled)	105 per 1000	50 per 1000 Difference: **55 fewer** per 1000 (CI 95% 96 fewer — 151 more)	**Low** Due to very serious imprecision [4]	There were too few who had died by day 30 to determine whether telmisartan makes a difference (6 events).
Invasive mechanical ventilation 15 days after commencing treatment 9 Critical	Relative risk 0.32 (CI 95% 0.03 — 2.91) Based on data from 78 patients in 1 studies. [5] (Randomized controlled)	79 per 1000	25 per 1000 Difference: **54 fewer** per 1000 (CI 95% 77 fewer — 151 more)	**Low** Due to very serious imprecision [6]	There were too few who required mechanical ventilation at day 15 to determine whether telmisartan makes a difference (4 events).
Invasive mechanical ventilation 30 days after commencing treatment 9 Critical	Relative risk 0.32 (CI 95% 0.03 — 2.91) Based on data from 78 patients in 1 studies. [7] (Randomized controlled)	79 per 1000	25 per 1000 Difference: **54 fewer** per 1000 (CI 95% 77 fewer — 151 more)	**Low** Due to very serious imprecision [8]	There were too few who required invasive mechanical ventilation at day 30 to determine whether telmisartan makes a difference (4 events).
ICU admission 30 days after commencing treatment 6 Important	Relative risk 0.76 (CI 95% 0.22 — 2.62) Based on data from 78 patients in 1 studies. [9] (Randomized controlled)	132 per 1000	100 per 1000 Difference: **32 fewer** per 1000 (CI 95% 103 fewer — 214 more)	**Low** Due to very serious imprecision [10]	There were too few who were admitted to intensive care to determine whether telmisartan makes a difference (9 events).
Discharge from hospital 15 days after commencing treatment 6 Important	Relative risk 1.43 (CI 95% 1.01 — 2.02) Based on data from 68 patients in 1 studies. [11] (Randomized controlled)	563 per 1000	805 per 1000 Difference: **242 more** per 1000 (CI 95% 6 more — 574 more)	**Low** Due to very serious imprecision [12]	Telmisartan may increase discharge from hospital (47 events).
Time to discharge from hospital Days 6 Important	Based on data from: 78 patients in 1 studies. [13] (Randomized controlled)	15 (Median)	9 (Median) CI 95%	**Low** Due to very serious imprecision [14]	Telmisartan may decrease time to discharge from hospital.

1. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Low number of patients, Only data from one study.
3. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very serious.** Low number of patients, Only data from one study.
5. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Low number of patients, Only data from one study.
7. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Low number of patients, Only data from one study.
11. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Low number of patients, Only data from one study.
13. Systematic review [336] . **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 *[334]*.

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 *[335]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Telmisartan	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality 15 days after commencing treatment 9 Critical	Relative risk 0.95 (CI 95% 0.14 — 6.41) Based on data from 78 patients in 1 studies. [1] (Randomized controlled)	53 per 1000	50 per 1000 Difference: **3 fewer** per 1000 (CI 95% 46 fewer — 287 more)	**Very low** Due to very serious imprecision and serious indirectness [2]	There were too few who had died by day 15 to determine whether telmisartan makes a difference (4 events).
All-cause mortality 30 days after commencing treatment 9 Critical	Relative risk 0.48 (CI 95% 0.09 — 2.44) Based on data from 78 patients in 1 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [4]	There were too few who had died by day 30 to determine whether telmisartan makes a difference (6 events).
Mechanical ventilation 15 days after commencing treatment 9 Critical	Relative risk 0.32 (CI 95% 0.03 — 2.91) Based on data from 78 patients in 1 studies. [5] (Randomized controlled)	79 per 1000	25 per 1000 Difference: **54 fewer** per 1000 (CI 95% 77 fewer — 151 more)	**Very low** Due to very serious imprecision and serious indirectness [6]	There were too few who required mechanical ventilation at day 15 to determine whether telmisartan makes a difference (4 events).
Mechanical ventilation 30 days after commencing treatment 9 Critical	Relative risk 0.32 (CI 95% 0.03 — 2.91) Based on data from 78 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [8]	There were too few who required mechanical ventilation at day 30 to determine whether telmisartan makes a difference (4 events).
ICU admission 30 days after commencing treatment 6 Important	Relative risk 0.76 (CI 95% 0.22 — 2.62) Based on data from 78 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to very serious imprecision and serious indirectness [10]	There were too few who were admitted to intensive care to determine whether telmisartan makes a difference (9 events).
Discharge from hospital	Relative risk 1.43 (CI 95% 1.01 — 2.02)			**Very low** Due to very	We are uncertain whether telmisartan

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Telmisartan	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
15 days after commencing treatment 6 Important	Based on data from 68 patients in 1 studies. [11] (Randomized controlled)			serious imprecision and serious indirectness [12]	may increase discharge from hospital (47 events).
Time to discharge from hospital Days 6 Important	Based on data from: 78 patients in 1 studies. [13] (Randomized controlled)	15 (Median)	9 (Median) CI 95%	Very low Due to very serious imprecision and serious indirectness [14]	We are uncertain whether telmisartan decreases time to discharge from hospital.

1. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, Only data from one study.
3. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, Only data from one study.
5. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, Only data from one study.
7. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, Only data from one study.
9. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, Only data from one study.
11. Systematic review [336] with included studies: Duarte 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, Only data from one study.
13. Systematic review [336] . **Baseline/comparator:** Control arm of reference used for intervention.
14. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Low number of patients, Only data from one study.

6.14.37. Triazavirin

Not recommended

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.

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

Very low

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

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
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

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, 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 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 *[338]*.

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 triazarivin 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).

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 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Triazavirin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.33 (CI 95% 0.01 — 7.82) Based on data from 52 patients in 1 studies. [1] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [2]	There were too few who died to determine whether triazavirin makes a difference (1 death).
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical					Data for patients requiring mechanical ventilation were not reported.
Serious adverse events	Relative risk 0.8 (CI 95% 0.24 — 2.65) Based on data from 52			**Very low** Due to very serious risk of	There were too few who experienced one or more serious adverse

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Triazavirin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Within 28 days of commencing treatment 9 Critical	patients in 1 studies. [3] (Randomized controlled)			bias and very serious imprecision [4]	events to determine whether triazavirin makes a difference (9 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.6 (CI 95% 0.26 — 1.41) Based on data from 52 patients in 1 studies. [5] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [6]	There were too few who experienced one or more adverse events to determine whether triazavirin made a difference (6 events).
Virological clearance (Negative PCR) Within 28 days of commencing treatment 6 Important	Relative risk 1.14 (CI 95% 0.92 — 1.42) Based on data from 52 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [8]	We are uncertain whether triazavirin increases virological clearance.
Time to improvement Within 28 days of commencing treatment 6 Important	Lower better [9] (Randomized controlled)	**12** Days (Median) CI 95%	**7** Days (Median)	**Very low** Due to very serious risk of bias and very serious imprecision [10]	We are uncertain whether triazavirin decreases time to improvement.

1. Systematic review [337] with included studies: Wu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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. , 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.**
3. Systematic review [337] with included studies: Wu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
5. Systematic review [337] with included studies: Wu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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. , Selective outcome reporting, due to [reason], Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **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. Systematic review [337] with included studies: Wu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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. , Selective outcome reporting, due to [reason], Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: No serious.**
9. Systematic reviewwith included studies: [338]. **Baseline/comparator:** Control arm of reference used for intervention.
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. , Selective outcome reporting, due to [reason], Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: No serious.**

6.14.38. Umifenovir

Not recommended

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.

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 Low

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 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
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 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 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 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

Population: Patients with COVID-19
Intervention: Umifenovir
Comparator: Standard care

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 *[131][339][341]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Umifenovir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause					No patients died.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Umifenovir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
mortality Within 21 days of commencing treatment 9 Critical	Based on data from 52 patients in 1 studies. [1]				
Adverse events Within 21 days of commencing treatment 6 Important	Relative risk 4.18 (CI 95% 0.51 — 34.19) Based on data from 135 patients in 3 studies. [2] (Randomized controlled)			**Low** Due to very serious imprecision [3]	There were too few who experienced one or more adverse events to determine whether umifenovir makes a difference (6 events).
Serious adverse events Within 21 days of commencing treatment 6 Important	Based on data from 82 patients in 2 studies. [4]				No patients experienced a serious adverse event.
Clinical deterioration (mild/mod to sev/crit) [5] Within 21 days of commencing treatment 6 Important	Relative risk 0.73 (CI 95% 0.13 — 3.96) Based on data from 82 patients in 2 studies. [6] (Randomized controlled)	**63** per 1000	**46** per 1000 Difference: **17 fewer** per 1000 (CI 95% 55 fewer — 186 more)	**Low** Due to very serious imprecision [7]	There were too few who experienced clinical deterioration to determine whether umifenovir makes a difference (5 events).
Clinical improvement [8] Based on chest CT scan 14 days after commencing treatment 6 Important	Relative risk 0.75 (CI 95% 0.57 — 0.98) Based on data from 47 patients in 1 studies. [9] (Randomized controlled)	**929** per 1000	**697** per 1000 Difference: **232 fewer** per 1000 (CI 95% 399 fewer — 19 fewer)	**Low** Due to very serious imprecision [10]	Umifenovir may decrease clinical improvement slightly at day 14 (36 events).
Negative PCR Within 14 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 0.9 — 1.59) Based on data from 52 patients in 1 studies. [11] (Randomized controlled)	**765** per 1000	**918** per 1000 Difference: **153 more** per 1000 (CI 95% 77 fewer — 451 more)	**Low** Due to very serious imprecision [12]	Umifenovir may have little impact on negative PCR (45 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Umifenovir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Discharge from hospital Within 21 days of commencing treatment 6 Important	Relative risk 1 (CI 95% 0.88 — 1.13) Based on data from 30 patients in 1 studies. [13] (Randomized controlled)	1,000 per 1000	1,000 per 1000 Difference: 0 fewer per 1000 (CI 95% 120 fewer — 130 more)	**Low** Due to very serious imprecision [14]	Umifenovir may have little impact on discharge from hospital (30 events).

1. Systematic review [340] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [340] with included studies: Yethindra 2020, Li 2020, [341]. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision: Very serious.** Low number of patients, due to few events.
4. Systematic review [340] with included studies: Li 2020, Yethindra 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. The number of patients who deteriorated from a mild or moderate form of disease to a severe or critical form.
6. Systematic review [340] with included studies: Li 2020, Yethindra 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
9. Systematic review [340] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Only data from one study, Low number of patients.
11. Systematic review [340] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very serious.** Only data from one study, Low number of patients.
13. Systematic review [340] with included studies: Yethindra 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Very serious.** Only data from one study, Low number of patients.

6.14.39. Vitamin C

Not recommended

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.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

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.

Certainty of the Evidence — Very low

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 — 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
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 — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

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 — 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.

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 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.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Vitamin C
Comparator: Standard care

Summary

There remains significant uncertainty whether vitamin C 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 vitamin C with standard care in 364 adults with COVID-19 *[344][345][346][354]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Vitamin C	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.72 (CI 95% 0.31 — 1.66) Based on data from 154 patients in 2 studies. [1] (Randomized controlled)			**Very low** Due to very serious risk of bias, serious inconsistency and serious imprecision [2]	We are uncertain whether vitamin C increases or decreases risk of death (17 deaths).
All-cause mortality End of follow-up 9 Critical	Relative risk 0.71 (CI 95% 0.33 — 1.54) Based on data from 210 patients in 2 studies. [3] (Randomized controlled)			**Very low** Due to very serious imprecision, serious inconsistency and serious risk of bias. [4]	We are uncertain whether vitamin C increases risk of death (24 deaths).
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.89 (CI 95% 0.49 — 1.62) Based on data from 210 patients in 2 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias, serious inconsistency and serious imprecision [6]	We are uncertain whether vitamin C increases or decreases invasive mechanical ventilation (36 events).
Invasive mechanical ventilation Day 7 of treatment 9 Critical	Relative risk 0.98 (CI 95% 0.5 — 1.92) Based on data from 56 patients in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious risk of bias and serious imprecision [8]	We are uncertain whether vitamin C increases or decreases invasive mechanical ventilation (21 events).
Hospitalisation 6 Important	Relative risk 0.69 (CI 95% 0.12 — 3.98) Based on data from 98 patients in 1 studies. [9] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious imprecision [10]	We are uncertain whether vitamin C increases or decreases hospitalisation (5 events).
Clinical deterioration 6 Important	Relative risk 0.64 (CI 95% 0.17 — 2.44) Based on data from 56 patients in 1 studies. [11] (Randomized controlled)			**Very low** Due to very serious risk of bias and very serious	We are uncertain whether vitamin C increases or decreases clinical deterioration (8 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Vitamin C	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
				imprecision [12]	

1. Systematic review [343] with included studies: Thomas 2021, Zhang 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
3. Systematic review [343] with included studies: JamaliMoghadamSiahkali 2021, Kumari 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
5. Systematic review [343] with included studies: JamaliMoghadamSiahkali 2021, Kumari 2020. **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: Serious.** The direction of the effect is not consistent between the included studies. **Imprecision: Serious.** Low number of patients.
7. Systematic review [343] with included studies: Zhang 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
9. Systematic review [343] with included studies: Thomas 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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.
11. Systematic review [343] with included studies: Zhang 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: Very 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.

6.14.40. Vitamin D analogues (calcifediol/cholecalciferol)

Not recommended

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.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

General adult population
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.

Certainty of the Evidence — Very low

General adult population
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).

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 — 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
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 — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

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 — No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

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 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.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Vitamin D analogues
Comparator: Standard care

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 *[347][350][351]*.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Vitamin D analogues	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk 0.58 (CI 95% 0.05 — 7.18)	56	32	Low Due to very	We are uncertain whether vitamin D

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Vitamin D analogues	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
End of follow-up 9 Critical	Based on data from 313 patients in 2 studies. [1] (Randomized controlled)	per 1000	per 1000 Difference: **24 fewer** per 1000 (CI 95% 53 fewer — 346 more)	serious imprecision [2]	analogues decrease death (16 deaths).
Invasive mechanical ventilation End of follow-up 6 Important	Relative risk 0.47 (CI 95% 0.21 — 1.04) Based on data from 237 patients in 1 studies. [3] (Randomized controlled)	**144** per 1000	**68** per 1000 Difference: **76 fewer** per 1000 (CI 95% 114 fewer — 6 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether vitamin D analogues decrease the requirement of invasive mechanical ventilation (25 events).
ICU admission End of follow-up 6 Important	Relative risk 0.2 (CI 95% 0.01 — 3.29) Based on data from 313 patients in 2 studies. [5] (Randomized controlled)	**264** per 1000	**53** per 1000 Difference: **211 fewer** per 1000 (CI 95% 261 fewer — 605 more)	**Low** Due to very serious imprecision [6]	Vitamin D analogues may decrease the requirement of ICU admission (57 events).
Discharge from hospital End of follow-up 6 Important	Relative risk 1.09 (CI 95% 0.96 — 1.23) Based on data from 76 patients in 1 studies. [7] (Randomized controlled)	**923** per 1000	**1,000** per 1000 Difference: **83 more** per 1000 (CI 95% 37 fewer — 212 more)	**Low** Due to very serious imprecision [8]	We are uncertain whether vitamin D analogues increase or decrease discharge from hospital.
Time to discharge from hospital Days 6 Important	Lower better Based on data from: 237 patients in 1 studies. (Randomized controlled)	**7** (Median)	**7** (Median) CI 95%	**Low** Due to very serious imprecision [9]	We are uncertain whether vitamin D analogues increase or decrease time to discharge from hospital.

1. Systematic review [349] with included studies: Murai 2020, Castillo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very serious.** Wide confidence intervals, Wide confidence intervals, due to few events.
3. Systematic review [349] with included studies: Murai 2020. **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.
5. Systematic review [349] with included studies: Murai 2020, Castillo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very serious.** Wide confidence intervals.
7. Systematic review [349] with included studies: Castillo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

6.14.41. Zinc

Not recommended

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.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

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.

Certainty of the Evidence — Low

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 all remaining outcomes 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.

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
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 — Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

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 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 three randomised trials. The first compared zinc with placebo in 33 adults hospitalised with COVID-19 *[355]*, the second compared zinc with standard care in 108 adult outpatients *[354]*, and the third compared zinc plus hydroxychloroquine with hydroxychloroquine alone in 191 adults hospitalised with COVID-19 *[353]*.

Study characteristics
Mean age of participants was ~43 years in two studies *[353][354]* and ~62 years in the other *[355]*. The proportion of women ranged from 36 to 63% across the studies.

What are the main results?
We are uncertain whether zinc increases or decreases death, the need for invasive mechanical ventilation, rate of hospitalisation or discharge from hospital, clinical recovery or duration of hospital stay.

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 all remaining outcomes 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 *[356]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Zinc	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.92 (CI 95% 0.35 — 2.44) Based on data from 332 patients in 3 studies. [1] (Randomized controlled)	49 per 1000	45 per 1000 Difference: **4 fewer** per 1000 (CI 95% 32 fewer — 71 more)	**Low** Due to serious risk of bias and serious imprecision [2]	We are uncertain whether zinc impacts death (15 events).
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.66 (CI 95% 0.19 — 2.26) Based on data from 191 patients in 1 studies. [3] (Randomized controlled)	63 per 1000	42 per 1000 Difference: **21 fewer** per 1000 (CI 95% 51 fewer — 79 more)	**Very low** Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether zinc increases or decreases invasive mechanical ventilation (10 events)
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 1.44 (CI 95% 0.36 — 5.71) Based on data from 108 patients in 1 studies. [5] (Randomized controlled)	60 per 1000	86 per 1000 Difference: **26 more** per 1000 (CI 95% 38 fewer — 283 more)	**Very low** Due to serious risk of bias and very serious imprecision [6]	We are uncertain whether zinc increases or decreases hospitalisation (8 events).
Discharged from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.86 (CI 95% 0.55 — 1.32) Based on data from 33 patients in 1 studies. [7] (Randomized controlled)	778 per 1000	669 per 1000 Difference: **109 fewer** per 1000 (CI 95% 350 fewer — 249 more)	**Low** Due to very serious imprecision [8]	We are uncertain whether zinc increases or decreases number of patients discharged from hospital (24 events).
Clinical recovery Within 28 days of commencing treatment	Relative risk 1 (CI 95% 0.87 — 1.16) Based on data from 191 patients in 1 studies. [9] (Randomized controlled)	789 per 1000	789 per 1000 Difference: **0 fewer** per 1000	**Very low** Due to serious risk of bias and very serious imprecision [10]	We are uncertain whether zinc improves or worsens clinical recovery.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Zinc	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important		(CI 95% 103 fewer — 126 more)			
Duration of hospital stay Days 6 Important	Based on data from: 191 patients in 1 studies. [11] (Randomized controlled)	14 (Mean)	13.5 (Mean) Difference: MD 0.5 lower (CI 95% 2.15 lower — 1.15 higher)	Very low Due to serious risk of bias and very serious imprecision [12]	We are uncertain whether zinc increases or decreases duration of hospital stay.

1. Systematic review [352] with included studies: Thomas 2021, Patel 2020, Abd-Elsalam 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **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, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: Serious.** Wide confidence intervals, due to few events.
3. Systematic review [352] with included studies: Abd-Elsalam 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: Very serious.** Wide confidence intervals, Only data from one study, due to few events.
5. Systematic review [352] with included studies: Thomas 2021. **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, 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.
7. Systematic review [352] with included studies: Patel 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals, due to few events, Only data from one study.
9. Systematic review [352] with included studies: Abd-Elsalam 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Selective outcome reporting. **Imprecision: Very serious.** Low number of patients, Only data from one study.
11. Systematic review [352] with included studies: Abd-Elsalam 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: Very serious.** Low number of patients, Only data from one study.

6.14.42. 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.

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.

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 Substantial variability is expected or uncertain

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 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, 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 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 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][127][128]*, 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.

6.15. 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.

6.15.1. Aspirin

We have found a new study comparing aspirin with usual care (RECOVERY trial medRxiv doi: 10.1101/2021.06.08.21258132). This study randomised nearly 15,000 patients hospitalised with COVID-19, of whom 1222 (17%) patients allocated to aspirin and 1299 (17%) patients allocated to usual care died within 28 days (RR 0.96; 95%CI 0.89 to 1.04; p=0.35). This study is currently under review and a recommendation will be included in a future version of the guideline.

6.15.2. Sotrovimab

We have found a new study comparing sotrovimab with placebo (Gupta et al. medRxiv doi: 10.1101/2021.05.27.21257096). This study is currently under review and a recommendation will be included in a future version of the guideline.

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. 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.

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.

Evidence To Decision

Benefits and harms — Important 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 — Low

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 aderse 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 — Substantial variability is expected or uncertain

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 — 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

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 — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

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 *[361][362][363]*.

We have found one new study 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). This study is currently under review and will be incorporated in a future version of the guideline.

Publication status
One study is only available as a preprint (Grau-Pujol et al. posted to Res Sq on 21 September 2020) and has therefore not been peer reviewed.

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 *[363]*. Participants in Grau-Pujol et al. were given 400 mg hydroxychloroquine daily for four days, followed by 400 mg once weekly for one month *[361]*. In the study by Abella et al. participants received 600 mg of hydroxychloroquine daily for eight weeks *[362]*.

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 *[361]*, one study did not specify whether pregnant or breastfeeding women were eligible *[362]*, and no pregnant women enrolled in the third study, although 30 women reported breastfeeding at baseline *[363]*.

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].

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Pre-exp HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Laboratory-confirmed diagnosis End of treatment 9 Critical	Relative risk 0.87 (CI 95% 0.4 — 1.88) Based on data from 1,877 patients in 3 studies. [1] (Randomized controlled)	16 per 1000	14 per 1000 Difference: **2 fewer** per 1000 (CI 95% 10 fewer — 14 more)	**Low** Due to serious risk of bias and serious imprecision [2]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on laboratory-confirmed diagnosis in healthcare workers (26 events).
All-cause mortality End of treatment 6 Important	Based on data from 1,608 patients in 2 studies. [3]				There were no deaths.
Serious adverse events End of treatment 6 Important	Relative risk 0.78 (CI 95% 0.31 — 2.01) Based on data from 1,752 patients in 2 studies. [4] (Randomized controlled)	11 per 1000	9 per 1000 Difference: **2 fewer** per 1000 (CI 95% 8 fewer — 11 more)	**Low** Due to serious risk of bias and serious imprecision [5]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on serious adverse events in healthcare workers (18 events).
Adverse events End of treatment 6 Important	Relative risk 1.45 (CI 95% 1.14 — 1.84) Based on data from 1,801 patients in 3 studies. [6] (Randomized controlled)	241 per 1000	349 per 1000 Difference: **108 more** per 1000 (CI 95% 34 more — 202 more)	**Moderate** Due to serious risk of bias [7]	Hydroxychloroquine pre-exposure prophylaxis probably increases adverse events in healthcare workers.
Symptoms compatible with COVID-19 12 weeks 6 Important	Relative risk 0.75 (CI 95% 0.5 — 1.11) Based on data from 1,483 patients in 1 studies. [8] (Randomized controlled)	77 per 1000	58 per 1000 Difference: **19 fewer** per 1000 (CI 95% 39 fewer — 8 more)	**Low** Due to serious risk of bias and serious imprecision [9]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on development of symptoms compatible with COVID-19 in healthcare workers (95 events).
Confirmed or probable infection 12 weeks 6 Important	Relative risk 0.87 (CI 95% 0.6 — 1.27) Based on data from 1,483 patients in 1 studies. [10] (Randomized controlled)	79 per 1000	69 per 1000 Difference: **10 fewer** per 1000 (CI 95% 32 fewer — 21 more)	**Moderate** Due to serious risk of bias [11]	Hydroxychloroquine pre-exposure prophylaxis probably has little or no impact on confirmed or probable infection (107 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Pre-exp HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Discontinuation due to adverse events 8 weeks 6 Important	Relative risk 0.95 (CI 95% 0.2 — 4.54) Based on data from 125 patients in 1 studies. [12] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [13]	There were too few events (6 events) to determine whether hydroxychloroquine pre-exposure prophylaxis increases or decreases discontinuation due to adverse events.

1. Systematic review [360] with included studies: Grau-Pujol 2020, Abella 2020, Rajasingham 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** due to few events.
3. Systematic review [360] with included studies: Rajasingham 2020, Abella 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [360] with included studies: Grau-Pujol 2020, Rajasingham 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: Serious.** due to few events.
6. Systematic review [360] with included studies: Abella 2020, Rajasingham 2020, Grau-Pujol 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
8. Systematic review [360] with included studies: Rajasingham 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **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: Serious.** Only data from one study.
10. Systematic review [360] with included studies: Rajasingham 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
12. Systematic review [360] with included studies: Abella 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.

7.2. Hydroxychloroquine for post-exposure prophylaxis

Not recommended

For people exposed to individuals with severe acute respiratory syndrome coronavirus 2 (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.

Evidence To Decision

Benefits and harms

Important 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.

Certainty of the Evidence

Very low

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.

Preference and values

We expect few to want the intervention

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.

Resources 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

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 *[364][366]*. 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 *[364]*. In the second trial of 2314 people, mean age was 49 years and 73% were women *[366]*.

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 *[134]*. There are several known and potential interactions with other drugs *[134]*. 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 *[134]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Laboratory-confirmed diagnosis 14 days after commencing treatment 9 Critical	Relative risk 0.96 (CI 95% 0.71 — 1.3) Based on data from 3,135 patients in 2 studies. [1] (Randomized controlled)	52 per 1000	50 per 1000 Difference: 2 fewer per 1000 (CI 95% 15 fewer — 16 more)	Moderate Due to serious imprecision [2]	Hydroxychloroquine post-exposure prophylaxis probably has no effect on the number of laboratory-confirmed diagnoses.
Symptoms compatible with	Relative risk 0.98 (CI 95% 0.82 — 1.18) Based on data from	128	125	**Low** Due to serious risk of bias and	Hydroxychloroquine post-exposure prophylaxis may have no

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
COVID-19 14 days after commencing treatment 6 Important	3,135 patients in 2 studies. [3] (Randomized controlled)	per 1000	per 1000 Difference: **3 fewer** per 1000 (CI 95% 23 fewer — 23 more)	imprecision [4]	effect on the number of symptoms compatible with COVID-19.
Confirmed or probable infection 14 days after commencing treatment 6 Important	Relative risk 0.83 (CI 95% 0.58 — 1.18) Based on data from 821 patients in 1 studies. [5] (Randomized controlled)	**143** per 1000	**119** per 1000 Difference: **24 fewer** per 1000 (CI 95% 60 fewer — 26 more)	**Low** Due to serious risk of bias and imprecision [6]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of patients with confirmed or probable infection.
All-cause mortality End of treatment 6 Important	Relative risk 0.68 (CI 95% 0.22 — 2.07) Based on data from 3,318 patients in 2 studies. [7] (Randomized controlled)	**5** per 1000	**3** per 1000 Difference: **2 fewer** per 1000 (CI 95% 4 fewer — 5 more)	**Low** Due to very serious imprecision [8]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis improves or worsens all-cause mortality (13 events).
Serious adverse events End of treatment 6 Important	Relative risk 0.89 (CI 95% 0.44 — 1.81) Based on data from 2,497 patients in 1 studies. [9] (Randomized controlled)	**13** per 1000	**12** per 1000 Difference: **1 fewer** per 1000 (CI 95% 7 fewer — 11 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases or decreases serious adverse events (31 events).
Adverse events End of treatment 6 Important	Relative risk 4.76 (CI 95% 1.19 — 19.1) Based on data from 3,197 patients in 2 studies. [11] (Randomized controlled)	**82** per 1000	**390** per 1000 Difference: **308 more** per 1000 (CI 95% 16 more — 1,484 more)	**Moderate** Due to serious risk of bias [12]	Hydroxychloroquine post-exposure prophylaxis probably increases the number of adverse events.
Discontinuation due to adverse events End of treatment 6 Important	Relative risk 4.1 (CI 95% 0.52 — 32.23) Based on data from 3,346 patients in 2 studies. [13] (Randomized controlled)	**5** per 1000	**20** per 1000 Difference: **15 more** per 1000 (CI 95% 2 fewer — 156 more)	**Very low** Due to serious risk of bias and very serious imprecision [14]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases discontinuation due to adverse events (33 events).

1. Systematic review [365] with included studies: Mitja 2020, Boulware 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.

3. Systematic review [365] with included studies: Boulware 2020, Mitja 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [365] with included studies: Boulware 2020. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [365] with included studies: Mitja 2020, Boulware 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very serious.** Only 13 events.
9. Systematic review [365] with included studies: Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very serious.** Only 31 events.
11. Systematic review [365] with included studies: Boulware 2020, Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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.
13. Systematic review [365] with included studies: Mitja 2020, Boulware 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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. **Imprecision: Very serious.** Only 33 events.

Clinical Question/ PICO

Population:	Special populations
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 *[364][366]*. 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 *[364]*. In the second trial of 2314 people, mean age was 49 years and 73% were women *[366]*.

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 *[134]*. There are several known and potential interactions with other drugs *[134]*. 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 *[134]*.

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, with no increase in fetal malformations *[139][140]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[139][140][141]*. While this evidence is reassuring, further research is needed.

Children and adolescents
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Laboratory-confirmed diagnosis 14 days after commencing treatment 9 Critical	Relative risk 0.96 (CI 95% 0.71 — 1.3) Based on data from 3,135 patients in 2 studies. [1] (Randomized controlled)	52 per 1000	50 per 1000 Difference: 2 fewer per 1000 (CI 95% 15 fewer — 16 more)	**Low** Due to serious imprecision and indirectness [2]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of laboratory-confirmed diagnoses.
Symptoms compatible with COVID-19 14 days after commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.82 — 1.18) Based on data from 3,135 patients in 2 studies. [3] (Randomized controlled)	128 per 1000	125 per 1000 Difference: 3 fewer per 1000 (CI 95% 23 fewer — 23 more)	**Very low** Due to serious risk of bias, imprecision and indirectness [4]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of symptoms compatible with COVID-19.
Confirmed or probable infection 14 days after commencing treatment 6 Important	Relative risk 0.83 (CI 95% 0.58 — 1.18) Based on data from 821 patients in 1 studies. [5] (Randomized controlled)	143 per 1000	119 per 1000 Difference: 24 fewer per 1000 (CI 95% 60 fewer — 26 more)	**Very low** Due to serious risk of bias, imprecision and indirectness [6]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of patients with confirmed or probable infection.
All-cause mortality End of treatment	Relative risk 0.68 (CI 95% 0.22 — 2.07) Based on data from	5	3	**Very low** Due to very serious	We are uncertain whether hydroxychloroquine

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	3,318 patients in 2 studies. [7] (Randomized controlled)	per 1000	per 1000 Difference: **2 fewer** per 1000 (CI 95% 4 fewer — 5 more)	imprecision and serious indirectness [8]	post-exposure prophylaxis improves or worsens all-cause mortality (13 events).
Serious adverse events End of treatment 6 Important	Relative risk 0.89 (CI 95% 0.44 — 1.81) Based on data from 2,497 patients in 1 studies. [9] (Randomized controlled)	**13** per 1000	**12** per 1000 Difference: **1 fewer** per 1000 (CI 95% 7 fewer — 11 more)	**Very low** Due to very serious imprecision and serious indirectness [10]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases or decreases serious adverse events (31 events).
Adverse events End of treatment 6 Important	Relative risk 4.76 (CI 95% 1.19 — 19.1) Based on data from 3,197 patients in 2 studies. [11] (Randomized controlled)	**82** per 1000	**390** per 1000 Difference: **308 more** per 1000 (CI 95% 16 more — 1,484 more)	**Low** Due to serious risk of bias and indirectness [12]	Hydroxychloroquine post-exposure prophylaxis may increase the number of adverse events.
Discontinuation due to adverse events End of treatment 6 Important	Relative risk 4.1 (CI 95% 0.52 — 32.23) Based on data from 3,346 patients in 2 studies. [13] (Randomized controlled)	**5** per 1000	**20** per 1000 Difference: **15 more** per 1000 (CI 95% 2 fewer — 156 more)	**Very low** Due to serious risk of bias, indirectness and very serious imprecision [14]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases or decreases discontinuation due to adverse events (33 events).

1. Systematic review [365] with included studies: Mitja 2020, Boulware 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [365] with included studies: Mitja 2020, Boulware 2020. **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, 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.
5. Systematic review [365] with included studies: Boulware 2020. **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, 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.
7. Systematic review [365] with included studies: Boulware 2020, Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.** Only 13 events.
9. Systematic review [365] with included studies: Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very serious.**

Only 31 events.
11. Systematic review [365] with included studies: Boulware 2020, Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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. **Indirectness: Serious.** Differences between the population of interest and those studied.
13. Systematic review [365] with included studies: Mitja 2020, Boulware 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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. **Indirectness: Serious. Imprecision: Very serious.** Only 33 events.

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 *[367]*. 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:

Recommendations	Primary Panel
HFNO and NIV	Hospital and Acute Care Panel
Respiratory management of the deteriorating patient, video-laryngoscopy, neuromuscular blockers, PEEP, prone positioning, recruitment manoeuvres and ECMO	Critical Care Panel
Respiratory support for pregnant and postpartum women	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.

Consensus recommendation

Guiding principles of care
For patients with COVID-19 for whom respiratory support (HFNO/NIV) is being considered, decisions should balance likelihood of patient benefit against the risk of infection for healthcare workers. For patients with COVID-19 receiving respiratory support (HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place. Closed circuit NIV should be used.

The relative risk of infection to healthcare workers associated with specific oxygen therapies remains uncertain and may vary from site to site.

8.1. High-flow nasal oxygen therapy

Info Box

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where oxygen is delivered, often in conjunction with compressed air and humidification. It delivers high flow oxygen via large diameter nasal cannula that is humidified and heated. Flow rates can be given up to 60 L/min with an oxygen/air blender supplying oxygen at 21–100%.

High-flow humidified oxygen should be considered when unable to maintain SaO2 ≥ 92% despite conventional oxygen delivery at > 6 L/min or an FiO2 = 0.4.

Conditional recommendation

Consider using HFNO therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If HFNO is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

HFNO can improve oxygenation in patients with hypoxaemia but may be associated with a high failure rate and delayed intubation. Evidence from non-COVID patients with acute hypoxaemic respiratory failure shows uncertainty for mortality and intubation. HFNO is a known aerosol-generating procedure, with possible increased risk of aerosolisation—harms associated with potential risk of transmission to healthcare workers need to be considered and the procedure used with caution and strict attention paid to staff safety *[18]*.

Certainty of the Evidence — Very low

No studies were identified in COVID-19 patients that address the interventions, comparators and outcomes of interest. A systematic review of non-COVID-19 patients of low to very low certainty evidence is included.

Preference and values — Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values at this point.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the recommendation and 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 — Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, there are likely to be resource issues associated with different settings. There are limited negative pressure rooms available in private and some public hospitals, although some hospitals have transformed 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.

Equity — Important issues, or potential issues not investigated

There may be equity issues due to the availability of negative pressure rooms and hospital spaces that are able to perform HFNO safely.

Acceptability — Important issues, or potential issues not investigated

We have no systematically collected information regarding acceptability. We are uncertain if HFNO is likely to be acceptable to both patients and healthcare providers.

Feasibility — Important issues, or potential issues not investigated

There may be feasibility issues due to the availability of negative pressure rooms and hospital spaces that are able to perform HFNO safely.

Rationale

HFNO can improve oxygenation in patients with hypoxaemia but it may be associated with a high failure rate and delayed intubation. HFNO is associated with an increased risk of aerosolisation and is only recommended in hospital spaces that limit transmission risk and where caution and strict attention is paid to staff safety.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: High-flow nasal oxygen therapy

Comparator: Conventional oxygen therapy

Summary

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 *[374]*.

Review 1: Effectiveness

Study design	Randomised trials
Population	Critically ill patients with acute hypoxaemic respiratory failure of any cause. No studies available in patients with COVID-19.
Intervention	High-flow nasal cannula (HFNC)
Comparison	Conventional oxygen therapy
Synthesis method	Meta-analysis
Results	Included 12 RCTs (n = 2217 patients). Decreased risk of requiring intubation and escalation of oxygen therapy (defined as crossover to HFNC in the control group or initiation of non-invasive or invasive ventilation in either group) in favour of HFNC over conventional oxygen therapy. There was no significant difference in mortality, intensive care unit length of stay, hospital length of stay, patient-reported dyspnoea and patient-reported comfort. Treatment-reported complications were not pooled due to variability in reporting but were generally minimal across studies and comparable between interventions.

Review 2: Risk of dispersal

Study design	Simulation studies and one prospective crossover study
Population	Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).
Intervention	High-flow nasal oxygen (HFNO)
Comparison	None (three simulation studies); CPAP (one simulation study); conventional therapy with face mask (one crossover study)
Synthesis method	None, individual study results only
Results	Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

For both reviews, certainty of the evidence is deemed to be low to very low due to indirectness (not based on COVID-19 patients), risk of bias and lack of presicion in some outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional therapy	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 9 Critical	Relative risk 0.94 (CI 95% 0.67 — 1.31) Based on data from 1,407 patients in 4 studies. [1] (Randomized	**272** per 1000	**256** per 1000 Difference: **16 fewer** per 1000	**Low** Due to serious imprecision and indirectness [2]	HFNO may have little or no difference on mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional therapy	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
	controlled) Follow up: 7 to 90 days.	(CI 95% 90 fewer — 84 more)			
Invasive ventilation 9 Critical	Relative risk 0.85 (CI 95% 0.74 — 0.99) Based on data from 1,687 patients in 8 studies. [3] Follow up: 2 to 28 days.	286 per 1000	243 per 1000 Difference: **43 fewer** per 1000 (CI 95% 74 fewer — 3 fewer)	**Very low** Due to serious risk of bias, imprecision and indirectness [4]	We are uncertain whether HFNO increases or decreases invasive ventilation.
Escalation of therapy (HFNC, NIV or intubation) 9 Critical	Relative risk 0.71 (CI 95% 0.51 — 0.98) Based on data from 1,703 patients in 8 studies. [5] Follow up: 2 to 28 days.	320 per 1000	227 per 1000 Difference: **93 fewer** per 1000 (CI 95% 157 fewer — 6 fewer)	**Very low** Due to serious risk of bias, imprecision and indirectness [6]	We are uncertain whether HFNO increases or decreases escalation of therapy (HFNC, NIV or intubation).
ICU length of stay (Days) 9 Critical	Based on data from: 972 patients in 2 studies.	Difference: **MD 1.38 fewer** (CI 95% 0.9 fewer — 3.66 fewer)		**Very low** Due to serious imprecision, inconsistency and indirectness [7]	We are uncertain whether HFNO increases or decreases ICU length of stay.
Hospital length of stay (Days) 9 Critical	Based on data from: 1,247 patients in 4 studies.	Difference: **MD 0.67 more** (CI 95% 1.41 fewer — 0.08 more)		**Low** Due to serious imprecision and indirectness [8]	HFNO may have little or no difference on hospital length of stay.
Patient-reported dyspnoea Variable score 9 Critical	Based on data from: 894 patients in 7 studies.	Difference: **SMD 0.66 lower** (CI 95% 1.68 lower — 0.35 higher)		**Very low** Due to serious risk of bias, imprecision and indirectness [9]	We are uncertain whether HFNO improves or worsens patient reported dyspnoea.
Patient-reported comfort Variable score 9 Critical	Based on data from: 1,233 patients in 7 studies.	Difference: **SMD 0.12 lower** (CI 95% 0.61 lower — 0.37 higher)		**Very low** Due to serious risk of bias, imprecision, inconsistency and indirectness [10]	We are uncertain whether HFNO improves or worsens patient reported comfort.
Dispersal of droplets and aerosols 9 Critical	Based on data from: patients in 5 studies. (Observational (non-randomized))	One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected		**Very low** Due to serious risk of bias and indirectness [11]	We are uncertain whether HFNO increases or decreases dispersal of droplets and aerosols.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional therapy	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).			

1. Systematic reviewwith included studies: [372]. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.**
3. Systematic reviewwith included studies: [372]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: Serious. Indirectness: Serious. Imprecision: Serious.**
5. Systematic reviewwith included studies: [372]. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: Serious. Indirectness: Serious. Imprecision: Serious.**
7. **Inconsistency: Serious. Indirectness: Serious. Imprecision: Serious.**
8. **Indirectness: Serious. Imprecision: Serious.**
9. **Risk of Bias: Serious. Indirectness: Serious. Imprecision: Serious.**
10. **Risk of Bias: Serious. Inconsistency: Serious. Indirectness: Serious. Imprecision: Serious.**
11. **Risk of Bias: Serious.** Substantial risk of bias in all five studies.. **Inconsistency: No serious. Indirectness: Serious.** No studies included patients with COVID-19.. **Imprecision: No serious. Publication bias: No serious.**

Not recommended

Do not use HFNO therapy for patients with hypoxaemia associated with COVID-19 in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval.

Evidence To Decision

Benefits and harms — Important harms

Since HFNO is a known aerosol-generating procedure there are important harms associated with the potential risk of transmission to healthcare workers and others in this setting.

Certainty of the Evidence — Very low

No studies were identified in COVID-19 patients that address the interventions, comparators and outcomes of interest. A systematic review of non-COVID-19 patients of low to very low certainty evidence is included.

Preference and values — Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values at this point.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the recommendation and 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 Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. We have not recommended HFNO in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval. However, if HFNO is clinically indicated and there is no access to negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, this has the potential to impact resourcing and other considerations.

Equity Important issues, or potential issues not investigated

We have not recommended HFNO in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval. However, if HFNO is clinically indicated and there is no access to negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, this has the potential to impact equity.

Acceptability Important issues, or potential issues not investigated

We have no systematically collected information regarding acceptability. We are uncertain if HFNO is likely to be acceptable to both patients and healthcare providers.

Feasibility Important issues, or potential issues not investigated

We have not recommended HFNO in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval. However, if HFNO is clinically indicated and there is no access to negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, this has the potential to impact feasibility.

Rationale

HFNO is associated with an increased risk of aerosolisation and is only recommended in hospital spaces that limit transmission risk and where caution and strict attention is paid to staff safety. It is therefore not appropriate for use in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval due to the increased risk of tranmission in these settings.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: High-flow nasal oxygen therapy
Comparator: Conventional oxygen therapy

Summary

See the Summary in the HFNO recommendation for negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients.

8.2. Non-invasive ventilation

Info Box

Non-invasive ventilation (NIV), also known as non-invasive positive pressure ventilation (NIPPV) or bilevel positive pressure support (BiPAP), is a form of respiratory support. Bilevel positive pressure is delivered throughout the respiratory cycle by a firm-fitting nasal-face mask. The patient breathes spontaneously and triggers the device to cycle.

A higher level of pressure is provided during the inspiratory phase to enhance ventilation, while a lower level of continuous positive pressure is delivered during the expiratory phase (also known as positive end-expiratory pressure or PEEP). Supplemental oxygen can also be delivered through the device.

Conditional recommendation

Consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If NIV is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only.

Practical Info

Some patients receiving NIV may have a low tolerance to the pressures/mask due to anxiety or delirium. If NIV is not tolerated after a trial then early consideration should be given to its cessation.

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.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

NIV can improve oxygenation in patients with hypoxaemia but may be associated with a high failure rate and delayed intubation. Evidence from non-COVID patients with acute hypoxaemic respiratory failure shows uncertainty for all-cause mortality and endotracheal intubation. NIV is a known aerosol-generating procedure, with possible increased risk of aerosolisation with poor mask fit *[18]*. Since there is a potential risk of transmission to healthcare workers, the procedure should be used with caution and follow strict attention to staff safety.

Certainty of the Evidence — Low

No studies were identified in COVID-19 patients that address the interventions, comparators and outcomes of interest. A network meta-analysis of NIV in non-COVID-19 patients of low to very low certainty evidence is included.

Preference and values — Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the recommendation and 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 — Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, 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 transformed 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.

Equity Important issues, or potential issues not investigated

There may be equity issues due to the availability of negative pressure rooms and hospital spaces that are able to perform NIV safely.

Acceptability Important issues, or potential issues not investigated

We have no systematically collected information regarding acceptability. We are uncertain if NIV is likely to be acceptable to both patients and healthcare providers.

Feasibility Important issues, or potential issues not investigated

There may be feasibility issues due to the availability of negative pressure rooms and hospital spaces that are able to perform NIV safely.

Rationale

NIV can improve oxygenation in patients with hypoxaemia but imay be associated with a high failure rate and delayed intubation. NIV is associated with an increased risk of aerosolisation and is only recommended in hospital spaces that limit transmission risk and where caution and strict attention is paid to staff safety.

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 *[377]*. 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 *[377]*. 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

	All-cause mortality	Endotracheal intubation		
Among the most effective or safest	**Helmet NIV** v SOT 0.40 (0.24–0.63) v HFNO 0.46 (0.26–0.80) v Face mask NIV 0.48 (0.29–0.76)	**Helmet NIV** v SOT 0.26 (0.14-0.46) v HFNO 0.35 (0.18-0.66) v Face mask NIV 0.35 (0.19-0.61)		**High-Mod certainty** **Most effective**
Among the effective	**Face mask NIV v SOT** 0.83 (0.68 – 0.99)	**Face mask NIV v SOT** 0.76 (0.62-0.90)		**High-Mod certainty** **Effective**
		HFNO v SOT 0.76 (0.55-0.99)		**High-mod certainty** **No difference**
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)		**High-mod certainty** **Harmful**

	HFNO v SOT 0.87 (0.62 – 1.15)			**Low-very low certainty** **Most effective**
Among the harmful				**Low-very low certainty** **No difference**
Trials (participants)	**22 (3,633)**	**26 (4,067)**		**Low-very low certainty** **Potentially harmful**

Note: Estimates are network risk ratios and 95% credible intervals

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO or SOT	**Intervention** Helmet or face mask NIV	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
See summary	Based on data from: 3,804 patients in 25 studies.	See summary for findings on all-cause mortality and endotracheal intubation.			

Not recommended

Do not use NIV therapy for patients with hypoxaemia associated with COVID-19 in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval.

Evidence To Decision

Benefits and harms — Important harms

Since NIV is a known aerosol-generating procedure, with possible increased risk of aerosolisation with poor mask fit *[18]*, there are important harms associated with the potential risk of transmission to healthcare workers and others in this setting.

Certainty of the Evidence — Very low

No studies were identified in COVID-19 patients that address the interventions, comparators and outcomes of interest. A network meta-analysis of NIV in non-COVID-19 patients of low to very low certainty is included.

Preference and values — Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the

recommendation and 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 Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. We do not recommend use of NIV in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval. If NIV is clinically indicated and there is no access to negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, this has the potential to impact resourcing and other considerations.

Equity Important issues, or potential issues not investigated

We do not recommend use of NIV in shared wards or emergency department cubicles. If NIV is clinically indicated and there is no access to negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, this has the potential to impact equity.

Acceptability Important issues, or potential issues not investigated

We have no systematically collected information regarding acceptability. We are uncertain if NIV is likely to be acceptable to both patients and healthcare providers.

Feasibility Important issues, or potential issues not investigated

We do not recommend use of NIV in shared wards or emergency department cubicles. If NIV is clinically indicated and there is no access to negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, this has the potential to impact feasibility.

Rationale

NIV is associated with an increased risk of aerosolisation and is only recommended in hospital spaces that limit transmission risk and where caution and strict attention is paid to staff safety. It is therefore not appropriate for use in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval due to the increased risk of tranmission in these settings.

Adaptation

The recommendation is adapted from published recommendations by ANZICS *[18]*. Wording has been adapted for clarity and applicability to the Australian context.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO or SOT	**Intervention** Helmet or face mask NIV	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
See summary	Based on data from: 3,804 patients in 25 studies. (Randomized controlled)	See summary for findings on all-cause mortality and endotracheal intubation.			

Conditional recommendation

In patients with COVID-19 for whom NIV is appropriate for an alternate clinical presentation (e.g. concomitant chronic obstructive pulmonary disease (COPD) with type 2 respiratory failure and hypercapnia, acute pulmonary oedema), ensure airborne and other infection control precautions are optimised.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

NIV may be associated with a high failure rate and delayed intubation. Evidence from non-COVID patients with acute hypoxaemic respiratory failure showed uncertainty for all-cause mortality and endotracheal intubation. Since NIV is a known aerosol-generating procedure, with possible increased risk of aerosolisation with poor mask fit *[18]*, harms associated with potential risk of transmission to healthcare workers need to be considered and the procedure should be 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

Very low

No studies were identified in COVID-19 patients that address the interventions, comparators and outcomes of interest. A network meta-analysis of NIV in non-COVID-19 patients of low to very low certainty is included

Preference and values

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the recommendation and 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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. There are likely to be resource issues associated with different settings. There are limited negative pressure rooms available in private hospitals and some public hospitals. although some hospitals have converted rooms into negative pressure rooms. There are additional resource considerations for areas where caution needs to be applied and strict attention paid to staff safety. In single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, there are additional resource considerations for use of PPE and performing NIV safely.

Equity Important issues, or potential issues not investigated

There may be equity issues due to the availability of negative pressure rooms and hospital spaces that are able to perform NIV safely.

Acceptability Important issues, or potential issues not investigated

We have no systematically collected information regarding acceptability. We are uncertain if NIV is likely to be acceptable to both patients and healthcare providers.

Feasibility Important issues, or potential issues not investigated

There may be feasibility issues due to the availability of negative pressure rooms and hospital spaces that are able to perform NIV safely.

Rationale

NIV is associated with an increased risk of aerosolisation and is only recommended in hospital spaces that reduce the risk of transmission and where caution and strict attention is paid to staff safety.

Adaptation

The recommendation is adapted from published recommendations by ANZICS *[18]*. Wording has been adapted for clarity and applicability to the Australian context.

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.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO or SOT	**Intervention** Helmet or face mask NIV	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
See summary	Based on data from: 3,804 patients in 25 studies. (Randomized controlled)	See summary for findings on all-cause mortality and endotracheal intubation.			

8.3. 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.

Evidence To Decision

Benefits and harms — Small net benefit, or little difference between alternatives

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.

Certainty of the Evidence

No studies were identified in COVID-19 patients that address the interventions, comparators and outcomes of interest.

Preference and values — Substantial variability is expected or uncertain

There is no systematically collected information regarding patients' preferences and values at this point. In some patients, comfort, sedation and intubation may lead to symptom management improvement. However, in other patients intubation may not be feasible or considered suitable. Some patients may decline intubation if offered. Decisions around proceeding to more invasive forms of ventilation should be made collaboratively with the patient or their medical treatment decision-maker.

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.

The Consumer Panel believes that in line with available evidence, some informed patients/carers would wish to have more invasive treatment initiated if this is consistent with their goals of care. 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 — Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, there are likely to be resource issues associated with different settings.

Equity — Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability, we expect some patients may decline intubation if offered.

Feasibility Important issues, or potential issues not investigated

More invasive ventilation options may be very limited in patients with frailty or underlying health issues, and in other circumstances where clinical judgement deems patients may be unlikely to benefit from intubation. In some situations and settings (where deterioration occurs outside the hospital), intensification of treatment may be further limited by access to suitably experienced clinicians.

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign *[367]*. Wording has been adapted for clarity and applicability to the Australian context.

8.4. 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.

Evidence To Decision

Benefits and harms Small net benefit, or little difference between alternatives

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 Very low

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 No substantial variability expected

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

Videolaryngoscopy is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility Important issues, or potential issues not investigated

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 *[382]*. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation *[387]*.

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
Comparison	Direct laryngoscopy
Synthesis method	Meta-analysis
Results	We included six of the eight randomised trials (1023 patients) in the Rombey review *[380][381][383][384][385][386]*. (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 *[379]*. 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
Comparison	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	**Study results and measurements**	**Comparator** Direct laryngoscopy	**Intervention** Videolaryngoscopy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
First-pass intubation success	Relative risk 1.05 (CI 95% 0.94 — 1.17) Based on data from 1,186 patients in 7 studies. [1] (Randomized controlled)	716 per 1000	752 per 1000 Difference: **36 more** per 1000 (CI 95% 43 fewer — 122 more)	**Very low** Due to serious risk of bias, inconsistency and indirectness [2]	We are uncertain whether videolaryngoscopy increases or decreases first-pass intubation success.
Oesophageal intubation	Relative risk 0.4 (CI 95% 0.17 — 0.93) Based on data from 795 patients in 4 studies. [3] (Randomized controlled)	50 per 1000	20 per 1000 Difference: **30 fewer** per 1000 (CI 95% 41 fewer — 3 fewer)	**Low** Due to serious risk of bias and indirectness [4]	Videolaryngoscopy may decrease oesophageal intubation.
Operator distance in cm [5] 8 Critical	Measured by: distance analysed from videorecording High better Based on data from: 25 patients in 1 studies. [6] (Randomized controlled)	16.4 centimetres (Mean)	35.6 centimetres (Mean) Difference: **MD 19.2 higher** (CI 95% 13.28 lower — 25.12 higher)	**Very low** Due to serious risk of bias, indirectness and imprecision [7]	Videolaryngoscopy may increase the operator distance.
Time to successful intubation 7 Critical	Based on data from: 988 patients in 6 studies. [8] (Randomized controlled)	The heterogeneity for this outcome was too high to combine in a meta-analysis. Two studies reported shorter time to successful intubation with direct laryngoscopy, two with videolaryngoscopy, and two reported the same or very similar durations.		**Very low** Due to serious risk of bias, indirectness and imprecision, and very serious inconsistency [9]	We are uncertain whether videolaryngoscopy increases or decreases time to successful intubation.

1. Systematic review [378] with included studies: Driver 2016, Silverberg 2015, Janz 2016, Sulser 2016, Griesdale 2012, Gao 2018, Lascarrou 2017. **Baseline/comparator:** Control arm of reference used for intervention.
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 [378] with included studies: Lascarrou 2017, Silverberg 2015, Janz 2016, Gao 2018. **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[387]. **Baseline/comparator:** Control arm of reference used for intervention[387].
7. **Risk of Bias: Serious.** Blinding of personnel not possible, resulting in potential for performance bias, unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias.. **Inconsistency: No serious. Indirectness: Serious.** Use of manikins not patients. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
8. Systematic review [382].
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.. **Inconsistency: Very serious.** Point estimates vary widely.. **Indirectness: Serious.** The included studies were in non COVID-19 populations, with mixed presentations of respiratory and other critically ill patients.. **Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.** Rombey et al 2018 visually evaluated the funnel plot for publication bias, with distribution for this outcome relatively symmetrical..

8.5. 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.

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 NMBAs *[389][390][391][392][393]*.

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 *[390]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
28-day mortality 6 Important	Relative risk 0.78 (CI 95% 0.58 — 1.06) Based on data from 1,461 patients in 5 studies. [1] (Randomized controlled)	372 per 1000	290 per 1000 Difference: 82 fewer per 1000 (CI 95% 156 fewer — 22 more)	Very low Due to serious inconsistency, indirectness and imprecision [2]	We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (513 events).
90-day mortality 9 Critical	Relative risk 0.81 (CI 95% 0.62 — 1.06) Based on data from 1,461 patients in 5 studies. [3] (Randomized controlled)	441 per 1000	357 per 1000 Difference: 84 fewer per 1000 (CI 95% 168 fewer — 26 more)	Very low Due to serious inconsistency, indirectness and imprecision [4]	We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (612 events).
ICU mortality 6 Important	Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 patients in 4 studies. [5] (Randomized controlled)	438 per 1000	315 per 1000 Difference: 123 fewer per 1000 (CI 95% 188 fewer — 39 fewer)	Very low Due to serious imprecision and very serious indirectness [6]	We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (171 events).
ICU weakness at day 28 9 Critical	Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 patients in 4 studies. [7] (Randomized controlled)	230 per 1000	283 per 1000 Difference: 53 more per 1000 (CI 95% 44 fewer — 202 more)	Very low Due to serious risk of bias and imprecision, and very serious indirectness [8]	We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (91 events).
Barotrauma 6 Important	Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 patients in 4 studies. [9] (Randomized controlled)	74 per 1000	41 per 1000 Difference: 33 fewer per 1000 (CI 95% 48 fewer — 11 fewer)	Very low Due to serious risk of bias, indirectness and indirectness [10]	We are uncertain whether neuromuscular blockers improve or worsen barotrauma (81 events).
Mechanical ventilation duration Days 6 Important	Measured by: Days Based on data from: 92 patients in 2 studies. [11] (Randomized controlled)	18 (Median)	20 (Median) Difference: 2 higher	Very low Due to serious risk of bias, inconsistency and indirectness, and very serious imprecision [12]	We are uncertain whether neuromuscular blockers increase or decrease mechanical ventilation duration.
Ventilator-free days at day 28	Measured by: Days Based on data from: 1,462 patients in 5 studies. [13] (Randomized	9.6 (Median)	9.9 (Median) Difference: 0.3 higher	Very low Due to serious risk of bias, indirectness and	We are uncertain whether neuromuscular blockers improve or worsen ventilator-free days at day 28.

Outcome Timeframe	Study results and measurements	Comparator No NMBA	Intervention NMBA	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important	controlled)			imprecision [14]	
MRC score at day 28 6 Important	Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High better Based on data from: 1,346 patients in 2 studies. [15] (Randomized controlled) Follow up: 28 days.	49.8 muscle strength (Median)	45.9 muscle strength (Median) Difference: MD 4.1 lower	Very low Due to serious risk of bias and indirectness, and very serious inconsistency [16]	We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.

1. Systematic review [388] with included studies: Papazian 2010, Guervilly 2017, Moss 2019, Forel 2006, Gainnier 2004. **Baseline/comparator:** Control arm of reference used for intervention.
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 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. Systematic review [388] with included studies: Guervilly 2017, Papazian 2010, Forel 2006, Moss 2019, Gainnier 2004. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
5. Systematic review [388] with included studies: Papazian 2010, Gainnier 2004, Guervilly 2017, Forel 2006. **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. Systematic review [388] with included studies: Gainnier 2004, Moss 2019, Papazian 2010, Forel 2006. **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 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.**
9. Systematic review [388] with included studies: Moss 2019, Papazian 2010, Gainnier 2004, Guervilly 2017. **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. Systematic review [388] with included studies: Gainnier 2004, Forel 2006. **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. Systematic review [388] with included studies: Moss 2019, Gainnier 2004, Guervilly 2017, Papazian 2010, Forel 2006. **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. Systematic review [388] with included studies: Papazian 2010, Moss 2019. **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 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.

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 — 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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 NMBAs *[389][390][391][392][393]*.

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 *[390]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
28-day mortality 6 Important	Relative risk 0.78 (CI 95% 0.58 — 1.06) Based on data from 1,461 patients in 5 studies. [1] (Randomized controlled)	372 per 1000	290 per 1000 Difference: 82 fewer per 1000 (CI 95% 156 fewer — 22 more)	Very low Due to serious inconsistency, indirectness and imprecision [2]	We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (513 events).
90-day mortality	Relative risk 0.81 (CI 95% 0.62 — 1.06) Based on data from	441	357	Very low Due to serious inconsistency,	We are uncertain whether neuromuscular blockers improve or

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical	1,461 patients in 5 studies. [3] (Randomized controlled)	per 1000	per 1000 Difference: **84 fewer** per 1000 (CI 95% 168 fewer — 26 more)	indirectness and imprecision [4]	worsen 90-day mortality (612 events).
ICU mortality 6 Important	Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 patients in 4 studies. [5] (Randomized controlled)	**438** per 1000	**315** per 1000 Difference: **123 fewer** per 1000 (CI 95% 188 fewer — 39 fewer)	**Very low** Due to serious imprecision and very serious indirectness [6]	We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (171 events).
ICU weakness at day 28 9 Critical	Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 patients in 4 studies. [7] (Randomized controlled)	**230** per 1000	**283** per 1000 Difference: **53 more** per 1000 (CI 95% 44 fewer — 202 more)	**Very low** Due to serious risk of bias and imprecision, and very serious indirectness [8]	We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (91 events).
Barotrauma 6 Important	Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 patients in 4 studies. [9] (Randomized controlled)	**74** per 1000	**41** per 1000 Difference: **33 fewer** per 1000 (CI 95% 48 fewer — 11 fewer)	**Very low** Due to serious risk of bias, indirectness and indirectness [10]	We are uncertain whether neuromuscular blockers improve or worsen barotrauma (81 events).
Mechanical ventilation duration Days 6 Important	Measured by: Days Based on data from: 92 patients in 2 studies. [11] (Randomized controlled)	**18** (Median)	**20** (Median) Difference: **2 higher**	**Very low** Due to serious risk of bias, inconsistency and indirectness, and very serious imprecision [12]	We are uncertain whether neuromuscular blockers increase or decrease mechanical ventilation duration.
Ventilator-free days at day 28 6 Important	Measured by: Days Based on data from: 1,462 patients in 5 studies. [13] (Randomized controlled)	**9.6** (Median)	**9.9** (Median) Difference: **0.3 higher**	**Very low** Due to serious risk of bias, indirectness and imprecision [14]	We are uncertain whether neuromuscular blockers improve or worsen ventilator-free days at day 28.
MRC score at day 28 6 Important	Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High better Based on data from: 1,346 patients in 2 studies. [15] (Randomized controlled) Follow up: 28 days.	**49.8** muscle strength (Median)	**45.9** muscle strength (Median) Difference: **MD 4.1 lower**	**Very low** Due to serious risk of bias and indirectness, and very serious inconsistency [16]	We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.

1. Systematic review [388] with included studies: Papazian 2010, Guervilly 2017, Moss 2019, Forel 2006, Gainnier 2004.
Baseline/comparator: Control arm of reference used for intervention.

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 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. Systematic review [388] with included studies: Guervilly 2017, Papazian 2010, Forel 2006, Moss 2019, Gainnier 2004. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
5. Systematic review [388] with included studies: Papazian 2010, Gainnier 2004, Guervilly 2017, Forel 2006. **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. Systematic review [388] with included studies: Gainnier 2004, Moss 2019, Papazian 2010, Forel 2006. **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 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.**
9. Systematic review [388] with included studies: Moss 2019, Papazian 2010, Gainnier 2004, Guervilly 2017. **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. Systematic review [388] with included studies: Gainnier 2004, Forel 2006. **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. Systematic review [388] with included studies: Moss 2019, Gainnier 2004, Guervilly 2017, Papazian 2010, Forel 2006. **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. Systematic review [388] with included studies: Papazian 2010, Moss 2019. **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 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.**

8.6. 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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

No substantial variability expected

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

No important issues with the recommended alternative

We have no systematically collected evidence regarding cost-benefit.

Equity

No important issues with the recommended alternative

There are likely no important equity issues.

Acceptability

Factor not considered

We are uncertain if a higher PEEP ventilation strategy would be acceptable to both patients and healthcare providers.

Feasibility

No important issues with the recommended alternative

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.

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign *[367]*.

8.7. 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.

8.7.1. 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.

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.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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.

Certainty of the Evidence

No studies were identified in COVID-19 patients that address the interventions or outcomes of interest.

Preference and values

Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

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 *[367]*. Wording has been adapted for clarity and applicability to the Australian context.

Consensus 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 it 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.

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 particularly 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, there is limited evidence to suggest prone positioning could be effective in improving oxygenation in patients 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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Prone positioning is recommended in mechanically ventilated patents 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 possible harms such as pressure injury.

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

No trials were identified in COVID-19 patients that address the interventions or outcomes of interest.

Preference and values

Substantial variability is expected or uncertain

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.

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

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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

No important issues with the recommended alternative

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

This is a consensus based recommendation. At present, there are no randomised trials that compare proning to not proning in patients with COVID-19 who are receiving supplementary oxygen but not yet intubated (awake proning). One prospective cohort study of 56 patients with confirmed COVID-19 reported patient comfort levels *[394]*. All 47 patients who received proning rated their comfort levels as acceptable, good or excellent. Proning was not feasible in five patients due to discomfort during positioning.

Outcome Timeframe	**Study results and measurements**	**Comparator** Not proning	**Intervention** Proning	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
See Summary					

8.7.2. 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.

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.

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

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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.

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.

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.

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

Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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.

8.8. Recruitment manoeuvres

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.

Evidence To Decision

Benefits and harms Small net benefit, or little difference between alternatives

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 Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, patients receiving recruitment manoeuvres may require more intensive monitoring.

Equity No important issues with the recommended alternative

There are likely no important equity issues.

Acceptability Important issues, or potential issues not investigated

We are uncertain if recruitment manoeuvres would be acceptable to both patients and healthcare providers.

Feasibility No important issues with the recommended alternative

There are likely no important feasibility issues.

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign *[367]*. Wording has been adapted for clarity and applicability to the Australian context.

8.9. 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.

8.9.1. 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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Very low

Two non-comparative observational studies were identified in COVID-19 patients receiving ECMO.

Preference and values

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

Equity Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 *[367]*. Wording has been adapted for clarity and applicability to the Australian context.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: ECMO
Comparator: No ECMO

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 *[395]* and the other included 83 patients *[396]*.

Study characteristics
The Extracorporeal Life Support Organization (ELSO) Registry included 1035 patients (median age of 49 years) from 213 hospitals in 36 countries *[395]*. The proportion of women was 26%, of whom 22 were pregnant. Ninety-four percent of patients received venovenous 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% *[396]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No ECMO	**Intervention** ECMO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality at 90 days [1] 90 days 9 Critical	Based on data from: 1,118 patients in 2 studies. (Observational (non-randomized))	Please see summary		**Very low** Due to very serious risk of bias and very serious indirectness. [2]	We are uncertain whether ECMO increases or decreases mortality at 90 days.

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.

8.9.2. 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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

Equity

Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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.

Evidence To Decision

Benefits and harms Small net benefit, or little difference between alternatives

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 *[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 Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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)

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff or training to offer prone positioning.

Acceptability

Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

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 *[367]*. Wording has been adapted for clarity and applicability to the Australian context.

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.

Evidence To Decision

Benefits and harms Small net benefit, or little difference between alternatives

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 Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, there are likely to be resource issues

associated with different settings.

Equity Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, we do not expect acceptability issues in neonates, children and adolescents.

Feasibility Important issues, or potential issues not investigated

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.

Evidence To Decision

Benefits and harms Substantial net benefits of the recommended alternative

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 Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff or training to offer prone positioning.

Acceptability Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

No important issues with the recommended alternative

There are likely no important equity issues.

Acceptability

Important issues, or potential issues not investigated

We are uncertain if a higher PEEP ventilation strategy would be acceptable to neonates, children, adolescents and their families, and healthcare providers.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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.

Certainty of the Evidence

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.

Preference and values

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, neonates, children and adolescents

receiving recruitment manoeuvres may require more intensive monitoring.

Equity No important issues with the recommended alternative

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.

Acceptability Important issues, or potential issues not investigated

We are uncertain if recruitment manoeuvres would be acceptable to neonates, children, adolescents and their families, and healthcare providers.

Feasibility No important issues with the recommended alternative

There are likely no important feasibility issues.

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.

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 neonates, children and adolescents, such as muscle weakness, oedema 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 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 Substantial variability is expected or uncertain

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 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.

Equity Important issues, or potential issues not investigated

There is a risk of creating inequity as some facilities may have limited access to neuromuscular blockers suitable for neonates, children and adolescents.

Acceptability Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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

Population: 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

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 NMBAs *[389][390][391][392][393]*.

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 *[390]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
28-day mortality 6 Important	Relative risk 0.78 (CI 95% 0.58 — 1.06) Based on data from 1,461 patients in 5 studies. [1] (Randomized controlled)	372 per 1000	290 per 1000 Difference: **82 fewer** per 1000 (CI 95% 156 fewer — 22 more)	**Very low** Due to serious inconsistency, indirectness and imprecision [2]	We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (513 events).
90-day mortality 9 Critical	Relative risk 0.81 (CI 95% 0.62 — 1.06) Based on data from 1,461 patients in 5 studies. [3] (Randomized controlled)	441 per 1000	357 per 1000 Difference: **84 fewer** per 1000 (CI 95% 168 fewer — 26 more)	**Very low** Due to serious inconsistency, indirectness and imprecision [4]	We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (612 events).
ICU mortality 6 Important	Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 patients in 4 studies. [5] (Randomized controlled)	438 per 1000	315 per 1000 Difference: **123 fewer** per 1000 (CI 95% 188 fewer — 39 fewer)	**Very low** Due to serious imprecision and very serious indirectness [6]	We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (171 events).
ICU weakness at day 28 9 Critical	Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 patients in 4 studies. [7] (Randomized controlled)	230 per 1000	283 per 1000 Difference: **53 more** per 1000 (CI 95% 44 fewer — 202 more)	**Very low** Due to serious risk of bias and imprecision, and very serious indirectness [8]	We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (91 events).
Barotrauma 6 Important	Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 patients in 4 studies. [9] (Randomized controlled)	74 per 1000	41 per 1000 Difference: **33 fewer** per 1000 (CI 95% 48 fewer — 11 fewer)	**Very low** Due to serious risk of bias, indirectness and indirectness [10]	We are uncertain whether neuromuscular blockers improve or worsen barotrauma (81 events).
Mechanical ventilation duration Days 6 Important	Measured by: Days Based on data from: 92 patients in 2 studies. [11] (Randomized controlled)	18 (Median)	20 (Median) Difference: **2 higher**	**Very low** Due to serious risk of bias, inconsistency and indirectness, and very serious imprecision [12]	We are uncertain whether neuromuscular blockers increase or decrease duration of mechanical ventilation.
Ventilator-free days at day 28	Measured by: Days	9.6	9.9	**Very low** Due to serious	We are uncertain whether neuromuscular

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	Based on data from: 1,462 patients in 5 studies. [13] (Randomized controlled)	(Median)	(Median) Difference: **0.3 higher**	risk of bias, indirectness and imprecision [14]	blockers improve or worsen ventilator-free days at day 28.
MRC score at day 28 6 Important	Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High better Based on data from: 1,346 patients in 2 studies. [15] (Randomized controlled) Follow up: 28 days.	**49.8** muscle strength (Median)	**45.9** muscle strength (Median) Difference: **MD 4.1 lower**	**Very low** Due to serious risk of bias and indirectness, and very serious inconsistency [16]	We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.

1. Systematic review [388] with included studies: Moss 2019, Forel 2006, Gainnier 2004, Papazian 2010, Guervilly 2017. **Baseline/comparator:** Control arm of reference used for intervention.
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 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. Systematic review [388] with included studies: Papazian 2010, Moss 2019, Forel 2006, Guervilly 2017, Gainnier 2004. **Baseline/comparator:** Control arm of reference used for intervention.
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.**
5. Systematic review [388] with included studies: Forel 2006, Guervilly 2017, Gainnier 2004, Papazian 2010. **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. Systematic review [388] with included studies: Moss 2019, Papazian 2010, Gainnier 2004, Forel 2006. **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 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.**
9. Systematic review [388] with included studies: Papazian 2010, Guervilly 2017, Moss 2019, Gainnier 2004. **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. Systematic review [388] with included studies: Forel 2006, Gainnier 2004. **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. Systematic review [388] with included studies: Moss 2019, Forel 2006, Papazian 2010, Guervilly 2017, Gainnier 2004. **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. Systematic review [388] with included studies: Moss 2019, Papazian 2010. **Baseline/comparator:** Primary study.
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.**

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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 Substantial variability is expected or uncertain

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.

Resources Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

HFOV can only be used in specialist critical care settings with appropriate equipment and staff, which may cause equity issues.

Acceptability Important issues, or potential issues not investigated

We are uncertain if HFOV would be acceptable to neonates, children or adolescents with COVID-19 or their families and healthcare providers. However, HFOV is an established intensive care therapy in neonates and children that has been accepted other aetiologies.

Feasibility Important issues, or potential issues not investigated

Different types of HFOV ventilators exist and some may not be compliant with infection control measures, which could impact the feasibility of this intervention.

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.

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Very low

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

No substantial variability expected

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

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

Videolaryngoscopy is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility Important issues, or potential issues not investigated

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 exposure.

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 *[382]*. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation *[387]*.

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
Comparison	Direct laryngoscopy
Synthesis method	Meta-analysis
Results	We included six of the eight randomised trials (1023 patients) in the Rombey review *[380][381][383][384][385][386]*. (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 *[379]*. 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
Comparison	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	**Study results and measurements**	**Comparator** Direct laryngoscopy	**Intervention** Videolaryngoscopy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
First-pass intubation success	Relative risk 1.05 (CI 95% 0.94 — 1.17) Based on data from 1,186 patients in 7 studies. [1] (Randomized controlled)	716 per 1000	752 per 1000 Difference: **36 more** per 1000 (CI 95% 43 fewer — 122 more)	**Very low** Due to serious risk of bias, inconsistency and indirectness [2]	We are uncertain whether videolaryngoscopy increases or decreases first-pass intubation success.
Oesophageal intubation	Relative risk 0.4 (CI 95% 0.17 — 0.93) Based on data from 795 patients in 4 studies. [3] (Randomized controlled)	50 per 1000	20 per 1000 Difference: **30 fewer** per 1000 (CI 95% 41 fewer — 3 fewer)	**Very low** Due to serious risk of bias and indirectness [4]	Videolaryngoscopy may decrease oesophageal intubation.
Operator distance in cm [5] 8 Critical	Measured by: distance analysed from videorecording High better Based on data from: 25 patients in 1 studies. [6] (Randomized controlled)	16.4 centimetres (Mean)	35.6 centimetres (Mean) Difference: **MD 19.2 higher** (CI 95% 13.28 lower — 25.12 higher)	**Very low** Due to serious risk of bias, indirectness and imprecision [7]	Videolaryngoscopy may increase the operator distance.
Time to successful intubation 7 Critical	Based on data from: 988 patients in 6 studies. [8] (Randomized controlled)	The heterogeneity for this outcome was too high to combine in a meta-analysis. Two studies reported shorter time to successful intubation with direct laryngoscopy, two with videolaryngoscopy, and two reported the same or very similar durations.		**Very low** Due to serious risk of bias, indirectness and imprecision, and very serious inconsistency [9]	We are uncertain whether videolaryngoscopy increases or decreases time to successful intubation.

1. Systematic review [378] with included studies: Silverberg 2015, Janz 2016, Griesdale 2012, Lascarrou 2017, Gao 2018, Driver 2016, Sulser 2016. **Baseline/comparator:** Control arm of reference used for intervention.
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 [378] with included studies: Silverberg 2015, Janz 2016, Gao 2018, Lascarrou 2017. **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[387]. **Baseline/comparator:** Control arm of reference used for intervention[387].
7. **Risk of Bias: Serious.** Blinding of personnel not possible, resulting in potential for performance bias, unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias.. **Inconsistency: No serious. Indirectness: Serious.** Use of manikins not patients. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
8. Systematic review [382].
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.. **Inconsistency: Very serious.** Point estimates vary widely.. **Indirectness: Serious.** The included studies were in non COVID-19 populations, with mixed presentations of respiratory and other critically ill patients.. **Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.** Rombey et al 2018 visually evaluated the funnel plot for publication bias, with distribution for this outcome relatively symmetrical..

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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 Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

Equity Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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

We have found one new study comparing therapeutic dose enoxaparin thromboprophylaxis with standard dose thromboprophylaxis (Lemos et al. Thromb Res doi: 10.1016/j.thromres.2020.09.026). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

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.

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.

10.1. VTE prophylaxis for adults

Consensus 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 or dalteparin 2500 IU 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.

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, 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 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, certainty of the evidence is low (due to serious imprecision and risk of bias) for all outcomes.

Preference and values

Substantial variability is expected or uncertain

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

No important issues with the recommended alternative

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 No important issues with the recommended alternative

We have no systematically collected evidence regarding equity.

Acceptability No important issues with the recommended alternative

Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

Feasibility No important issues with the recommended alternative

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.

Adaptation

The recommendation for use of DVT prophylaxis is adapted from published recommendations by the International Society on Thrombosis and Haemostasis *[397]*, University of Miami *[398]* and British Haematological Society *[399]*. Wording has been adapted for clarity and applicability to the Australian context.

Clinical Question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Increased-dose thromboprophylaxis
Comparator: Conventional treatment

Summary

Evidence indicates that increased dosage 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 three randomised trials in patients with severe or critical COVID-19. One study of 1074 patients was an open-label, adaptive, multiplatform study that included data from three trials (REMAP-CAP, ACTIV-4a, ATTACC) and which compared standard/intermediate dose anticoagulants with therapeutic dose anticoagulants (78% received therapeutic dosing in the therapeutic dose group) *[424]*. An additional 20-patient trial also compared standard dose anticoagulants with therapeutic dose anticoagulants *[417]*. A third study (INSPIRATION Trial) included 562 patients that compared standard with intermediate dose anticoagulants *[425]*.

The 90-day results from the INSPIRATION Trial were published in Thrombosis and Haemostasis on 17 April 2021 and will be incorporated in a future version of the guideline *[426]*.

Publication status
One study is only available as a preprint (REMAP-CAP, ACTIV-4a, ATTACC Investigators posted to medRxiv on 12 March 2021 *[424]*) and has therefore not been peer reviewed.

Study characteristics
Mean or median age of participants ranged from 56 to 62 years. The proportion of women ranged from 10 to 43%.

What are the main results?
Evidence indicates that increased dose anticoagulants probably have little or no difference when compared with standard dose anticoagulants on critical outcomes in patients with severe or critical COVID-19.

Our confidence in the results
In patients with severe or critical COVID-19, comparing standard/intermediate dose anticoagulants with therapeutic dose anticoagulants, 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 compared with intermediate dose anticoagulants, certainty of the evidence is moderate (due to serious imprecision) for all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Low dose	**Intervention** Intermediate dose	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adjudicated venous thromboembolism 7 Critical	Relative risk 0.93 (CI 95% 0.38 — 2.26) Based on data from 562 patients in 1 studies. [1] (Randomized controlled)	35 per 1000	33 per 1000 Difference: **2 fewer** per 1000 (CI 95% 22 fewer — 44 more)	**Moderate** Due to serious imprecision [2]	Intermediate dose prophylaxis probably has little or no difference on adjudicated venous thromboembolism.
All-cause mortality (Day 28) 9 Critical	Relative risk 1.05 (CI 95% 0.87 — 1.28) Based on data from 562 patients in 1 studies. [3] (Randomized controlled)	409 per 1000	429 per 1000 Difference: **20 more** per 1000 (CI 95% 53 fewer — 115 more)	**Moderate** Due to serious imprecision [4]	Intermediate dose prophylaxis probably has little or no difference on all-cause mortality (day 28).
Composite of VTE, arterial thrombosis, ECMO, or all-cause mortality 8 Critical	Relative risk 1.04 (CI 95% 0.86 — 1.24) Based on data from 562 patients in 1 studies. [5] (Randomized controlled)	441 per 1000	459 per 1000 Difference: **18 more** per 1000 (CI 95% 62 fewer — 106 more)	**Moderate** Due to serious imprecision [6]	Intermediate dose prophylaxis probably has little or no difference on composite of VTE, arterial thrombosis, ECMO, or all-cause mortality.
Major bleeding 7 Critical	Relative risk 1.81 (CI 95% 0.54 — 6.13) Based on data from 562 patients in 1 studies. [7] (Randomized controlled)	14 per 1000	25 per 1000 Difference: **11 more** per 1000 (CI 95% 6 fewer — 72 more)	**Moderate** Due to serious imprecision [8]	Intermediate dose prophylaxis probably has little or no difference on major bleeding.
Clinically-relevant non-major bleeding 6 Important	Relative risk 2.49 (CI 95% 0.86 — 6.97) Based on data from 562 patients in 1 studies. [9] (Randomized controlled)	17 per 1000	42 per 1000 Difference: **25 more** per 1000 (CI 95% 2 fewer — 101 more)	**Moderate** Due to serious imprecision [10]	Intermediate dose prophylaxis probably has little or no difference on clinically-relevant non-major bleeding.

Outcome Timeframe	Study results and measurements	Comparator Low dose	Intervention Intermediate dose	Certainty of the Evidence (Quality of evidence)	Plain text summary
Ventilator-free days 6 Important	Based on data from: 567 patients in 1 studies. [11] (Randomized controlled)	30 (Median)	30 (Median)	Moderate Due to serious imprecision [12]	Intermediate dose prophylaxis probably has little or no difference on ventilator-free days.

1. Systematic review [422] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals, Only data from one study.
3. Systematic review [421] with included studies: Sadeghipour 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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7. Systematic review [421] with included studies: Sadeghipour 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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9. Systematic review [421] with included studies: Sadeghipour 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Serious.** Wide confidence intervals, Only data from one study.
11. Systematic review [422] . **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Serious.** Wide confidence intervals, Only data from one study.

Clinical Question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Therapeutic anticoagulation
Comparator: Prophylactic anticoagulation (standard or intermediate)

Summary

Evidence indicates that increased dosage 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 three randomised trials in patients with severe or critical COVID-19. One study of 1074 patients was an open-label, adaptive, multiplatform study that included data from three trials (REMAP-CAP, ACTIV-4a, ATTACC) and which compared standard/intermediate dose anticoagulants with therapeutic dose anticoagulants (78% received therapeutic dosing in the therapeutic dose group) *[424]*. An additional 20-patient trial also compared standard dose anticoagulants with therapeutic dose anticoagulants *[417]*. A third study (INSPIRATION Trial) included 562 patients that compared standard with intermediate dose anticoagulants *[425]*.

The 90-day results from the INSPIRATION Trial were published in Thrombosis and Haemostasis on 17 April 2021 and will be incorporated in a future version of the guideline *[426]*.

Publication status
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Study characteristics
Mean or median age of participants ranged from 56 to 62 years. The proportion of women ranged from 10 to 43%.

What are the main results?
Evidence indicates that increased dose anticoagulants probably have little or no difference when compared with standard dose anticoagulants on critical outcomes in patients with severe or critical COVID-19.

Our confidence in the results
In patients with severe or critical COVID-19, comparing standard/intermediate dose anticoagulants with therapeutic dose anticoagulants, 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 compared with intermediate dose anticoagulants, certainty of the evidence is moderate (due to serious imprecision) for all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Prophylactic anticoagulation	**Intervention** Therapeutic anticoagulation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Major thrombotic events or death 9 Critical	Relative risk 0.97 (CI 95% 0.84 — 1.22) Based on data from 947 patients in 1 studies. [1] (Randomized controlled)	103 per 1000	100 per 1000 Difference: 3 fewer per 1000 (CI 95% 16 fewer — 23 more)	Low Due to serious imprecision and serious risk of bias [2]	Therapeutic anticoagulation may have little or no difference on major thrombotic events or death.
In-hospital mortality 9 Critical	Relative risk 0.83 (CI 95% 0.38 — 1.81) Based on data from 1,094 patients in 2 studies. [3] (Randomized controlled)	350 per 1000	290 per 1000 Difference: 60 fewer per 1000 (CI 95% 217 fewer — 283 more)	Low Due to serious imprecision and serious risk of bias [4]	Therapeutic anticoagulation may have little or no difference on in-hospital mortality.
All-cause mortality Day 28 9 Critical	Relative risk 0.33 (CI 95% 0.04 — 2.69) Based on data from 20 patients in 1 studies. [5] (Randomized controlled)	300 per 1000	99 per 1000 Difference: 201 fewer per 1000 (CI 95% 288 fewer — 507 more)	Very low Due to very serious imprecision and serious risk of bias [6]	Therapeutic anticoagulation may have little or no difference on all-cause mortality (day 28).
Major bleeding 6 Important	Relative risk 1.28 (CI 95% 0.61 — 2.71) Based on data from 977 patients in 1 studies. [7] (Randomized controlled)	24 per 1000	31 per 1000 Difference: 7 more per 1000 (CI 95% 9 fewer — 41 more)	Low Due to serious imprecision and serious risk of bias [8]	Therapeutic anticoagulation may have little or no difference on major bleeding.
Hospital survival 6 Important	Relative risk 0.98 (CI 95% 0.9 — 1.07) Based on data from 1,074 patients in 1 studies. [9] (Randomized controlled)	653 per 1000	640 per 1000 Difference: 13 fewer per 1000 (CI 95% 65 fewer — 46 more)	Moderate Due to serious risk of bias [10]	Therapeutic anticoagulation may have little or no difference on hospital survival.
Minor bleeding - Baseline 6 Important	Relative risk 5 (CI 95% 0.27 — 92.62) Based on data from 20 patients in 1 studies. [11] (Randomized controlled)			Very low Due to serious risk of bias and very serious imprecision [12]	There were too few who experienced minor bleeding to determine whether therapeutic dose

Outcome Timeframe	**Study results and measurements**	**Comparator** Prophylactic anticoagulation	**Intervention** Therapeutic anticoagulation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
					thromboprophylaxis makes a difference (2 patients).
Days free of organ support 21 days 6 Important	Based on data from: 1,074 patients in 1 studies. (Randomized controlled)	Median (IQR) in therapeutic anticoagulation arm is 3 (-1, 16). In usual care pharmacological thromboprophylaxis arm is 5 (-1, 16).		**Low** Due to serious risk of bias and serious imprecision [13]	Therapeutic anticoagulation may have little or no difference on days free of organ support.

1. Systematic review [423] with included studies: Zarychanski 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: Serious. Inconsistency: Serious. Indirectness: No serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
3. Systematic review [423] with included studies: Zarychanski 2021, Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was moderate, with I^2:43 %.. **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: No serious. Publication bias: No serious.**
5. Systematic review [423] with included studies: Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
7. Systematic review [423] with included studies: Zarychanski 2021, Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious. Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
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13. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. Publication bias: No serious.**

Conditional recommendation against

Do not routinely offer therapeutic anticoagulant dosing in adults with 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.

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, 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 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, 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 — No important issues with the recommended alternative

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 — No important issues with the recommended alternative

We have no systematically collected evidence regarding equity.

Acceptability — No important issues with the recommended alternative

We have no systematically collected evidence regarding acceptability.

Feasibility — No important issues with the recommended alternative

We have no systematically collected evidence regarding feasibility.

Clinical Question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Increased-dose thromboprophylaxis
Comparator: Conventional treatment

Summary

Evidence indicates that increased dosage 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 three randomised trials in patients with severe or critical COVID-19. One study of 1074 patients was an open-label, adaptive, multiplatform study that included data from three trials (REMAP-CAP, ACTIV-4a, ATTACC) and which compared standard/intermediate dose anticoagulants with therapeutic dose anticoagulants (78% received therapeutic dosing in the therapeutic dose group) *[424]*. An additional 20-patient trial also compared standard dose anticoagulants with therapeutic dose anticoagulants *[417]*. A third study (INSPIRATION Trial) included 562 patients that compared standard with intermediate dose anticoagulants *[425]*.

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Mean or median age of participants ranged from 56 to 62 years. The proportion of women ranged from 10 to 43%.

What are the main results?
Evidence indicates that increased dose anticoagulants probably have little or no difference when compared with standard dose anticoagulants on critical outcomes in patients with severe or critical COVID-19.

Our confidence in the results
In patients with severe or critical COVID-19, comparing standard/intermediate dose anticoagulants with therapeutic dose anticoagulants, 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 compared with intermediate dose anticoagulants, certainty of the evidence is moderate (due to serious imprecision) for all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Low dose	**Intervention** Intermediate dose	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adjudicated venous thromboembolism 7 Critical	Relative risk 0.93 (CI 95% 0.38 — 2.26) Based on data from 562 patients in 1 studies. [1] (Randomized controlled)	35 per 1000	33 per 1000 Difference: **2 fewer** per 1000 (CI 95% 22 fewer — 44 more)	**Moderate** Due to serious imprecision [2]	Intermediate dose prophylaxis probably has little or no difference on adjudicated venous thromboembolism.
All-cause mortality (Day 28) 9 Critical	Relative risk 1.05 (CI 95% 0.87 — 1.28) Based on data from 562 patients in 1 studies. [3] (Randomized controlled)	409 per 1000	429 per 1000 Difference: **20 more** per 1000 (CI 95% 53 fewer — 115 more)	**Moderate** Due to serious imprecision [4]	Intermediate dose prophylaxis probably has little or no difference on all-cause mortality (day 28).
Composite of VTE, arterial thrombosis, ECMO, or all-	Relative risk 1.04 (CI 95% 0.86 — 1.24) Based on data from 562 patients in 1 studies. [5] (Randomized controlled)	441 per 1000	459 per 1000 Difference: **18 more** per 1000	**Moderate** Due to serious imprecision [6]	Intermediate dose prophylaxis probably has little or no difference on composite of VTE, arterial thrombosis,

Outcome Timeframe	**Study results and measurements**	**Comparator** Low dose	**Intervention** Intermediate dose	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
cause mortality 8 Critical		(CI 95% 62 fewer — 106 more)			ECMO, or all-cause mortality.
Major bleeding 7 Critical	Relative risk 1.81 (CI 95% 0.54 — 6.13) Based on data from 562 patients in 1 studies. [7] (Randomized controlled)	14 per 1000	25 per 1000 Difference: 11 more per 1000 (CI 95% 6 fewer — 72 more)	Moderate Due to serious imprecision [8]	Intermediate dose prophylaxis probably has little or no difference on major bleeding.
Clinically-relevant non-major bleeding 6 Important	Relative risk 2.49 (CI 95% 0.86 — 6.97) Based on data from 562 patients in 1 studies. [9] (Randomized controlled)	17 per 1000	42 per 1000 Difference: 25 more per 1000 (CI 95% 2 fewer — 101 more)	Moderate Due to serious imprecision [10]	Intermediate dose prophylaxis probably has little or no difference on clinically-relevant non-major bleeding.
Ventilator-free days 6 Important	Based on data from: 567 patients in 1 studies. [11] (Randomized controlled)	30 (Median)	30 (Median)	Moderate Due to serious imprecision [12]	Intermediate dose prophylaxis probably has little or no difference on ventilator-free days.

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Clinical Question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Therapeutic anticoagulation
Comparator: Prophylactic anticoagulation (standard or intermediate)

Summary

Evidence indicates that increased dosage of anticoagulants probably has little or no difference on critical outcomes in patients with severe or critical COVID-19.

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Outcome Timeframe	**Study results and measurements**	**Comparator** Prophylactic anticoagulation	**Intervention** Therapeutic anticoagulation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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In-hospital mortality 9 Critical	Relative risk 0.83 (CI 95% 0.38 — 1.81) Based on data from 1,094 patients in 2 studies. [3] (Randomized controlled)	350 per 1000	290 per 1000 Difference: 60 fewer per 1000 (CI 95% 217 fewer — 283 more)	**Low** Due to serious imprecision and serious risk of bias [4]	Therapeutic anticoagulation may have little or no difference on in-hospital mortality.
All-cause mortality Day 28 9 Critical	Relative risk 0.33 (CI 95% 0.04 — 2.69) Based on data from 20 patients in 1 studies. [5] (Randomized controlled)	300 per 1000	99 per 1000 Difference: 201 fewer per 1000 (CI 95% 288 fewer — 507 more)	**Very low** Due to very serious imprecision and serious risk of bias [6]	Therapeutic anticoagulation may have little or no difference on all-cause mortality (day 28).

Outcome Timeframe	**Study results and measurements**	**Comparator** Prophylactic anticoagulation	**Intervention** Therapeutic anticoagulation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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Hospital survival 6 Important	Relative risk 0.98 (CI 95% 0.9 — 1.07) Based on data from 1,074 patients in 1 studies. [9] (Randomized controlled)	653 per 1000	640 per 1000 Difference: **13 fewer** per 1000 (CI 95% 65 fewer — 46 more)	Moderate Due to serious risk of bias [10]	Therapeutic anticoagulation may have little or no difference on hospital survival.
Minor bleeding - Baseline 6 Important	Relative risk 5 (CI 95% 0.27 — 92.62) Based on data from 20 patients in 1 studies. [11] (Randomized controlled)			Very low Due to serious risk of bias and very serious imprecision [12]	There were too few who experienced minor bleeding to determine whether therapeutic dose thromboprophylaxis makes a difference (2 patients).
Days free of organ support 21 days 6 Important	Based on data from: 1,074 patients in 1 studies. (Randomized controlled)	Median (IQR) in therapeutic anticoagulation arm is 3 (-1, 16). In usual care pharmacological thromboprophylaxis arm is 5 (-1, 16).		Low Due to serious risk of bias and serious imprecision [13]	Therapeutic anticoagulation may have little or no difference on days free of organ support.

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4. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was moderate, with I^2:43 %.. **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: No serious. Publication bias: No serious.**
5. Systematic review [423] with included studies: Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: Very serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
7. Systematic review [423] with included studies: Zarychanski 2021, Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious. Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
9. Systematic review [423] with included studies: Zarychanski 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: No serious. Publication bias: No serious.**
11. Systematic review [423] with included studies: Lemos 2020. **Baseline/comparator:** Control arm of reference used for

intervention.
12. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. Publication bias: No serious.**
13. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. Publication bias: No serious.**

Info Box

The Taskforce acknowledges the publication of two joint media releases from the REMAP-CAP, ACTIV-4 and ATTACC trial teams on 22 December 2020 [here] and 22 January 2021 [here]. The media releases noted that therapeutic doses of anticoagulation drugs may be more beneficial than lower doses for the prevention of VTE in hospitalised patients. However, among critically ill COVID-19 patients requiring intensive care unit (ICU) support, therapeutic doses of anticoagulation drugs did not reduce the need for organ support and a potential for harm in this subgroup could not be excluded; all trial sites have paused enrolment of this group of patients.

The results from the REMAP-CAP, ACTIV-4 and ATTACC study groups have been published for critical patients and have been used to inform current recommendations *[427]*. The Taskforce notes the preprint publication of the results in hospitalised non-critical patients (posted to medRxiv on 17 May 2021). These results are currently under review and an updated recommendation will be included in a future version of the guideline.

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.*

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

No important issues with the recommended alternative

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

No important issues with the recommended alternative

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 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.

- *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.*

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

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 — Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability — No important issues with the recommended alternative

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 — No important issues with the recommended alternative

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 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.*

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

No important issues with the recommended alternative

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 No important issues with the recommended alternative

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.*

Evidence To Decision

Benefits and harms Substantial net benefits of the recommended alternative

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 Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability No important issues with the recommended alternative

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 No important issues with the recommended alternative

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.*

Evidence To Decision

Benefits and harms Substantial net benefits of the recommended alternative

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 No substantial variability expected

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 Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity No important issues with the recommended alternative

It is unlikely that the use of thromboprophylaxis will create equity issues as it is common practice.

Acceptability No important issues with the recommended alternative

Thromboprophylaxis is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility No important issues with the recommended alternative

There are no major feasibility issues as the recommendation reflects usual 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.

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

The primary panel for the recommendations 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. The remaining panels review recommendations when relevant to their specific population group. In addition, all our recommendations are reviewed by the Consumer Panel.

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.

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

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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

No substantial variability expected

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

No important issues with the recommended alternative

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

No important issues with the recommended alternative

There are no identified equity issues.

Acceptability

No important issues with the recommended alternative

Continued concomitant ACEI/ARB medication is likely to be acceptable to both patients and clinicians.

Feasibility No important issues with the recommended alternative

There are likely no important feasiblity 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 *[428][429][430][431][432][433][434][435][436][437][438][439][440][441]*. 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 *[442][443][444][445]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Stopping concomitant ACEIs/ARBs	**Intervention** Continued use of concomitant ACEIs/ARBs	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 9 Critical	Odds Ratio 0.86 (CI 95% 0.63 — 1.16) Based on data from 7,492 patients in 12 studies. [1] (Observational (non-randomized))	287 per 1000	262 per 1000 Difference: 25 fewer per 1000 72 fewer — 28 more	Very low Due to serious risk of bias, inconsistency and imprecision [2]	We are uncertain whether continued use of concomitant ACEIs/ ARBs increases or decreases death in patients with COVID-19.
Risk of severe or lethal COVID-19 6 Important	Odds Ratio 1 (CI 95% 0.84 — 1.18) Based on data from 11,334 patients in 5 studies. [3] (Observational (non-randomized))	309 per 1000	309 per 1000 Difference: 0 fewer per 1000 (CI 95% 36 fewer — 36 more)	Very low Due to serious risk of bias, inconsistency and imprecision [4]	We are uncertain whether continued use of concomitant ACEIs/ ARBs increases or decreases the risk of death or progression to severe COVID-19.

Outcome Timeframe	**Study results and measurements**	**Comparator** Stopping concomitant ACEIs/ARBs	**Intervention** Continued use of concomitant ACEIs/ARBs	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Severity (narrative analysis) 6 Important	Based on data from: 23,565 patients in 13 studies. [5] (Observational (non-randomized))	Continued use of ACEIs/ARBs in patients with COVID-19 does not appear to increase the likelihood of more severe COVID-19 illness.		**Very low** Due to serious risk of bias and imprecision [6]	We are uncertain whether continued use of concomitant ACEIs/ ARBs increases or decreases the risk of progression to severe COVID-19.

1. Systematic review [444] . **Baseline/comparator:** Systematic review [443] .
2. **Risk of Bias: Serious.** Selective outcome reporting, Missing intention-to-treat analysis. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2 =6479%.. **Indirectness: No serious. Imprecision: Serious.**
3. Systematic review [443] . **Baseline/comparator:** Systematic review [443] .
4. **Risk of Bias: Serious.** Selective outcome reporting, Missing intention-to-treat analysis. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:50 %.. **Imprecision: Serious.** The review was limited only to studies where patient records included a diagnosis of hypertension. Other reviews have identified patients receiving ACEI/ARBs without confirming a diagnosis of hypertension..
5. Systematic review [442].
6. **Risk of Bias: Serious.** Missing intention-to-treat analysis, Selective outcome reporting. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** No meta-analysis was possible. **Publication bias: No serious.**

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.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

ACE inhibitors, such as enalapril, captopril and quinapril, are used for the management of postpartum hypertension and are considered compatible with breastfeeding *[446]*. 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

Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

There are no identified equity issues as the recommendation reflects usual care.

Acceptability Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability, this recommendation is likely to be acceptable to both patients and clinicians.

Feasibility No important issues with the recommended alternative

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.

Evidence To Decision

Benefits and harms Substantial net benefits of the recommended alternative

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 COPD.

Certainty of the Evidence

There is no available evidence about outcomes for inhaled or oral corticosteroids for patients with COVID-19 and asthma or COPD.

Preference and values No substantial variability expected

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 corticosteroids for COVID-19, there are likely harms associated with an exacerbation of asthma or COPD, as well as harms associated with a sudden stopping of

corticosteroids, and thus patients may prefer to take steroids as prescribed.

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 prescribed treatment for their pre-existing conditions.

Resources No important issues with the recommended alternative

We have no systematically collected information regarding cost-benefit. Continued use of inhaled or oral corticosteroids as per usual care is unlikely to have an impact on availability of these drugs.

Equity No important issues with the recommended alternative

There are no identified equity issues.

Acceptability No important issues with the recommended alternative

The treatment is likely to be acceptable to both patients and clinicians.

Feasibility No important issues with the recommended alternative

There are likely no important feasibility issues as the recommendation reflects usual care.

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 *[447]*, NICE [NG168] *[448]* and NICE [NG 166] *[449]*. 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) *[447]*. 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 *[449]*.

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 *[448]*. 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 *[450][451]*.

Abrupt withdrawal of corticosteroids can lead to acute adrenal insufficiency or exacerbation of symptoms of asthma or COPD.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Coticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
See summary					

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.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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 — Substantial variability is expected or uncertain

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 — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

There are no identified equity issues.

Acceptability — Important issues, or potential issues not investigated

The treatment is likely to be acceptable to both patients and clinicians.

Feasibility — No important issues with the recommended alternative

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.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

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 — Substantial variability is expected or uncertain

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 — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

There are no identified equity issues.

Acceptability — Important issues, or potential issues not investigated

The treatment is likely to be acceptable to both patients and clinicians.

Feasibility — No important issues with the recommended alternative

There are likely no important feasibility 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.

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.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

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.

Certainty of the Evidence

No studies were identified that address the risk of VTE associated with the use of oestrogen-containing contraception in women with COVID-19.

Preference and values — Substantial variability is expected or uncertain

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients would agree with this recommendation. The panel recognises that some informed patients may choose not to proceed with this recommendation based on reasons unrelated to COVID-19.

Resources — Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Use of contraception as per usual care is unlikely to have an impact on availability of these drugs.

Equity — Important issues, or potential issues not investigated

There are no identified equity issues.

Acceptability — No important issues with the recommended alternative

The treatment is likely to be acceptable to both patients and clinicians.

Feasibility — No important issues with the recommended alternative

There are likely no important feasibility issues.

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Low

Certainty of the evidence is low due to serious imprecision (reliance on a single study) and risk of bias.

Preference and values

Substantial variability is expected or uncertain

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 variablity is expected.

Resources

No important issues with the recommended alternative

We have no systematically collected evidence regarding cost-benefit.

Equity

No important issues with the recommended alternative

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 consulation.

Acceptability

Important issues, or potential issues not investigated

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

No important issues with the recommended alternative

We have no systematically collected evidence regarding feasibility.

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.

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) *[452]*. 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) *[454]*. 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 *[453]*. They recommended no elective surgery within seven weeks of diagnosis with SARS-CoV-2 infection.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surgery	**Intervention** Surgery	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
30-day postoperative mortality in elective surgery patients	Based on data from: 1,762 patients in 1 studies. (Observational (non-randomized))	Timing of surgery was associated with an increased risk of 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). No increased risk was reported at ≥7 weeks (OR 1.03, 95% CI 0.50 to 2.09) from time of diagnosis with SARS-CoV-2.		**Low** Due to serious imprecision and risk of bias [1]	Timing of surgery less than 7 weeks after COVID-19 diagnosis may increase risk of 30-day postoperative mortality in elective surgery patients.

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Low

Certainty of the evidence is low due to serious imprecision (reliance on a single study) and risk of bias.

Preference and values

Substantial variability is expected or uncertain

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

No important issues with the recommended alternative

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. 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 consulation.

Acceptability Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

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) *[452]*. 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) *[454]*. 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 *[453]*. They recommended no elective surgery within seven weeks of diagnosis with SARS-CoV-2 infection.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surgery	**Intervention** Surgery	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
30-day postoperative mortality in elective surgery patients	Based on data from: 1,762 patients in 1 studies. (Observational (non-randomized))	Timing of surgery was associated with an increased risk of 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). No increased risk was reported at ≥7 weeks (OR 1.03, 95% CI 0.50 to 2.09) from time of diagnosis with SARS-CoV-2.		**Low** Due to serious imprecision and risk of bias [1]	Timing of surgery less than 7 weeks after COVID-19 diagnosis may increase risk of 30-day postoperative mortality in elective surgery patients.

1. **Risk of Bias: Serious.** Residual confounding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**

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.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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 *[455]*. 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

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 the available evidence suggests no additional harm to mother or newborn.

Resources

Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

There are no identified equity issues as the recommendation reflects usual care.

Acceptability Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability, this recommendation is likely to be acceptable to both patients and clinicians.

Feasibility No important issues with the recommended alternative

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. 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.

Evidence To Decision

Benefits and harms Small net benefit, or little difference between alternatives

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 Very low

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 No substantial variability expected

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

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) *[456]*. 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.

Mode of birth	Total newborns*	Infected	Not infected	Not tested	Died	% Infected
Vaginal	292	8	261	21	7	2.7% (8/292)
Caesarean	374	20	313	26	1	5.3%

Mode of birth	Total newborns*	Infected	Not infected	Not tested	Died	% Infected
						(20/374)

*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 *[457]* (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 *[469]*. 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 *[458]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Vaginal birth	**Intervention** Caesarean section	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Number of infected newborns 9 Critical	Based on data from: 666 patients in 49 studies. (Observational (non-randomized))	See summary for details. No cases of COVID-19 infection met the criteria for confirmed vertical transmission. Number of infected newborns was reported as 2.7% (8/292) for vaginal birth and 5.3% (20/374) for caesarean section. Based on data from 655 women and 666 newborns.		Very low Due to very serious risk of bias and serious imprecision and inconsistency [1]	We are uncertain whether caesarean section increases or decreases the number of infected newborns.

1. **Risk of Bias: Very serious.** Evidence is derived from case studies and case reports.. **Inconsistency: Serious.** Variations in outcome definitions, disease severity and availability of different testing modalities.. **Indirectness: No serious. Imprecision: Serious.** Variations in outcome definitions, disease severity and availability of different testing modalities.. **Publication bias: No serious.**

13.3. 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.

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 *[459][460]*.

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.

Resources — Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for women or newborns with COVID-19 requires greater resources than for those without COVID-19.

Equity — Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability — No important issues with the recommended alternative

Delayed umbilical cord clamping is routinely performed during the provision of neonatal care and is therefore likely to be acceptable to all stakeholders.

Feasibility — No important issues with the recommended alternative

There are likely no important feasibility issues as the recommendation reflects usual care.

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

Population: Pregnant women with COVID-19
Intervention: Delayed cord clamping
Comparator:

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 prospective observational study of 403 women with SARS-CoV-2 infection admitted for childbirth across 70 centres in Spain *[461]*.

Study characteristics
The study assessed differences in transmission to newborns at 14 days postpartum, stratified by whether early (< 30 seconds) or delayed (> 30 seconds) cord clamping was used. In total 231 babies (57%) received early cord clamping and 172 babies (43%) received delayed cord clamping.

What are the main results?
Five babies were diagnosed with COVID-19—two from the early cord clamping group and three from the delayed cord clamping group. None of the five babies was identified as confirmed vertical transmission.

Our confidence in the results
Evidence comes from a non-comparative observational study that is 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 *[458]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** Delayed cord clamping	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Please see evidence summary					

13.4. Skin-to-skin contact

Consensus recommendation

Early skin-to-skin contact after birth and during the postnatal period is supported, irrespective 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.

Evidence To Decision

Benefits and harms Substantial net benefits of the recommended alternative

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 *[462][463]*. 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).

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 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.

Resources Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

There are likely no important feasibility issues as the recommendation reflects usual care.

Clinical Question/ PICO

Population: Women with COVID-19 who have given birth
Intervention: Skin-to-skin contact
Comparator: No skin-to-skin contact

Summary

No direct evidence is available for the risk of transmission of COVID-19 with skin-to-skin contact. However, indirect evidence is available from a systematic review of 49 case reports or case series comprising 666 newborns *[456]*. The review reported that 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).

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 *[458]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No skin-to-skin contact	**Intervention** Skin-to-skin contact	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Number of infected newborns [1] Within 30 days of exposure 9 Critical	Based on data from: 106 patients in 1 studies. (Observational (non-randomized))	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.		**Very low** Due to very serious risk of bias and imprecision, and serious indirectness [2]	We are uncertain whether skin-to-skin contact increases or decreases the number of infected newborns.

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.**

13.5. 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.

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 breastmilk or formula, these same infection prevention and control measures should be used.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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 *[465]*. 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

Very low

Certainty of the evidence is very low due to reliance on case reports and case series.

Preference and values — Substantial variability is expected or uncertain

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 — 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.

Feasibility — No important issues with the recommended alternative

There are likely no important feasibility issues as the recommendation reflects usual care.

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 a living systematic review including ~~36~~7 studies ~~(28 case reports and nine case series)~~ reporting newborn SARS-CoV-2 infection status and detection of SARS-CoV-2 in breast milk from mothers with confirmed SARS-CoV-2 infection *[466]*. ~~The authors also identified a further 303 case reports and case series reporting newborn SARS-CoV-2 infection status by feeding practice where breast milk samples from mothers with confirmed SARS-CoV-2 infection were not available.~~

A separate systematic review on the same topic included 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 *[467]*.

~~Additional evidence is available from an observational cohort study in the US of newborns whose mothers had confirmed COVID-19 *[469]*. This study reported on 106 newborns born to 116 mothers with confirmed COVID-19 infection and was not included in the living systematic review due to a later publication date.~~

Study characteristics
Living systematic review *[466]*: SARS-CoV-2 infection status by feeding type was available from 6637 ~~studies~~ for 48577 ~~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). ~~No study attempted to culture the SARS-CoV-2 from breast milk isolates. In the additional 303 studies, infection status by feeding type was available for an additional 917 newborns and infants where breast milk samples were not available.~~

Systematic review *[467]*: among 213 women with SARS-CoV-2 infection, 183 women had SARS-CoV-2 genome testing of their breast milk, 89 had both SARS-CoV-2 genome testing and antibody testing of their breast milk, and 30 had antibody testing ~~-~~only of their breast milk.

~~Cohort study *[469]*: comprised 106 newborns born to 116 mothers who were positive for COVID-19. Mothers could hold their newborns for feeding after appropriate hand hygiene, breast cleansing and placement of surgical mask, both during their hospital stay and after discharge. 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~~.

What are the main results?
Living systematic review *[466]*:
- Of the 6637 ~~included studies~~ where breast milk samples were available, 314 ~~out of~~ 35072 ~~newborns~~ had confirmed COVID-19, diagnosed either by viral RNA detection or by serology (Table 1).
- Of the 8527 ~~newborns~~ who were breastfed (n=4423) or received mixed feeding (n=414), 1710 had COVID-19 confirmed by viral RNA detection (Table 1).
- Of the 303 included studies where breast milk samples were not available, 110 out of 917 newborns were diagnosed with COVID-19 by viral RNA detection. Of the 163 newborns who were breastfed or received mixed feeding, 19 were diagnosed with COVID-19 by viral RNA detection (Table 2).
- ThirteenNine out of 41368 breast milk samples collected from COVID-19 positive mothers tested positive for SARS-CoV-2 via RT-PCR assay. Of the elevensix newborns and infants who were known to be exposed to breast milk with detectable viral RNA, sixfour tested positive and fivetwo tested negative for SARS-CoV-2.

The authors of the living systematic review note the following important considerations:
- The 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.

Systematic review *[467]*:
- Of the 214 infants, 32 infants (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, 6 out of 12 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

- ~~Cohort study *[469]*:~~
  - ~~Of the 82 newborns with follow-up data, 64/82 (78%) were breastfed at 5–7 days and 45/53 (85%) were breastfed at one month of life.~~
  - ~~All newborns returned negative tests at all timepoints. There was no evidence that breastfeeding (with specified precautions) increased the risk of SARS-CoV-2 infection for newborns.~~
  - ~~While the study describes the routine use of breast cleansing in participating hospitals, the Pregnancy and Perinatal Care panel noted there is no evidence that this practice is beneficial.~~

Our confidence in the results
Certainty of the evidence (included in the two reviews) is very low for both outcomes due to the inclusion of case reports and case series likely to be at high risk of bias (including publication bias) and possible duplication of cases between studies.

Table 1 Studies (n=~~66~~37) in the living systematic review where breast milk samples were available

Feeding type	Confirmed COVID-19	Negative COVID-19	Total
Newborns ≤ 28 days			
Breast milk	158	2915	4423
Mixed feeding	2	292	414
Formula	23	2416	2718
Not reported feeding practice	26	22225	22827
Subtotal	**14**	**58**	**72**
Infants > 28 days			
Breast milk	32	10	42
Mixed feeding	43	0	43
Formula	0	0	0
Not reported feeding practice	10	01	02
Subtotal	**5**	**0**	**5**

Table 2 Studies (n=303) in the living systematic review where breast milk samples were not available

Feeding type	Confirmed COVID-19	Negative COVID-19	Total
Newborns ≤ 28 days			
Breast milk	16	137	153
Mixed feeding	3	7	10

Feeding type	Confirmed COVID-19	Negative COVID-19	Total
Formula	15	67	82
Not reported feeding practice	76	596	672
Subtotal	**110**	**807**	**917**
Infants > 28 days			
Breast milk	12	0	12
Mixed feeding	3	0	3
Formula	6	0	6
Not reported feeding practice	125	2	127
Subtotal	**146**	**2**	**148**

Additional information

The Taskforce notes the publication of a WHO scientific brief on 8 February 2021 on the definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2 *[458]*. 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. WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

Further, a June 2020 WHO scientific brief on breastfeeding and COVID-19 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) outweighs potential risk *[468]*.

Additional evidence is available from an observational cohort study in the US of newborns whose mothers had confirmed COVID-19 *[469]*. This study reported on 106 newborns born to 116 mothers with confirmed COVID-19 infection and was not included in the living systematic review due to a later publication date. Mothers could hold their newborns for feeding after appropriate hand hygiene, breast cleansing and placement of surgical mask, both during their hospital stay and after discharge. 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. Of the 82 newborns with follow-up data, 64/82 (78%) were breastfed at 5–7 days and 45/53 (85%) were breastfed at one month of life. All newborns returned negative tests at all timepoints. There was no evidence that breastfeeding (with specified precautions) increased the risk of SARS-CoV-2 infection for newborns.While the study describes the routine use of breast cleansing in participating hospitals, the Pregnancy and Perinatal Care panel noted there is no evidence that this practice is beneficial.

Outcome Timeframe	**Study results and measurements**	**Comparator** No breastfeeding or breast milk	**Intervention** Breastfeeding or breast milk	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Number of infected newborns (No breast milk testing) [1] Within 30 days of breastfeeding 9 Critical	Based on data from: 1,142 patients in 340 studies. [2] (Observational (non-randomized))	See summary for details.		**Very low** Due to very serious risk of bias, and serious imprecision, indirectness, inconsistency and publication bias [3]	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).
Number of infected newborns (Breast milk testing) Within 30 days of breastfeeding 8 Critical	Based on data from: 485 patients in 67 studies. [4] (Observational (non-randomized))	See summary for details.		**Very low** Due to very serious risk of bias, serious inconsistency, imprecision and publication bias [5]	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).

1. Number of infected newborns within 30 days of breastfeeding or receiving expressed breastmilk
2. Systematic review [466]. **Supporting references:** [469], 106 newborns.
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 [466].
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.

13.6. 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).

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.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

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 *[470]* as well as duration of breastfeeding *[471]*. 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 — Very low

Certainty of the evidence is very low due to reliance on case reports and case series.

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.

Resources — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability — Important issues, or potential issues not investigated

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 — Important issues, or potential issues not investigated

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.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively for different rooming-in practices, though evidence is currently limited.

Therefore, the use of rooming-in should be considered as per usual care, taking into consideration 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

Evidence informing this recommendation comes from a systematic review that reported the number of newborns infected with COVID-19 whose mothers had confirmed or suspected COVID-19 *[456]*. The review included 49 case reports or case series comprising 666 newborns, of whom 28 had confirmed postnatal infection. Newborn infection status by rooming-in approach was reported for 159 newborns (see table).

Rooming-in approach	Total neborns	Infected	Not infected	Not tested
Mother-baby isolation	52	6	32	14
Rooming-in of mother and baby	107	6	100	1

Of the 28 newborns infected with COVID-19, six were isolated from their mother and six were cared for in the same room—for the remaining 16 newborns the approach taken was not reported. Overall, 52 newborns were isolated and 107 were cared for in the same room.

Additional evidence is available from an observational cohort study in the US of newborns whose mothers had confirmed COVID-19 *[469]*. The Salvatore study reported on 106 newborns born to 116 mothers who were positive for COVID-19. Newborns roomed-in with mothers (in closed Giraffe isolette) with the exception of 17 newborns who were separated from their mothers, either at parental request or due to a maternal or newborn medical condition (e.g. preterm). 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.

For 82 newborns with follow-up data, 68/82 (83%) roomed-in with their mother during their hospital stay. All newborns returned negative tests at all timepoints. There was no evidence that rooming-in (with specified precautions) increased the risk of SARS-CoV-2 infection for newborns.

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 *[458]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No rooming-in	**Intervention** Rooming-in	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Number of infected newborns [1] Within 30 days of	Based on data from: 666 patients in 49 studies. (Observational (non-randomized))	See summary for details. Included newborns who had confirmed postnatal infection (28/666 newborns). Of the 28 newborns infected, six were kept isolated from		**Very low** Due to very serious risk of bias, and serious imprecision,	We are uncertain whether rooming-in increases or decreases the number of infected newborns.

Outcome Timeframe	**Study results and measurements**	**Comparator** No rooming-in	**Intervention** Rooming-in	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
exposure 9 Critical		their mother, six were cared for in the same room as their mother and for 16 newborns the approach taken was not reported.		indirectness and inconsistency [2]	

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.

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.

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 *[475]*. The US Centers for Disease Control and Prevention has named it multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) *[473]*. WHO has also defined this condition and used the label MIS-C *[474]*.

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 *[472]*. 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) *[475]* 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 *[476]*).

Royal College of Paediatrics and Child Health (PIMS-TS) case definition *[475]*

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:

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 (ECHO) 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
- 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**, high IL-6**, neutrophilia, proteinuria, raised CK, raised LDH, raised triglycerides, raised troponin, thrombocytopaenia, transaminitis

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

CDC MIS-C case definition *[473]*

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 *[474]*

Children and adolescents 0–19 years of age with fever > 3 days.

AND

Two of the following:

- rash or bilateral non-purulent conjunctivitis or muco-cutaneous 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.

Info Box

The Taskforce endorses the PIMS-TS case definition from the Royal College of Paediatrics and Child Health (United Kingdom) *[475]*.

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, thrombocytopaenia, 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

Consensus 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.

Practical Info

Primary classification of PIMS-TS should be based on the presenting phenotype (adapted from Harwood *[478]*:

1. Kawasaki disease-like: complete and incomplete, classified using the American Heart Association criteria *[479]*
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

Benefits and harms — Substantial net benefits of the recommended alternative

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 — Very low

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 — Substantial variability is expected or uncertain

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.

Resources — Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. There may be potential issues accessing this treatment in certains areas.

Equity Important issues, or potential issues not investigated

There is a risk of creating inequity as people who live in rural and remote areas may have limited access to intravenous immunoglobulin.

Acceptability Important issues, or potential issues not investigated

Intravenous immunoglobulin and corticosteroids are generally a well-accepted intervention, and there are no important issues regarding acceptability. However, some groups may decline intravenous immunoglobulin tas it is a blood-derived product and prefer corticosteroids alone.

Feasibility No important issues with the recommended alternative

There are no expected feasibility issues.

Rationale

Intravenous immunoglobulin is the standard first-line treatment for Kawasaki disease. Corticosteroids may be used as adjunctive primary therapy in selected patients. Initial reports show that both have been used to treat PIMS-TS patients, usually sequentially. One observational study has found a potential benefit of the combination therapy in comparison with immunoglobulin alone *[480]*. No randomised trials have been identified.

Children of older age and with more manifestations of myocardial dysfunction may benefit especially from the combination therapy, or from corticosteroids alone.

Clinical Question/ PICO

Population: Children and adolescents with COVID-19
Intervention: Intravenous immunoglobulin plus methylprednisolone
Comparator: Intravenous immunoglobulin

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG	**Intervention** IVIG + MP	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Treatment failure 5 Important	Odds Ratio 0.25 (CI 95% 0.09 — 0.7) Based on data from 106 patients in 1 studies. (Observational (non-randomized))	375 per 1000	130 per 1000 Difference: **245 fewer** per 1000 (CI 95% 324 fewer — 79 fewer)	**Very low** Due to serious imprecision [1]	We are uncertain whether IVIG + MP improves or worsens treatment failure.
Second-line treatment 5 Important	Odds Ratio 0.19 (CI 95% 0.06 — 0.61) Based on data from 106 patients in 1 studies. [2] (Observational (non-randomized))	310 per 1000	79 per 1000 Difference: **231 fewer** per 1000 (CI 95% 284 fewer — 95 fewer)	**Very low** Due to serious imprecision [3]	We are uncertain whether IVIG + MP improves or worsens need for second-line treatment.
Need for hemodynamic support	Odds Ratio 0.21 (CI 95% 0.06 — 0.76) Based on data from 106	230 per 1000	59 per 1000	**Very low** Due to serious imprecision [4]	We are uncertain whether IVIG + MP improves or worsens

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG	**Intervention** IVIG + MP	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
5 Important	patients in 1 studies.	Difference: **171 fewer** per 1000 (CI 95% 212 fewer — 45 fewer)			the need for hemodynamic support.
Acute left ventricular dysfunction [5] 5 Important	Odds Ratio 0.2 (CI 95% 0.06 — 0.66) Based on data from 106 patients in 1 studies.	350 per 1000	97 per 1000 Difference: **253 fewer** per 1000 (CI 95% 319 fewer — 88 fewer)	Very low Due to serious imprecision [6]	We are uncertain whether IVIG + MP improves or worsens acute left ventricular dysfunction.
Duration of PICU stay 5 Important	Lower better Based on data from: 106 patients in 1 studies. (Observational (non-randomized))	6 (Median)	4 (Median) Difference: **MD 2.4 lower** (IQR 4 lower — 0.7 lower)	Very low Due to serious imprecision [7]	We are uncertain whether IVIG + MP increases or decreases duration of PICU stay.

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.**
2. Systematic review [477] with included studies: Cavalcanti 2020, Mitja 2020, Abd-Elsalam 2020, Horby 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision: Serious. Publication bias: No serious.**
4. **Imprecision: Serious.**
5. LVEF < 55% occuring at least 1 dat after first line therapy introduction
6. **Imprecision: Serious.**
7. **Imprecision: Serious.** Only data from one study.

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 prior to, 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.

For selected cases of PIMS-TS with severe myocardial dysfunction, corticosteroid treatment alone and/or delayed use of IVIG may be beneficial.

Practical Info

Primary classification of PIMS-TS should be based on the presenting phenotype (adapted from Harwood *[478]*:

1. Kawasaki disease-like: complete and incomplete, classified using the American Heart Association criteria *[479]*
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 — Substantial net benefits of the recommended alternative

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 — Very low

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 — No substantial variability expected

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 — No important issues with the recommended alternative

We have no systematically collected evidence regarding cost-benefit. There are unlikely to be issues as corticosteroids are widely available.

Equity — No important issues with the recommended alternative

It is unlikely that the use of corticosteroids will create equity issues as they are widely available.

Acceptability — No important issues with the recommended alternative

Corticosteroids are generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility — No important issues with the recommended alternative

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 *[480]*.

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

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG	**Intervention** IVIG + MP	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Treatment failure 5 Important	Odds Ratio 0.25 (CI 95% 0.09 — 0.7) Based on data from 106 patients in 1 studies. (Observational (non-randomized))	375 per 1000	130 per 1000 Difference: **245 fewer** per 1000 (CI 95% 324 fewer — 79 fewer)	**Very low** Due to serious imprecision [1]	We are uncertain whether IVIG + MP improves or worsens treatment failure.
Second-line treatment 5 Important	Odds Ratio 0.19 (CI 95% 0.06 — 0.61) Based on data from 106 patients in 1 studies. [2] (Observational (non-randomized))	310 per 1000	79 per 1000 Difference: **231 fewer** per 1000 (CI 95% 284 fewer — 95 fewer)	**Very low** Due to serious imprecision [3]	We are uncertain whether IVIG + MP improves or worsens need for second-line treatment.
Need for hemodynamic support 5 Important	Odds Ratio 0.21 (CI 95% 0.06 — 0.76) Based on data from 106 patients in 1 studies.	230 per 1000	59 per 1000 Difference: **171 fewer** per 1000 (CI 95% 212 fewer — 45 fewer)	**Very low** Due to serious imprecision [4]	We are uncertain whether IVIG + MP improves or worsens the need for hemodynamic support.
Acute left ventricular dysfunction [5] 5 Important	Odds Ratio 0.2 (CI 95% 0.06 — 0.66) Based on data from 106 patients in 1 studies.	350 per 1000	97 per 1000 Difference: **253 fewer** per 1000 (CI 95% 319 fewer — 88 fewer)	**Very low** Due to serious imprecision [6]	We are uncertain whether IVIG + MP improves or worsens acute left ventricular dysfunction.
Duration of PICU stay 5 Important	Lower better Based on data from: 106 patients in 1 studies. (Observational (non-randomized))	6 (Median)	4 (Median) Difference: **MD 2.4 lower** (IQR 4 lower — 0.7 lower)	**Very low** Due to serious imprecision [7]	We are uncertain whether IVIG + MP increases or decreases duration of PICU stay.

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.**
2. Systematic review [477] with included studies: Cavalcanti 2020, Mitja 2020, Abd-Elsalam 2020, Horby 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision: Serious. Publication bias: No serious.**

4. **Imprecision: Serious.**
5. LVEF < 55% occuring at least 1 dat after first line therapy introduction
6. **Imprecision: Serious.**
7. **Imprecision: Serious.** Only data from one study.

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.

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.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

There is a risk of creating inequity as people who live in rural and remote areas may have limited access to immunomodulatory agents.

Acceptability Important issues, or potential issues not investigated

Immunomodulatory therapies are generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility Important issues, or potential issues not investigated

Feasibility is affected by the availability of immunomodulatory agents, prompt diagnosis of PIMS-TS and access to a multidisciplinary team for discussion.

Rationale

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 *[481][482]*.

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)*

Evidence To Decision

Benefits and harms Substantial net benefits of the recommended alternative

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 Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity No important issues with the recommended alternative

It is unlikely that the use of aspirin will create equity issues as it is widely available.

Acceptability No important issues with the recommended alternative

Aspirin is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility Important issues, or potential issues not investigated

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. Abbreviations and Acronyms

ACE	Angiotensin-converting enzyme
ACEIs	Angiotensin-converting enzyme inhibitors
AEs	Adverse events
AHPPC	Australian Health Protection Principal Committee
ALT	Alanine aminotransferase
ANZICS	Australian and New Zealand Intensive Care Society
ANZPID	Australia and New Zealand Paediatric Infectious Diseases Group
ARBs	Angiotensin receptor blockers
ARDS	Acute respiratory distress syndrome
BiPAP	Bilevel positive airway pressure
BSA	Body surface area
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CMCS	Combined metabolic cofactor supplementation
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019 (disease caused by the virus SARS-CoV-2)
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CT	Computed tomography
CXR	Chest x-ray
DMTs	Disease-modifying treatments
DOI	Digital Object Identifier
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
FiO2	Fraction of inspired oxygen
GRADE	Grading of recommendations, assessment, development and evaluation
HCP	Healthcare professionals
HFNC	High-flow nasal cannula
HFNO	High-flow nasal oxygen
HFOV	High-frequency oscillatory ventilation
HRT	Hormone replacement therapy
hUC-MSCs	Human umbilical cord mesenchymal stem cells
HR	Hazard ratio
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IFN-κ	Interferon kappa
IHPS	Infantile hypertrophic pyloric stenosis
IL	Interleukin
IQR	Interquartile range
IU	International units
IV	Intravenous
LMWH	Low molecular weight heparin
MERS	Middle East respiratory syndrome
MET	Medical Emergency Team
MIS-C	Multisystem inflammatory syndrome in children
mIU	Milli-international units
MHT	Menopausal hormone therapy
NAb	Neutralising antibodies
NC19CET	National COVID-19 Clinical Evidence Taskforce
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NMBAs	Neuromuscular blocking agents
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PaO2	Partial pressure of arterial oxygen
PCR	Polymerase chain reaction
PEEP	Positive end-expiratory pressure
PICU	Paediatric intensive care unit
PIMS-TS	Paediatric multisystem inflammatory syndrome - temporally associated with SARS-CoV-2

PPE	Personal protective equipment
RACS	Royal Australasian College of Surgeons
rhG-CSF	Recombinant human granulocyte colony-stimulating factor
RR	Risk ratio
RT-PCR	Reverse transcription-polymerase chain reaction
SAEs	Serious adverse events
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 (the virus that causes the disease COVID-19)
SOT	Supplementary oxygen therapy

SpO2	Oxygen saturation
SSRIs	Selective serotonin reuptake inhibitors
TFF2	Trefoil factor 2
TID	Three times a day
TNF	Tumour necrosis factor
ULN	Upper limit of normal
VA ECMO	Venoarterial extracorporeal membrane oxygenation
VTE	Venous thromboembolism
VV ECMO	Venovenous extracorporeal membrane oxygenation
WHO	World Health Organization

References

1. World Health Organization : Critical preparedness, readiness and response actions for COVID-19: interim guidance. 2020; Website

2. World Health Organization : Integrating palliative care and symptom relief into responses to humanitarian emergencies and crises: a WHO guide. 2018; Website

3. Hilmer SN, Gnjidic D : Prescribing for frail older people. Australian Prescriber 2017;40(5):174-178 Pubmed Journal

4. UNICEF : Policy Brief: the impact of COVID-19 on children. United Nations Children's Fund 2020; Website

5. Consumers Health Forum of Australia : What is Consumer-Centred Care?. Website

6. Australian Commission on Safety and Quality in Health Care : Patient-centred care - Improving quality and safety through partnerships with patients and consumers. Website

7. SA Health : Equity of Access to Health Care Policy Directive v1.1. 2020; Website

8. Australian Commission on Safety and Quality in Health Care : Australian Charter of Healthcare Rights. 2019; Website

9. Consumers Health Forum of Australia : Informed Consent Issues Paper. 2013; Website

10. Australian Commission on Safety and Quality in Health Care : National Safety and Quality Health Service (NSQHS) Standards. Website

11. Australian Health Practitioners Regulation Authority : Code of conduct for registered health practitioners. 2014;

12. Institute for Patient and Family-Centred Care : Patient- and Family-Centred Care. 2010; Website

13. National Health and Medical Research Council : NHMRC Guidelines: Communicating with Patients: Advice for Medical Practitioners. 2004;

14. HNMRC approval.

15. First Affiliated Hospital, Zhejiang University School of Medicine : Handbook of COVID-19 Prevention and Treatment. 2020;

16. Nicastri E, Petrosillo N, Bartoli TA, Lepore L, Mondi A, Palmieri F, et al. : National Institute for the Infectious Diseases “L. Spallanzani” IRCCS. Recommendations for COVID-19 Clinical Management. Infectious Disease Reports 2020;12(1): Pubmed Journal

17. Alfred Health : Clinical management guideline for hospitalised patients on the ward with COVID-19 (version 5). 2020;

18. Australian and New Zealand Intensive Care Society (ANZICS) : COVID-19 Guidelines (version 1). 2020; Website

19. Beeching NJ, Fletcher TE, Fowler R : BMJ Best Practice: COVID-19. BMJ 2020; Website

20. Australasian Society for Infectious Diseases (ASID) : Interim guidelines for the clinical management of COVID-19 in adults (version 1). 2020; Website

21. [Baricitinib] for [COVID-19].

22. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. : Baricitinib plus remdesivir for hospitalized adults with Covid-19. New England Journal of Medicine 2020; Pubmed Journal

23. [Baricitinib] for [COVID-19].

24. Marconi V, Ramanan A, Bono SD : Baricitinib plus standard of care for hospitalized adults with COVID-19. medRxiv 2021; Journal Website

25. Therapeutic Goods Administration : Australian Product Information - Olumiant (baricitinib). 23 April 2021; Website

26. Systemic corticosteroids for COVID-19.

27. Systemic corticosteroids for COVID-19.

28. World Health Organization : Corticosteroids for COVID-19, Living Guidance. 2 September 2020; Website

29. Ye Z, Wang Y, Colunga-Lozano LE, Prasad M, Tangamornsuksan W, Rochwerg B, et al. : Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ 2020;192(27):E756-E767 Pubmed Journal

30. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F, et al. : Corticosteroids in sepsis: an updated systematic review and meta-analysis. Critical Care Medicine 2018;46(9):1411-1420 Pubmed Journal

31. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. : Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020; Pubmed Journal

32. Dequin P-F, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. : Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. JAMA 2020; Pubmed Journal

33. Du B, Weng LI : Glucocorticoid therapy for COVID-19 critically ill patients with severe acute respiratory failure. ClinicalTrials.gov 2020; Website

34. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. : Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 2020; Pubmed Journal

35. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. : Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020; Pubmed Journal

36. Petersen MW, Meyhoff TS, Helleberg M, Kjær M-BN, Granholm A, Hjortsø CJS, et al. : Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial: protocol and statistical analysis plan. Acta Anaesthesiologica Scandinavica 2020; Pubmed Journal

37. Villar J, Añón JM, Ferrando C, Aguilar G, Muñoz T, Ferreres J, et al. : Efficacy of dexamethasone treatment for patients with the acute respiratory distress syndrome caused by COVID-19: study protocol for a randomized controlled superiority trial. Trials 2020;21(1):717 Pubmed Journal

38. Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. : Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. Clinical Infectious Diseases 2020; Pubmed Journal

39. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. : Dexamethasone in hospitalized patients with Covid-19. New England Journal of Medicine 2021; Pubmed Journal Website

40. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. : Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. European Respiratory Journal 2020; Pubmed Journal

41. Systemic corticosteroids for COVID-19.

42. European Medicines Agency : Remdesivir Gilead: summary on compassionate use EMEA/H/K/5622/CU. 2020; Website

43. Remdesivir for COVID-19. 2020;

44. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS : Remdesivir for the treatment of Covid-19 - final report. New England Journal of Medicine 2020; Pubmed Journal Website

45. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. : Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; Pubmed Journal Website

46. Goldman JD, Lye DC, Hui DS, Marks KM, Bruno R, Montejano R, et al. : Remdesivir for 5 or 10 days in patients with severe Covid-19. New England Journal of Medicine 2020; Pubmed Journal Website

47. US Food and Drug Administration : Emergency use authorization (EUA) of remdesivir (GS-5734). 2020; Website

48. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. : Effect of Remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020; Pubmed Journal

49. [Remdesivir study characteristics 09-09-20].

50. Remdesivir dosage for COVID-19.

51. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo A-M, Preziosi M-P, Sathiyamoorthy V, et al. : Repurposed antiviral drugs for Covid-19 - interim WHO Solidarity Trial results. New England Journal of Medicine 2020; Pubmed Journal

52. Update to living WHO guideline on drugs for covid-19. BMJ 2020;371 m4475 Pubmed Journal

53. Remdesivir for COVID-19. 2020;

54. Remdesivir for COVID-19. 2020;

55. Remdesivir for COVID-19. 2020;

56. Pan H, Peto R, Karim AQ, on behalf of the WHO Solidarity trial consortium : Repurposed antiviral drugs for COVID-19 - interim WHO SOLIDARITY trial results. medRxiv 2020; Journal Website

57. Remdesivir for COVID-19. 2020;

58. Taskforce : Methods brief. 2020;

59. Remdesivir for COVID-19. 2020;

60. Remdesivir for COVID-19. 2020;

61. Remdesivir for COVID-19. 2020;

62. Mahajan L, Singh AP, Gifty : Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study. Indian Journal of Anaesthesia 2021;65(Suppl 1):S41-S46 Pubmed Journal

63. Burwick RM, Yawetz S, Stephenson KE, Collier A-RY, Sen P, Blackburn BG, et al. : Compassionate use of remdesivir in pregnant women with severe Covid-19. Clinical Infectious Diseases 2020; Pubmed Journal

64. Gilead : Veklury(Remdesivir) [package insert]. U.S. Food and Drug Administration 2020; Website

65. Tocilizumab for COVID-19.

66. Tocilizumab for COVID-19.

67. Therapeutic Goods Administration : Australian Product Information: Actemra (tocilizumab). March 2020; Website

68. Tocilizumab for COVID-19.

69. Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P : Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Internal Medicine 2020; Pubmed Journal

70. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. : Efficacy of tocilizumab in patients hospitalized with Covid-19. New England Journal of Medicine 2020; Pubmed Journal

71. Tocilizumab for COVID-19.

72. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. : Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Internal Medicine 2020; Pubmed Journal

73. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. : Tocilizumab in patients hospitalized with Covid-19 pneumonia. New England Journal of Medicine 2020; Pubmed Journal

74. Tocilizumab for COVID-19.

75. Tocilizumab for COVID-19.

76. Tocilizumab for COVID-19.

77. Tocilizumab for COVID-19.

78. Tocilizumab for COVID-19.

79. Tocilizumab for COVID-19.

80. ICEMAN analysis of moderate/severe and critical subgroups.

81. Tocilizumab for COVID-19.

82. Veiga VC, Prats JAGG, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. : Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021;372 n84 Pubmed Journal

83. Tocilizumab for COVID-19.

84. Horby P, Pessoa-Amorim G, Peto L : Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. medRxiv 2021; Journal Website

85. Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, et al. : Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. Annals of the Rheumatic Diseases 2017;76(3):504-510 Pubmed Journal

86. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. : Interleukin-6 receptor antagonists in critically ill patients with Covid-19. New England Journal of Medicine 2021; Pubmed Journal

87. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. : Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. New England Journal of Medicine 2021; Pubmed Journal

88. Wang D, Fu B, Peng Z, Yang D, Han M, Li M, et al. : Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. Frontiers of Medicine 2021; Pubmed Journal

89. Mallalieu NL, Wimalasundera S, Hsu JC, Douglass W, Wells C, Penades IC, et al. : Intravenous dosing of tocilizumab in patients younger than two years of age with systemic juvenile idiopathic arthritis: results from an open-label phase 1 clinical trial. Pediatric Rheumatology Online Journal 2019;17(1):57 Pubmed Journal

90. RECOVERY Collaborative Group : Randomised evaluation of COVID-19 therapy (RECOVERY) Protocol version 14 (2021-02-15). 2021; Website

91. RECOVERY Collaborative Group : Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397(10285):1637-1645 Pubmed Journal

92. Tocilizumab for COVID-19.

93. Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. : Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respiratory Medicine 2021;9(5):511-521 Pubmed Journal

94. Nakajima K, Watanabe O, Mochizuki M, Nakasone A, Ishizuka N, Murashima A : Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan. Modern Rheumatology 2016;26(5):667-71 Pubmed Journal

95. Jiménez-Lozano I, Caro-Teller JM, Fernández-Hidalgo N, Miarons M, Frick MA, Batllori Badia E, et al. : Safety of tocilizumab in COVID-19 pregnant women and their newborn: A retrospective study. Journal of Clinical Pharmacy and Therapeutics 2021; Pubmed Journal

96. Chappell L, Knight M : Randimised evaluation of COVID-19 Therapy (RECOVERY) for pregnant and breastfeeding women. 2020; Website

97. Medicines in Pregnancy : Tocilizumab - best use of medicines in pregnancy (bumps). UK Teratology Information Service (UKTIS) 2020; Website

98. Australian Immunisation Handbook : Tuberculosis: disease, vaccines and recommendations for vaccination. Australian Government Department of Health Accessed 12 April 2021; Website

99. Saito J, Yakuwa N, Kaneko K, Takai C, Goto M, Nakajima K, et al. : Tocilizumab during pregnancy and lactation: drug levels in maternal serum, cord blood, breast milk and infant serum. Rheumatology (Oxford) 2019;58(8):1505-1507 Pubmed Journal

100. Saito J, Yakuwa N, Takai C, Nakajima K, Kaneko K, Goto M, et al. : Tocilizumab concentrations in maternal serum and breast milk during breastfeeding and a safety assessment in infants: a case study. Rheumatology (Oxford) 2018;57(8):1499-1501 Pubmed Journal

101. Azithromycin for COVID-19.

102. Furtado RHM, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, et al. : Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet 2020; Pubmed Journal

103. Sekhavati E, Jafari F, SeyedAlinaghi S, Jamalimoghadamsiahkali S, Sadr S, Tabarestani M, et al. : Safety and effectiveness of azithromycin in patients with COVID-19: an open-label randomised trial. International Journal of Antimicrobial Agents 2020; 106143 Pubmed Journal

104. Therapeutic Goods Administration : Australian Product Information - APO- Azithromycin (Azithromycin Dihydrate) Tablets. January 2019; Website

105. [Azithromycin study characteristics 14-09-20].

106. Azithromycin for COVID-19.

107. RECOVERY Collaborative Group : Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021; Pubmed Journal

108. Azithromycin for COVID-19.

109. Azithromycin for COVID-19.

110. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet 2021;397(10279):1063-1074 Pubmed Journal

111. Convalescent plasma for COVID-19.

112. Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, et al. : Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database of Systematic Reviews 2020;7 CD013600 Pubmed Journal

113. Li L, Zhang W, Hu YU, Tong X, Zheng S, Yang J, et al. : Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020; Pubmed Journal

114. Gharbharan A, Jordans CC, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FP, et al. : Convalescent plasma for COVID-19. A randomized clinical trial. medRxiv 2020; 2020.07.01.20139857 Journal Website

115. [Convalescent plasma study characteristics 14-09-20].

116. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E : Convalescent plasma for COVID-19: a multicenter, randomized clinical trial. medRxiv 2020; Journal Website

117. Convalescent plasma for COVID-19.

118. Rasheed AM, Fatak DF, Hashim HA, Maulood MF, Kabah KK, Almusawi YA, et al. : The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. Le Infezioni in Medicina 2020;28(3):357-366 Pubmed

119. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P : Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371 m3939 Pubmed Journal

120. Convalescent plasma for COVID-19.

121. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. : A randomized trial of convalescent plasma in Covid-19 severe pneumonia. New England Journal of Medicine 2020; Pubmed Journal

122. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. : Early high-titer plasma therapy to prevent severe Covid-19 in older adults. New England Journal of Medicine 2021; Pubmed Journal

123. Convalescent plasma for COVID-19.

124. AlQahtani M, Abdulrahman A, Almadani A, Alali SY, Al Zamrooni AM, Hejab AH, et al. : Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. Scientific Reports 2021;11(1):9927 Pubmed Journal

125. RECOVERY Collaborative Group : Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021; Pubmed Journal

126. Hydroxychloroquine for COVID-19.

127. Australian Health Protection Principal Committee (AHPPC) : AHPPC coronavirus (COVID-19) statements on 7 Apr 2020. Advice on off-label medicines for treatment and prophylaxis of COVID-19. 2020; Website

128. Bhimraj A : Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients With COVID-19. Clinical Infectious Diseases 2020; Pubmed Journal

129. Chen J, Liu D, Lui L : A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Zhejiang Da Xue Xue Bao Yi Xue Ban 2020;49(2):215-9 Pubmed Journal

130. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. : Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020; 2020.03.22.20040758 Journal Website

131. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. : Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. Med (N Y) 2020; 2020.03.19.20038984 Pubmed Journal Website

132. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. : A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine 2020; Pubmed Journal

133. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. : Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020; Pubmed Journal

134. Therapeutic Goods Administration : Australian Product Information: Plaquenil (hydroxychloroquine sulfate). December 2019; Website

135. Chloroquine for COVID-19.

136. Chen L, Zhang Z-Y, Fu J-G : Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. medRxiv 2020; Journal Website

137. Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, et al. : Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. Clinical Infectious Diseases 2020; Pubmed Journal

138. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. : Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Annals of Internal Medicine 2020; Pubmed Journal

139. Kaplan YC, Ozsarfati J, Nickel C, Koren G : Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. British Journal of Clinical Pharmacology 2016;81(5):835-48 Pubmed Journal

140. Fiehn C, Ness T, Weseloh C, Specker C, Hadjiski D, Detert J, et al. : Safety management in treatment with antimalarials in rheumatology. Interdisciplinary recommendations on the basis of a systematic literature review. Zeitschrift fur Rheumatologie 2020; Pubmed Journal

141. Gaffar R, Pineau CA, Bernatsky S, Scott S, Vinet É : Risk of Ocular Anomalies in children exposed In utero to antimalarials: a systematic literature review. Arthritis Care & Research 2019;71(12):1606-1610 Pubmed Journal

142. Hydroxychloroquine for COVID-19.

143. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. : Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. New England Journal of Medicine 2020; Pubmed Journal

144. Hydroxychloroquine for COVID-19.

145. Abd-Elsalam S, Esmail ES, Khalaf M, Abdo EF, Medhat MA, Abd El Ghafar MS, et al. : Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. American Journal of Tropical Medicine and Hygiene 2020; Pubmed Journal

146. Lyngbakken MN, Berdal J-E, Eskesen A, Kvale D, Olsen IC, Rueegg CS, et al. : A pragmatic randomized controlled trial reports the efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. Nature Communications 2020; Pubmed Journal

147. Hydroxychloroquine for COVID-19.

148. Ulrich R, Troxel A, Carmody E : Treating COVID-19 with hydroxychloroquine (TEACH): a multicenter, double-blind, randomzied controlled trial in hospitalized patients. Open Forum Infectious Diseases 2020; Journal Website

149. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. : Effect of hydroxychloroquine in hospitalized patients with Covid-19. New England Journal of Medicine 2020; Pubmed Journal

150. Hydroxychloroquine for COVID-19.

151. Hydroxychloroquine for COVID-19.

152. Hydroxychloroquine for COVID-19.

153. Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, et al. : Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. JAMA 2020; Pubmed Journal

154. Chen C-P, Lin Y-C, Chen T-C, Tseng T-Y, Wong H-L, Kuo C-Y, et al. : A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). PloS one 2020;15(12):e0242763 Pubmed Journal

155. Dubée V, Roy P-M, Vielle B, Parot-Schinkel E, Blanchet O, Darsonval A, et al. : Hydroxychloroquine in mild-to-moderate COVID-19: a placebo-controlled double blind trial. Clinical Microbiology and Infection 2021; Pubmed Journal

156. Hydroxychloroquine for COVID-19.

157. Hydroxychloroquine + Azithromycin for COVID-19.

158. Hydroxychloroquine + Azithromycin for COVID-19.

159. Johnston C, Brown ER, Stewart J, Karita HCS, Kissinger PJ, Dwyer J, et al. : Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: A randomized clinical trial. EClinicalMedicine 2021;33 100773 Pubmed Journal

160. Omrani AS, Pathan SA, Thomas SA, Harris TRE, Coyle PV, Thomas CE, et al. : Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. EClinicalMedicine 2020;29 100645 Pubmed Journal

161. Therapeutic Goods Administration : Australian Product Information: Rebif (interferon beta-1a). 2020; Website

162. Therapeutic Goods Administration : Australian Product Information: Avonex (interferon beta-1a). 2019; Website

163. Hellwig K, Geissbuehler Y, Sabidó M, Popescu C, Adamo A, Klinger J, et al. : Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. Journal of Neurology 2020;267(6):1715-23 Pubmed Journal

164. Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, et al. : Efficacy and safety of interferon β-1a in treatment of severe COVID-19: a randomized clinical trial. Antimicrobial Agents and Chemotherapy 2020; Pubmed Journal

165. Interferon beta-1a for COVID-19.

166. Interferon beta-1a for COVID-19.

167. Interferon beta-1a for COVID-19.

168. Interferon beta-1a for COVID-19.

169. Interferon beta-1a for COVID-19.

170. [Intervention] for [COVID-19].

171. [Intervention] for [COVID-19].

172. [Intervention] for [COVID-19].

173. Therapeutic Goods Administration : Australian Product Information: Kaletra (lopinavir/ritonavir) tablets and oral solution (version 32). 2019; Website

174. Zheng F, Zhou Y, Zhou Z, Ye F, Huang B, Huang Y, et al. : SARS-CoV-2 clearance in COVID-19 patients with novaferon treatment: a randomized, open-label, parallel group trial. International Journal of Infectious Diseases 2020; 2020.04.24.20077735 Pubmed Journal Website

175. Pasley MV, Martinez M, Hermes A, d'Amico R, Nilius A : Safety and efficacy of lopinavir/ritonavir during pregnancy: a systematic review. AIDS Reviews 2013;15(1):38-48 Pubmed

176. Tookey PA, Thorne C, van Wyk J, Norton M : Maternal and foetal outcomes among 4118 women with HIV infection treated with lopinavir/ritonavir during pregnancy: analysis of population-based surveillance data from the national study of HIV in pregnancy and childhood in the United Kingdom and Ireland. BMC Infectious Diseases 2016;16 65 Pubmed Journal

177. White AB, Mirjahangir JF, Horvath H, Anglemyer A, Read JS : Antiretroviral interventions for preventing breast milk transmission of HIV. Cochrane Database of Systematic Reviews 2014;(10):CD011323 Pubmed Journal

178. rhG-CSF for COVID-19.

179. Sturt AS, Dokubo EK, Sint TT : Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. Cochrane Database of Systematic Reviews 2010;(3):CD008440 Pubmed Journal

180. Roberts SS, Martinez M, Covington DL, Rode RA, Pasley MV, Woodward WC : Lopinavir/ritonavir in pregnancy. Journal of Acquired Immune Deficiency Syndromes 2009;51(4):456-61 Pubmed Journal

181. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2020; Pubmed Journal

182. Lopinavir/Ritonavir for COVID-19.

183. Lopinavir/Ritonavir for COVID-19.

184. Lopinavir/Ritonavir for COVID-19.

185. Reis G, Moreira Silva EADS, Medeiros Silva DC, Thabane L, Singh G, Park JJH, et al. : Effect of early treatment with hydroxychloroquine or lopinavir and ritonavir on risk of hospitalization among patients with COVID-19: The TOGETHER randomized clinical trial. JAMA Network Open 2021;4(4):e216468 Pubmed Journal

186. Anakinra for COVID-19.

187. Therapeutic Goods Administration : Australian Product Information - Kineret (anakinra). 16 February 2021; Website

188. CORIMUNO-19 Collaborative Group : Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild to moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respiratory Medicine 2020; Pubmed Journal Website

189. [Intervention] for [COVID-19].

190. Mehboob R, Ahmad F, Qayyum A : Aprepitant as a combinant with dexamethasone reduces the inflammation via neurokinin 1 receptor antagonism in severe to critical Covid-19 patients and potentiates respiratory recovery: a novel therapeutic approach. medRxiv 2020; Journal Website

191. Therapeutic Goods Administration : Product Information Emend capsule (aprepitant). 2014; Website

192. Aprepitant for COVID-19.

193. Baloxavir Marboxil for COVID-19.

194. Lou Y, Yao H, Hu Z : Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. medRxiv 2020; Journal Website

195. Therapeutic Goods Administration : Australian Product Information: Xofluza (baloxavir marboxil) tablets. 2020; Website

196. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. : Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. European Journal of Pharmaceutical Sciences 2020; 105631 Pubmed Journal

197. Bamlanivimab for COVID-19.

198. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. : SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. New England Journal of Medicine 2020; Pubmed Journal

199. Bamlanivimab for COVID-19.

200. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. : Effect of bamlanivimab as monotherapy or in combination with

etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021; Pubmed Journal

201. Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, et al. : A neutralizing monoclonal antibody for hospitalized patients with Covid-19. New England Journal of Medicine 2020; Pubmed Journal

202. Bamlanivimab plus etesevimab for COVID-19.

203. [Bromhexine] for [COVID-19].

204. Li T, Sun L, Zhang W, Zheng C, Jiang C, Chen M, et al. : Bromhexine hydrochloride tablets for the treatment of moderate COVID-19: an open-label randomized controlled pilot study. Clinical and Translational Science 2020; Pubmed Journal

205. Ansarin K, Tolouian R, Ardalan M, Taghizadieh A, Varshochi M, Teimouri S, et al. : Effect of bromhexine on clinical outcomes and mortality in COVID-19 patients: A randomized clinical trial. BioImpacts : BI 2020;10(4):209-215 Pubmed Journal

206. [Intervention] for [COVID-19].

207. [Intervention] for [COVID-19].

208. [Intervention] for [COVID-19].

209. Tolouian R, Mulla ZD, Jamaati H, Babamahmoodi A, Marjani M, Eskandari R, et al. : Effect of bromhexine in hospitalized patients with COVID-19. Journal of Investigative Medicine 2021; Pubmed Journal

210. [Intervention] for [COVID-19].

211. [Intervention] for [COVID-19].

212. Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. : Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respiratory Medicine 2021; Pubmed Journal

213. [Intervention] for [COVID-19].

214. Sridharan K, Sivaramakrishnan G, Kanters S : Adverse pregnancy outcomes between the anti-malarial drugs: Is there a difference between the drugs recommended by World Health Organization? Results of a mixed treatment comparison analysis of randomized clinical trials and cohort studies. International Journal of Risk & Safety in Medicine 2019;30(2):73-89 Pubmed Journal

215. Therapeutic Goods Administration : Australian Product Information: Colchicine. 2020; Website

216. Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, et al. : Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. JAMA Network Open 2020;3(6):e2013136 Pubmed Journal

217. Indraratna PL, Virk S, Gurram D, Day RO : Use of colchicine in pregnancy: a systematic review and meta-analysis. Rheumatology 2018;57(2):382-387 Pubmed Journal

218. Lopes MI, Bonjourno LP, Giannini MC : Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial. medRxiv 2020; Journal Website

219. Colchicine for COVID-19.

220. Salehzadeh F, Pourfarzi F, Ataei S : The impact of colchicine on the COVID-19 patients; a clinical trial study. Research Square 2020;

Journal

221. Colchicine for COVID-19.

222. Tardif J-C, Bouabdallaoui N, L'Allier P, Gaudet D, Shah B : Efficacy of colchicine in non-hospitalized patients with COVID-19. medRxiv 2021; Journal Website

223. Colchicine for COVID-19.

224. Colchicine for COVID-19.

225. Combined metabolic cofactor supplementation (CMCS) for COVID-19.

226. Altay O, Yang H, Aydin M : Combined metabolic cofactor supplementation accelerates recovery in mild-to-moderate COVID-19. medRxiv 2020; Journal Website

227. [Intervention] for [COVID-19].

228. Joong Sik E, Michael I, Anca S-C, Oana S, Liliana-Lucia P, Yeon-Sook K, et al. : Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. Research Square 2021; Journal Website

229. Darunavir/Cobicistat for COVID-19.

230. Devasenapathy N, Ye Z, Loeb M, Fang F, Najafabadi BT, Xiao Y, et al. : Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. CMAJ 2020;192(27):E745-E755 Pubmed Journal

231. van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. : Evaluation of convalescent plasma for Ebola virus disease in Guinea. New England Journal of Medicine 2016;374(1):33-42 Pubmed Journal

232. Chen J, Xia LU, Liu LI, Xu Q, Ling Y, Huang D, et al. : Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. Open Forum Infectious Diseases 2020;7(7):ofaa241 Pubmed Journal

233. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. 2020; Website

234. Dutasteride for [COVID-19].

235. Therapeutic Goods Administration : Australian Product Information: APO-Dutasteride (Dutasteride) Soft Capsules. 24 September 2020; Website

236. Cadegiani FA, McCoy J, Wambier CG, Goren A : Early antiandrogen therapy with dutasteride reduces viral shedding, inflammatory responses, and time-to-remission in males with COVID-19: a randomized, double-blind, placebo-controlled interventional trial (EAT-DUTA AndroCoV Trial – Biochemical). Cureus 2021;13(2):e13047 Journal

237. Holubovska O, Bojkova D, Elli S : Enisamium is an inhibitor of the SARS-CoV-2 RNA polymerase and shows improvement of recovery in COVID-19 patients in an interim analysis of a clinical trial. medRxiv 2021; Journal Website

238. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. : AVIFAVIR for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial. Clinical Infectious Disease 2020; Pubmed Journal Website

239. Favipiravir for COVID-19.

240. Favipiravir for COVID-19.

241. Favipiravir for COVID-19.

242. Ruzhentsova T, Chukhliaev P, Khavkina D, Garbuzov A, Ploskireva A : Efficacy and safety of favipiravir in a complex therapy of mild to moderate COVID-19. Infectious Diseases [RU] 2020; Website

243. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. : Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. International Journal of Infectious Diseases 2020; Pubmed Journal

244. Fluvoxamine for COVID-19.

245. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. : Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA 2020; Pubmed Journal

246. Therapeutic Goods Administration : Australian Product Information - APO-Fluvoxamine (Fluvoxamine Maleate) Film Coated Tablets. 22 May 2020; Website

247. Therapeutic Goods Administration : Regulation of stem cell treatments: information for practitioners. May 2020; Website

248. Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, et al. : Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Research & Therapy 2020;11(1):361 Pubmed Journal

249. Mesenchymal stem cells versus Standard care for COVID-19.

250. Mesenchymal stem cells (hU-MSC) for COVID-19.

251. Lanzoni G, Linetsky E, Correa D, Messinger Cayetano S, Alvarez RA, Kouroupis D, et al. : Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: a double-blind, phase 1/2a, randomized controlled trial. Stem Cells Translational Medicine 2021; Pubmed Journal

252. Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, et al. : Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduction and Targeted Therapy 2021;6(1):58 Pubmed Journal

253. Interferon beta-1a for COVID-19.

254. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, et al. : Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respiratory Medicine 2020; Pubmed Journal

255. Rahmani H, Davoudi-Monfared E, Nourian A, Khalili H, Hajizadeh N, Jalalabadi NZ, et al. : Interferon β-1b in treatment of severe COVID-19: a randomized clinical trial. International Immunopharmacology 2020;88 106903 Pubmed Journal

256. Interferon beta-1b for COVID-19.

257. Interferon beta-1b for COVID-19.

258. Therapeutic Goods Administration : Australian Product Information: Betaferon (interferon beta-1b). July 2019; Website

259. Interferon gamma for COVID-19.

260. Moynelo E, Escribano P, Roberts D : Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. medRxiv 2020; Journal Website

261. Therapeutic Goods Administration : Australian Product Information: Imukin. 13 September 2019; Website

262. IFN kappa + TFF-2 for COVID-19.

263. Fu W, Liu Y, Liu LI, Hu H, Cheng X, Liu P, et al. : An open-label, randomized trial of the combination of IFN-κ plus TFF2 with standard care in the treatment of patients with moderate COVID-19. EClinicalMedicine 2020; 100547 Pubmed Journal

264. [Immunoglobulin] for [COVID-19].

265. Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi S-R, Hajizadeh R : The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infectious Diseases 2020;20(1):786 Pubmed Journal

266. Immunoglobulin for COVID-19.

267. Guo YI, Tian X, Wang X, Xiao Z : Adverse effects of immunoglobulin therapy. Frontiers in Immunology 2018;9 1299 Pubmed Journal

268. Sakoulas G, Geriak M, Kullar R, Greenwood KL, Habib M, Vyas A, et al. : Intravenous immunoglobulin plus methylprednisolone mitigate respiratory morbidity in coronavirus disease 2019. Critical Care Explorations 2020;2(11):e0280 Pubmed Journal

269. Podder CS, Chowdhury N, Sina MI, Ul Haque WMM : Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC Journal of Medical Science 2020; Website

270. Niaee MS, Gheibi N, Namdar P, Allami A, Zolghadr L, Javadi A, et al. : Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial. Research Square 2020; Journal

271. Krolewiecki A, Lifschitz A, Moragas M, Travacio M, Valentini R, Alonso DF, et al. : Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial. SSRN preprint 2020; Journal

272. Therapeutic Goods Administration : Australian Product Information: Stromectol (ivermectin). August 2020; Website

273. Australian Medicines Handbook 2020 (online). 2020; Website

274. Ivermectin versus standard care for COVID-19.

275. Ivermectin versus standard care for COVID-19.

276. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. : A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International Journal of Infectious Diseases 2020;103 214-216 Pubmed Journal

277. Chachar A, Khan K, Asif M : Effectiveness of ivermectin in SARS-CoV-2/COVID-19 patients. International Journal of Sciences 2020; Journal Website

278. Kirti R, Roy R, Pattader C, Raj R : Ivermectin as a potential treatment for mild to moderate COVID-19: a double blind randomized placebo-controlled trial. medRxiv 2021; Journal Website

279. Chaccour C, Casellas A, Blanco-Di Matteo A, Pineda I, Fernandez-Montero A, Ruiz-Castillo P, et al. : The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine 2021; 100720 Pubmed Journal

280. Ivermectin versus standard care for COVID-19.

281. Mohan A, Tiwari P, Suri T : Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial. Research Square 2021; Journal Website

282. Beltran-Gonzalez JL, Gamez MG, Encisco EAM : Efficacy and safety of ivermectin and hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. medRxiv 2021; Journal Website

283. Shah Bukhari KH, Asghar A, Perveen N : Efficacy of ivermectin in COVID-19 patients with mild to moderate disease. medRxiv 2021; Journal Website

284. Ivermectin versus standard care for COVID-19.

285. López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, et al. : Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA 2021; Pubmed Journal

286. Ivermectin versus standard care for COVID-19.

287. Pott-Junior H, Bastos Paoliello MM, Miguel ADQC, da Cunha AF, de Melo Freire CC, Neves FF, et al. : Use of ivermectin in the treatment of Covid-19: A pilot trial. Toxicology Reports 2021;8 505-510 Pubmed Journal

288. Kishoria N, Mathur S.L, Parmar V : Ivermectin as adjuvant to hydroxychloroquine in patients resistant to standard treatment for SARS-CoV-2: Results of an open-label randomized clinical study. Indian Journal of Research 2020;9(8): Journal Website

289. [Ivermectin plus Doxycycline] for [COVID-19].

290. [Ivermectin plus Doxycycline] for [COVID-19].

291. [Intervention] for [COVID-19].

292. Hashim H, Maulood M, Rasheed A : Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. medRxiv 27 October 2020; Journal Website

293. Therapeutic Goods Administration : Australian Product Information - APO-Doxycycline (Doxycycline monohydrate) tablets. 14 September 2020; Website

294. Mahmud R : Clinical trial of ivermectin plus doxycycline for the treatment of confirmed Covid-19 infection. ClinicalTrials.gov 2020; Website

295. Lenzilumab for COVID-19.

296. Lenzilumab for COVID-19.

297. Temesgen Z, Burger C, Baker J : Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: results from the live-air phase 3 randomized double-blind placebo-controlled trial. medRxiv 2021; Journal Website

298. N-acetylcysteine for COVID-19.

299. de Alencar JCG, Moreira CDL, Müller AD, Chaves CE, Fukuhara MA, da Silva EA, et al. : Double-blind, randomized, placebo-controlled trial with N-acetylcysteine for treatment of severe acute respiratory syndrome caused by COVID-19. Clinical Infectious Diseases 2020; Pubmed Journal

300. Therapeutic Goods Administration : Australian Product Information: DBL Acetylcysteine Injection Concentrate. May 2019; Website

301. [Nitazoxanide] for [COVID-19].

302. Rocco PRM, Silva PL, Cruz FF, Junior MACM, Tierno PFGMM, Moura MA, et al. : Early use of nitazoxanide in mild Covid-19 disease: randomised, placebo-controlled trial. European Respiratory Journal 2021; Pubmed Journal

303. [Nitazoxanide] for [COVID-19].

304. Silva M, Espejo A, Pereyra M : Efficacy of nitazoxanide in reducing the viral load in COVID-19 patients. medRxiv 2021; Journal Website

305. Rossignol J-F, Bardin M, Oaks J : Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization. medRxiv 2021; Journal Website

306. Peginterferon alpha for COVID-19.

307. Jagannathan P, Andrews J, Bonilla H : Peginterferon lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. medRxiv 2020; Journal Website

308. Feld JJ, Kandel C, Biondi MJ, Kozak RA, Zahoor MA, Lemieux C, et al. : Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Respiratory Medicine 2021; Pubmed Journal

309. Jagannathan P, Andrews JR, Bonilla H, Hedlin H, Jacobson KB, Balasubramanian V, et al. : Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. Nature Communications 2021;12(1):1967 Pubmed Journal

310. Cheng L-L, Guan W-J, Duan C-Y, Zhang N-F, Lei C-L, Hu YU, et al. : Effect of recombinant human granulocyte colony-stimulating factor for patients with coronavirus disease 2019 (COVID-19) and lymphopenia: a randomized clinical trial. JAMA Internal Medicine 2020; Pubmed Journal

311. Therapeutic Goods Administration : Product Information: Zarzio (Filgrastim; Recombinant Human Granulocyte Colony Stimulating Factor). May 2013; Website

312. [REGN-COV2] for [COVID-19].

313. [REGN-COV2] for [COVID-19].

314. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. : REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. New England Journal of Medicine 2021;384(3):238-251 Pubmed Journal

315. Ruxolitinib for COVID-19.

316. Therapeutic Goods Administration : Australian Product Information: Jakavi (ruxolitinib). 2018; Website

317. Cao Y, Wei J, Zou L : Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-2019): a multicenter, single-blind, randomized controlled trial. Journal of Allergy and Clinical Immunology 2020; Pubmed Journal Website

318. Therapeutic Goods Administration : Australian Product Information: Kevzara (Sarilumab) pre-filled pen and pre-filled syringe. 2018; Website

319. Sarilumab for COVID-19.

320. Lescure F-X, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, et al. : Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respiratory Medicine 2021; Pubmed Journal

321. Sarilumab for COVID-19.

322. Sarilumab for COVID-19.

323. Sarilumab for COVID-19.

324. Sadeghi A, Ali Asgari A, Norouzi A, Kheiri Z, Anushirvani A, Montazeri M, et al. : Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. Journal of Antimicrobial Chemotherapy 2020; Pubmed Journal

325. Therapeutic Goods Administration : Australian Product Information: Sovaldi (sofosbuvir). August 2020; Website

326. Therapeutic Goods Administration : Australian Product Information: Daklinza (daclatasvir). April 2019; Website

327. Sofosbuvir/daclatasvir for COVID-19.

328. Sofosbuvir/daclatasvir for COVID-19.

329. Yakoot M, Eysa B, Gouda E : Efficacy and safety of sofosbuvir/daclatasvir in the treatment of COVID-19: a randomized, controlled study. SSRN preprint 2020; Journal Website

330. Sofosbuvir/daclatasvir for COVID-19.

331. Roozbeh F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Merat S, Wentzel H, et al. : Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. Journal of Antimicrobial Chemotherapy 2020;76(3):753-757 Pubmed Journal

332. Sulodexide for COVID-19.

333. Gonzalez Ochoa AJ, Raffetto J, Hernandez Ibarra AG, Zavala N, Gutierrez O, Vargas A, et al. : Sulodexide in the treatment of patients with early stages of COVID-19: a randomized controlled trial. Thrombosis and Haemostasis 2021; Pubmed Journal

334. Duarte M, Pelorosso F, Nicolosi L : Telmisartan for treatment of Covid-19 patients: an open randomized clinical trial. Preliminary report. medRxiv 2020; Journal Website

335. Therapeutic Goods Administration : Australian Product Information: Alkem Telmisartan (telmisartan). 27 March 2020; Website

336. Telmisartan for COVID-19.

337. Triazavirin for COVID-19.

338. Wu X, Yu K, Wang Y, Xu W, Ma H, Hou Y, et al. : Efficacy and safety of triazavirin therapy for coronavirus disease 2019: a pilot randomized controlled trial. Engineering (Beijing, China) 2020; Pubmed Journal

339. Yethindra V, Tagaev T, Uulu M : Efficacy of umifenovir in the treatment of mild and moderate COVID-19 patients. International Journal of Research in Pharmaceutical Sciences 2020; Journal Website

340. Arbidol for COVID-19.

341. Ghaderkhani S, Khaneshan A, Salami A : Efficacy and safety of Arbidol in treatment of patients with COVID-19 infection: a randomized clinical trial. Research Square 2020; Journal

342. [Vitamin C] for [COVID-19].

343. [Vitamin C] for [COVID-19].

344. Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, et al. : Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Annals of Intensive Care 2021;11(1):5 Pubmed Journal

345. Kumari P, Dembra S, Dembra P, Bhawna F, Gul A, Ali B, et al. : The role of vitamin C as adjuvant therapy in COVID-19. Cureus 2020;12(11):e11779 Pubmed Journal

346. JamaliMoghadamSiahkali S, Zarezade B, Koolaji S, SeyedAlinaghi S, Zendehdel A, Tabarestani M, et al. : Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. European Journal of Medical Research 2021;26(1):20 Pubmed Journal

347. Castillo ME, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, Miranda JL, Bouillon R, et al. : Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. Journal of Steroid Biochemistry and Molecular Biology 2020; 105751 Pubmed Journal

348. Calcifediol for COVID-19.

349. Calcifediol for COVID-19.

350. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. : Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). Postgraduate Medical Journal 2020; Pubmed Journal

351. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. : Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA 2021; Pubmed Journal

352. Zinc for COVID-19.

353. Abd-Elsalam S, Soliman S, Esmail ES, Khalaf M, Mostafa EF, Medhat MA, et al. : Do zinc supplements enhance the clinical efficacy of hydroxychloroquine?: a randomized, multicenter trial. Biological Trace Element Research 2020; Pubmed Journal

354. Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, et al. : Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Network Open 2021;4(2):e210369 Pubmed Journal

355. Patel O, Chinni V, El-Khoury J, Perera M, Neto AS, McDonald C, et al. : A pilot double-blind safety and feasibility randomised controlled trial of high-dose intravenous zinc in hospitalised COVID-19 patients. Journal of Medical Virology 2021; Pubmed Journal

356. Therapeutic Goods Administration : Australian Product Information: DBL Zinc Chloride. 27 February 2019; Website

357. Ivermectin versus standard care for COVID-19.

358. Ivermectin versus standard care for COVID-19.

359. [Intervention] for [COVID-19].

360. HCQ pre-exp prophylaxis in HCW for COVID-19.

361. Grau-Pujol B, Camprubi D, Marti-Soler H : Pre-exposure prophylaxis with hydroxychloroquine for COVID- 19: initial results of a double-blind, placebo-controlled randomized clinical trial. Research Square 2020; Journal Website

362. Abella BS, Jolkovsky EL, Biney BT, Uspal JE, Hyman MC, Frank I, et al. : Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. JAMA Internal Medicine 2020; Pubmed Journal

363. Rajasingham R, Bangdiwala AS, Nicol MR, Skipper CP, Pastick KA, Axelrod ML, et al. : Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. Clinical Infectious Diseases 2020; Pubmed Journal

364. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. : A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. New England Journal of Medicine 2020; Pubmed Journal

365. Hydroxychloroquine post-exposure prophylaxis for COVID-19.

366. Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, et al. : A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. New England Journal of Medicine 2020; Pubmed Journal

367. Alhazzani W, Møller MH, Arabi YM, Loeb YM, Gong MN, Fan E, et al. : Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Critical Care Medicine 2020; Pubmed Website

368. Ashraf-Kashani N, Kumar R : High-flow nasal oxygen therapy. BJA Education 2017;17(2):57-62 Journal

369. World Health Organization : Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. 2020; Website

370. Murthy S, Gomersall CD, Fowler RA : Care for critically ill patients with COVID-19. JAMA 2020; Pubmed Journal Website

371. Institute of Tropical Medicine (Antwerp) : Interim clinical guidance for patients suspected of/confirmed with COVID-19 in Belgium (version 4). 2020; Website

372. Effectiveness, safety and risk of dispersion or aerosol generation and infection transmission with high flow nasal cannula use for acute hypoxemic respiratory failure in patients with COVID-19: two systematic reviews. 2020;

373. Rochwerg B, Granton D, Wang DX, Helviz Y, Einav S, Frat JP, et al. : High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Medicine 2019;45(5):563-572 Pubmed Journal

374. Agarwal A, Basmaji J, Muttalib F, Granton D, Chaudhuri D, Chetan D, et al. : High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Canadian Journal of Anaesthesia 2020; Pubmed Journal

375. British Thoracic Society Standards of Care Committee : Non-invasive ventilation in acute respiratory failure. Thorax 2002;57(3):192-211 Pubmed

376. Non-invasive ventilation for hypoxaemia in patients with COVID-19.

377. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, et al. : Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. JAMA 2020; Pubmed Journal

378. Videolaryngoscopy versus Direct laryngoscopy for emergency intubation.

379. Gao Y-X, Song Y-B, Gu Z-J, Zhang J-S, Chen X-F, Sun H, et al. : Video versus direct laryngoscopy on successful first-pass

endotracheal intubation in ICU patients. World Journal of Emergency Medicine 2018;9(2):99-104 Pubmed Journal

380. Sulser S, Ubmann D, Schlaepfer M, Brueesch M, Goliasch G, Seifert B, et al. : C-MAC videolaryngoscope compared with direct laryngoscopy for rapid sequence intubation in an emergency department: a randomised clinical trial. European Journal of Anaesthesiology 2016;33(12):943-948 Pubmed

381. Silverberg MJ, Li N, Acquah SO, Kory PD : Comparison of video laryngoscopy versus direct laryngoscopy during urgent endotracheal intubation: a randomized controlled trial. Critical Care Medicine 2015;43(3):636-41 Pubmed Journal

382. Rombey T, Schieren M, Pieper D : Video versus direct laryngoscopy for inpatient emergency intubation in adults. Deutsches Arzteblatt International 2018;115(26):437-444 Pubmed Journal

383. Lascarrou JB, Boisrame-Helms J, Bailly A, Le Thuaut A, Kamel T, Mercier E, et al. : Video laryngoscopy vs direct laryngoscopy on successful first-pass orotracheal intubation among ICU patients: a randomized clinical trial. JAMA 2017;317(5):483-493 Pubmed Journal

384. Janz DR, Semler MW, Lentz RJ, Matthews DT, Assad TR, Norman BC, et al. : Randomized trial of video laryngoscopy for endotracheal intubation of critically ill adults. Critical Care Medicine 2016;44(11):1980-1987 Pubmed

385. Griesdale DEG, Chau A, Isac G, Ayas N, Foster D, Irwin C, et al. : Video-laryngoscopy versus direct laryngoscopy in critically ill patients: a pilot randomized trial. Canadian Journal of Anaesthesia 2012;59(11):1032-9 Pubmed Journal

386. Driver BE, Prekker ME, Moore JC, Schick AL, Reardon RF, Miner JR : Direct versus video laryngoscopy using the C-MAC for tracheal intubation in the emergency department: a randomized controlled trial. Academic Emergency Medicine 2016;23(4):433-9 Pubmed Journal

387. Hall D, Steel A, Heij R, Eley A, Young P : Videolaryngoscopy increases 'mouth-to-mouth' distance compared with direct laryngoscopy. Anaesthesia 2020;75(6):822-823 Pubmed Journal

388. Neuromuscular blockers versus No neuromuscular blockers for Mechanically ventilated adults with COVID-19 and persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures.

389. Papazian L, Forel J-M, Gacouin A : Neuromuscular blockers in early acute respiratory distress syndrome. New England Journal of Medicine 2010; Pubmed Journal

390. Moss M, Huang D, Brower R : Early neuromuscular blockade in the acute respiratory distress syndrome. New England Journal of Medicine 2019; Pubmed Journal

391. Guervilly C, Bisbal M, Forel J : Effects of neuromuscular blockers on transpulmonary pressures in moderate to severe acute respiratory distress syndrome. Intensive Care Medicine 2017; Pubmed Journal

392. Gainnier M, Roch A, Forel J : Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Critical Care Medicine 2004; Pubmed Journal

393. Forel J, Roch A, Marin V : Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Critical Care Medicine 2006; Pubmed Journal

394. Coppo A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P, et al. : Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respiratory Medicine 2020; Pubmed Journal

395. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, et al. : Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet 2020;396(10257):1071-1078 Pubmed Journal

396. Schmidt M, Hajage D, Lebreton G, Monsel A, Voiriot G, Levy D, et al. : Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. Lancet Respiratory medicine 2020; Pubmed Journal

397. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. : ISTH interim guidance on recognition and management of coagulopathy in COVID-19. Journal of Thrombosis and Haemostasis 2020;18(5):1023-6 Journal Website

398. Parker B, Hart V, Rattan R : Coagulopathy in COVID-19: review and recommendations. University of Miami 2020; Website

399. Hunt B, Retter A, McClintock C : Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. British Haematological Society 2020; Website

400. Thrombosis and Haemostasis Society of Australia and New Zealand : Thromboprophylaxis and thrombosis in COVID 19 infected patients admitted to hospital. 2020; Website

401. Therapeutic Goods Administration : Australian Product Information: DBL heparin sodium injection BP (heparin sodium). 2018; Website

402. Therapeutic Goods Administration : Australian Product Information: Fragmin injection (dalteparin sodium). 2020; Website

403. VTE prophylaxis for COVID-19.

404. Wichmann D, Sperhake J-P, Lutgehetmann M : Autopsy findings and venous thromboembolism in patients with COVID-19. Annals of Internal Medicine 2020; Pubmed Journal Website

405. Poissy J, Goutay J, Caplan M : Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. Circulation 2020; Pubmed Journal Website

406. Middledorp S, Coppens M, van Haaps T : Incidence of venous thromboembolism in hospitalized patients with COVID-19. Journal of Thrombosis and Haemostasis 2020; Pubmed Journal Website

407. Lodigiani C, Iapichino G, Carenzo L : Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thrombosis Research 2020; Pubmed Journal Website

408. Llitjos J-F, Leclerc M, Chochois C : High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. Journal of Thrombosis and Haemostasis 2020; Pubmed Journal Website

409. Klok F.A, Kruip M.J.H.A, van der Meer N.J.M : Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thrombosis Research 2020; Pubmed Journal Website

410. Cui S, Chen S, Li X : Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis 2020; Pubmed Journal Website

411. Helms J, Tacquard C, Severac F : High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Medicine 2020; Pubmed Journal Website

412. Zhang LI, Feng X, Zhang D : Deep vein thrombosis in hospitalized patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: prevalence, risk factors, and outcome. Circulation 2020; Pubmed Journal Website

413. Lippi G, Plebani M, Henry BM : Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clinica Chimica Acta 2020; Pubmed Journal Website

414. Paranjpe I, Fuster V, Lala A : Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. Journal of the American College of Cardiology 2020; Pubmed Journal Website

415. Goyal P, Choi J, Pinheiro L : Clinical characteristics of Covid-19 in New York City. New England Journal of Medicine 2020; Pubmed Journal Website

416. VTE prophylaxis for COVID-19.

417. Lemos ACB, do Espírito Santo DA, Salvetti MC, Gilio RN, Agra LB, Pazin-Filho A, et al. : Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thrombosis research 2020;196 359-366 Pubmed Journal

418. Therapeutic Goods Administration : Australian Product Information - Clexane and Clexane Forte (enoxaparin sodium). 2020; Website

419. Flumignan RLG, Tinôco JD, Pascoal PIF, Areias LL, Cossi MS, Fernandes MICD, et al. : Prophylactic anticoagulants for people hospitalised with COVID-19. Cochrane Database of Systematic Reviews 2020; Journal

420. Therapeutic Goods Information : Lovenox and Lovenox Forte Consumer Medicine Information. 2018;

421. Anticoagulation intermediate dose for COVID-19.

422. Anticoag VTE COV2.

423. Anticoagulation for COVID-19.

424. , , , Zarychanski R : Therapeutic Anticoagulation in Critically Ill Patients with Covid-19 – Preliminary Report. medRxiv 2021/01/01; 2021.03.10.21252749 Journal Website

425. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, et al. : Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA 2021; Pubmed Journal

426. Bikdeli B, Talasaz AH, Rashidi F, Bakhshandeh H, Rafiee F, Matin S, et al. : Intermediate vs standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to ICU: ninety-day results from the INSPIRATION Trial. Thrombosis and Haemostasis 2021; Pubmed Journal

427. Zarychanski R, on behalf of the REMAP-CAP, ACTIV-4a and ATTACC Investigators : Therapeutic Anticoagulation in Critically Ill Patients with COVID-19 - Preliminary Report. medRxiv 12 March 2021; Journal Website

428. Zaman S, MacIsaac AI, Jennings GL, Schlaich M, Inglis SC, Arnold R, et al. : Cardiovascular disease and COVID-19: Australian/New Zealand consensus statement. Medical Journal of Australia 2020; Website

429. High Blood Pressure Research Council of Australia : A statement on COVID-19 and blood pressure medication (ACE-inhibitors/ARBs). 2020; Website

430. Australian Diabetes Society : Australian Diabetes Society Communique for Diabetes Health Professionals regarding COVID-19 pandemic. 2020; Website

431. European Society of Cardiology Council on Hypertension : Position Statement of the ESC Council on Hypertension on ACE Inhibitors and Angiotensin Receptor Blockers. 2020; Website

432. International Pharmaceutical Federation : FIP position statement on the association between the use of non-steroidal anti-inflammatory medicines (including ibuprofen), ACE inhibitors, angiotensin receptor blockers (ARBs) and corticosteroids, and an increased risk of coronavirus/COVID-19 infection or disease severity. 2020; Website

433. Renal Association UK : Position statement on COVID-19 and ACE Inhibitor/Angiotensin Receptor Blocker use. 2020; Website

434. International Society of Hypertension : A statement from the International Society of Hypertension on COVID-19. 2020; Website

435. Sparks M, Hiremath S, South A, Welling P, Luther M, Cohen J, et al. : ACE2 and hypertension. Nephrology Journal Club 2020; Website

436. Hypertension Canada : Hypertension Canada's Statement on: Hypertension, ACE-Inhibitors and Angiotensin Receptor Blockers and COVID-19. 2020; Website

437. Canadian Cardiovascular Society : Guidance from the CCS COVID-19 rapid response team. 2020; Website

438. American College of Physicians : COVID-19: An ACP Physician's Guide. 2020; Website

439. Spanish Society of Hypertension : Comunicado Urgente COVID-19. 2020; Website

440. American Heart Association, Heart Failure Society of America and American College of Cardiology : Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician. 2020; Website

441. Australian Commission on Safety and Quality in Health Care : Position Statement ACE inhibitors and ARBs in COVID-19. 2020; Website

442. Mackey K, King VJ, Gurley S, Kiefer M, Liederbauer E, Vela K, et al. : Update Alert 4: Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults: a living systematic review. Annals of Internal Medicine 2020; Pubmed Journal

443. Flacco ME, Acuti Martellucci C, Bravi F, Parruti G, Cappadona R, Mascitelli A, et al. : Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart 2020; Pubmed Journal

444. Baral R, White M, Vassiliou VS : Effect of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients. Current Atherosclerosis Reports 2020;22(10):61 Pubmed Journal

445. Barochiner J, Martínez R : Use of inhibitors of the renin-angiotensin system in hypertensive patients and COVID-19 severity: a systematic review and meta-analysis. Journal of Clinical Pharmacy and Therapeutics 2020; Pubmed Journal

446. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, et al. : SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Australian & New Zealand Journal of Obstetrics & Gynaecology 2015;55(5):e1-29 Pubmed Journal

447. National Asthma Council : Managing asthma during the COVID-19 (SARS-CoV-2) pandemic. National Asthma Council 2020; Website

448. NICE : COVID-19 rapid guideline: community-based care of patients with chronic obstructive pulmonary disease (COPD) [NG168]. 2020; Website

449. NICE : COVID-19 rapid guideline: severe asthma [NG166]. 2020; Website

450. Therapeutic Goods Administration : Australian Product Information: Dexmethsone (dexamethasone) tablets. 2018; Website

451. Therapeutic Goods Administration : Australian Product Information: Predsolone (prednisolone) tablets. 2019; Website

452. COVIDSurg Collaborative, GlobalSurg Collaborative : Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia 2021; Pubmed Journal

453. El-Boghdadly K, Cook TM, Goodacre T, Kua J, Blake L, Denmark S, et al. : SARS-CoV-2 infection, COVID-19 and timing of elective surgery: A multidisciplinary consensus statement on behalf of the Association of Anaesthetists, the Centre for Peri-operative Care, the Federation of Surgical Specialty Associations, the Royal College of Anaesthetists and the Royal College of Surgeons of England. Anaesthesia 2021; Pubmed Journal

454. Kovoor JG, Scott NA, Tivey DR, Babidge WJ, Scott DA, Beavis VS, et al. : Proposed delay for safe surgery after COVID-19. ANZ Journal of Surgery 2021;91(4):495-506 Pubmed Journal

455. Roberts D, Brown J, Medley N, Dalziel SR : Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2017;3 CD004454 Pubmed Journal

456. Walker KF, O'Donoghue K, Grace N, Dorling J, Comeau JL, Li W, et al. : Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. BJOG : an international journal of obstetrics and gynaecology 2020; Pubmed Journal

457. Shah PS, Diambomba Y, Acharya G, Morris SK, Bitnun A : Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. Acta Obstetricia et Gynecologica Scandinavica 2020;99(5):565-568 Pubmed Journal

458. World Health Organization : Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2: scientific brief, 8 February 2021. Geneva: World Health Organization 2021; Website

459. McDonald SJ, Middleton P, Dowswell T, Morris PS : Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Evidence-Based Child Health : A Cochrane Review Journal 2014;9(2):303-97 Pubmed Journal

460. Rabe H, Gyte GM, Díaz-Rossello JL, Duley L : Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database of Systematic Reviews 2019;9 CD003248 Pubmed Journal

461. Mejía Jiménez I, Salvador López R, García Rosas E, Rodriguez de la Torre I, Montes García J, de la Cruz Conty ML, et al. : Umbilical cord clamping and skin-to-skin contact in deliveries from women positive for SARS-CoV-2: a prospective observational study. BJOG 2021;128(5):908-915 Pubmed Journal

462. Moore ER, Bergman N, Anderson GC, Medley N : Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database of Systematic Reviews 2016;11 CD003519 Pubmed Journal

463. McCall EM, Alderdice F, Halliday HL, Vohra S, Johnston L : Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2018;2 CD004210 Pubmed Journal

464. World Health Organization : Breastfeeding and COVID-19. 2020; Website

465. World Health Organization : Breastfeeding. Website

466. Centeno-Tablante E, Medina-Rivera M, Finkelstein JL, Rayco-Solon P, Garcia-Casal MN, Rogers L, et al. : Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review. Annals of the New York Academy of Sciences 2020; Pubmed Journal

467. Zhu F, Zozaya C, Zhou QI, De Castro C, Shah PS : SARS-CoV-2 genome and antibodies in breastmilk: a systematic review and meta-analysis. Archives of Disease in Childhood. Fetal and Neonatal edition 2021; Pubmed Journal

468. World Health Organization : Breastfeeding and COVID-19: scientific brief, 23 June 2020. Geneva: World Health Organization 2020; Website

469. Salvatore CM, Han J-Y, Acker KP, Tiwari P, Jin J, Brandler M, et al. : Neonatal management and outcomes during the COVID-19 pandemic: an observation cohort study. Lancet Child & Adolescent Health 2020; Pubmed Journal

470. Jaafar SH, Ho JJ, Lee KS : Rooming-in for new mother and infant versus separate care for increasing the duration of breastfeeding. Cochrane Database of Systematic Reviews 2016;(8):CD006641 Pubmed Journal

471. Murray EK, Ricketts S, Dellaport J : Hospital practices that increase breastfeeding duration: results from a population-based study. Birth 2007;34(3):202-11 Pubmed

472. Advice for clinicians: Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS). National Centre for Immunisation Research and Surveillance 2020; Website

473. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). CDC Health Alert Network 2020; Website

474. World Health Organization : Multisystem inflammatory syndrome in children and adolescents with COVID-19: scientific brief, 15 May 2020. Geneva: World Health Organization 2020; Website

475. Guidance - Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS). Royal College of Paediatrics and Child Health 2020; Website

476. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. : American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. Arthritis & Rheumatology 2020;

477. Hydroxychloroquine for COVID-19.

478. Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, et al. : A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child & Adolescent Health 2020; Pubmed Journal

479. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. : Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135(17):e927-e999 Pubmed Journal

480. Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, et al. : Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. JAMA 2021;325(9):855-864 Pubmed Journal

481. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A : Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. European Journal of Pediatrics 2020; Pubmed Journal

482. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. : Multisystem inflammatory syndrome in children: a systematic review. EClinicalMedicine 2020;26 100527 Pubmed Journal

483. Sivapalasingam S, Lederer D, Bhore R : A randomized placebo-controlled trial of sarilumab in hospitalized patients with COVID-19. medRxiv 2021; Journal Website

484. Hernandez-Cardenas C, Thirion-Romero I, Rivera-Martinez N : Hydroxychloroquine for the treatment of severe respiratory infection by COVID-19: A randomized controlled trial. medRxiv 2021; Journal Website

485. Gonzalez JLB, Gamez MG, Enciso EAM : Efficacy and safety of ivermectin and hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. medRxiv 23 February 2021; Journal Website

486. Amaravadi R, Giles L, Carberry M : Hydroxychloroquine for SARS-CoV-2 positive patients quarantined at home: The first interim analysis of a remotely conducted randomized trial. medRxiv 2021; Journal Website

487. Réa-Neto Á, Bernardelli RS, Câmara BMD, Reese FB, Queiroga MVO, Oliveira MC : An open-label randomized controlled trial evaluating the efficacy of chloroquine/hydroxychloroquine in severe COVID-19 patients. Scientific Reports 2021;11(1):9023 Pubmed Journal

488. Horby P, Campbell M, Spata E, on behalf of the RECOVERY Collaborative Group : Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randmised, controlled, open-label platform trial. medRxiv 2021; Journal Website

489. Tornling G, Batta R, Porter J, Bengtsson T, Parmar K, Kashiva R, et al. : The angiotensin type 2 receptor agonist C21 restores respiratory function in COVID19 - a double-blind, randomized, placebo-controlled Phase 2 trial. medRxiv 2021; Journal

490. Gunst JD, Staerke NB, Pahus MH, Kristensen LH, Bodilsen J, Lohse N, et al. : Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial. EClinicalMedicine 2021;35 100849 Pubmed Journal

491. Ader F, Peiffer-Smadja N, Poissy J, Bouscambert-Duchamp M, Belhadi D, Diallo A, et al. : An open-label randomized, controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19. Clinical Microbiology and Infection 2021; Pubmed Journal

492. Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, et al. : Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. Nature Communications 2021;12(1):3189 Pubmed Journal

493. N95/P2 versus Sx mask for Prevent SARS-CoV-2 transmission.

494. Tardif J-C, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, et al. : Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. Lancet Respiratory Medicine 2021; Pubmed Journal

495. [Intervention] for [COVID-19].

496. Therapeutic anticoagulation for COVID-19.

497. Ivermectin versus standard care for COVID-19.

498. Costanzo G, Firinu D, Losa F, Deidda M, Barca MP, Del Giacco S : Baricitinib exposure during pregnancy in rheumatoid arthritis. Therapeutic advances in musculoskeletal disease 2020;12 1759720X19899296 Pubmed Journal

499. Gerosa M, Argolini LM, Artusi C, Chighizola CB : The use of biologics and small molecules in pregnant patients with rheumatic diseases. Expert review of clinical pharmacology 2018;11(10):987-998 Pubmed Journal

500. Summary of Product Characteristics - Olumiant. Website

501. Australian Public Assessment Report for Sarilumab (rch). Australian Government Department of Health - Therapeutic Goods Administration 2018; Website

502. [Intervention] for [COVID-19].

503. [Intervention] for [COVID-19].

504. [Intervention] for [COVID-19].

505. [REGN-COV2] for [COVID-19].

506. [REGN-COV2] for [COVID-19].

507. [REGN-COV2] for [COVID-19].

508. [REGN-COV2] for [COVID-19].

509. [REGN-COV2] for [COVID-19].