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

NATIONAL
COVID-19
CLINICAL
EVIDENCE
TASKFORCE

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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 - Corticosteroids

6.1.1 - 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.

6.1.2 - 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.

6.1.3 - 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.

6.2 - Remdesivir

6.2.1 - 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 *[47]*. 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.

6.2.2 - 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 *[47]*. 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 to 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 *[42]*.

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.

6.2.3 - 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 *[42]*.

6.3 - Tocilizumab

Conditional recommendation New

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.

6.4 - 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.

6.5 - Hydroxychloroquine

Not recommended

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

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

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

6.6 - 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.

6.7 - 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.

6.8 - Disease-modifying treatments not recommended outside of clinical trials

6.8.1 - 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.

6.8.2 - 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.

6.8.3 - 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.

6.8.4 - Baricitinib

Not recommended

Do not use baricitinib 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 baricitinib for the treament COVID-19 in these populations unless they are eligible to be enrolled in trials.

6.8.5 - 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.

6.8.6 - 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.

6.8.7 - Colchicine

Not recommended

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

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

6.8.8 - 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.

6.8.9 - Convalescent plasma

Not recommended

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

Remark: The Taskforce notes the statement from the chief investigators of the RECOVERY trial on 11 January that found no significant difference in the primary endpoint of 28-day mortality in patients receiving convalescent plasma compared with usual care. The preliminary analysis is based on 1873 reported deaths among 10,406 randomised patients (RR 1.04 95% CI 0.95 to 1.14). Once the data have been published, an updated recommendation will be included in a future version of the guideline.

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

6.8.10 - 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.

6.8.11 - 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.

6.8.12 - 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.

6.8.13 - 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.

6.8.14 - 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.

6.8.15 - Hydroxychloroquine plus azithromycin

Not recommended

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

Remark: Hydroxychloroquine plus azithromycin 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 hydroxychloroquine plus azithromycin for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

6.8.16 - 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.

6.8.17 - 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.

6.8.18 - 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.

6.8.19 - 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.

6.8.20 - 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.

6.8.21 - 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.

6.8.22 - 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.

6.8.23 - 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.

6.8.24 - 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.

6.8.25 - 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.

6.8.26 - 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.

6.8.27 - 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.

6.8.28 - Sarilumab

Not recommended

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

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

The Taskforce notes the preprint of the adaptive, multicentre trial by Lescure et al., posted to medRxiv on 3 February, which randomised 420 patients with severe or critical COVID-19 to sarilumab (200 mg or 400 mg) or placebo. This study is currently under review and an updated recommendation will be included in a future version of the guideline.

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 sarilumab for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

6.8.29 - Sofosbuvir-daclatasvir

Not recommended Updated

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.

6.8.30 - Sulodexide

Not recommended New

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.

6.8.31 - 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.

6.8.32 - 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.

6.8.33 - 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.

6.8.34 - 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.

6.8.35 - 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.

6.9 - Disease-modifying treatments under review

6.9.1 - Anakinra

6.9.2 - Ivermectin plus doxycycline

6.9.3 - Nitazoxanide

6.9.4 - Zinc

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 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.

Consensus recommendation

Consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) in **adults with severe or critical COVID-19 or other indications**, unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 10^9/L. Where 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 40 mg once daily or dalteparin 5000 IU once daily).

Remark: For body weights outside 50-90 kg or heights outside 150-180 cm, calculate the 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.

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 Taskforce awaits publication of the relevant trial results to consider changes to the recommendations above.

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 - 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.

12.1 - 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.

12.2 - 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.

12.3 - 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.

12.4 - 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.

12.5 - 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.

12.6 - 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.

13 - 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.

13.1 - 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) *[381]*.

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 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.

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.

13.1.1 - Intravenous immunoglobulin

Consensus recommendation

Consider using intravenous immunoglobulin (2 g/kg per dose) in children and adolescents who meet PIMS-TS criteria or have features of Kawasaki disease related to COVID-19.

13.1.2 - Corticosteroids

Consensus recommendation

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

Remark: Intravenous 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.

In certain cases, Intravenous corticosteroids may be indicated as a first-line option in combination with intravenous immunoglobulin.

13.1.3 - 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.

13.1.4 - 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)

14 - 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 *[289]*.

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 professionals 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

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- [Vancouver style] National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. 2020 [version 35.1]. 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	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

		OR Other organ failure	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 *[289]*, National Institute for the Infectious Diseases (Italy) *[16]* and Surviving Sepsis Campaign *[287]*. 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 - Corticosteroids

6.1.1 - 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 panel believes that since there are mortality benefits most patients would opt for corticosteroids.

The Consumer Panel believes that most informed patients would agree with the recommendation and opt for this treatment.

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 *[23]* of seven randomised trials of patients with critical COVID-19 *[27][28][29][30][31][32][33]*, one study of patients with moderate, severe and critical COVID-19 *[34]*, and one study of patients with severe COVID-19 *[35]*. 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 *[24]* and sepsis *[25]*—provided indirect evidence for serious adverse events.

We have found two new studies comparing corticosteroids with standard care (Corral-Gudino et al. (GLUCOCOVID) Wien Klin Wochenschr doi: 10.1007/s00508-020-01805-8 and Tang et al. Respiration doi: 10.1159/000512063). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
Three studies compared dexamethasone with standard care *[32][30][34]*, three compared hydrocortisone with standard care *[31][29][27]* and three compared methylprednisolone with standard care *[28][33][35]*.

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**	**Absolute effect estimates** Standard care	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.
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	Relative risk 0.88 (CI 95% 0.79 - 0.97) Based on data from	320 per 1000	282 per 1000	**Moderate** Due to only one study [7]	Corticosteroids probably decrease invasive mechanical

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
death [adults requiring oxygen] [5] Within 28 days of commencing treatment 9 Critical	3,883 patients in 1 studies. [6] (Randomized controlled)	Difference: **38 fewer** per 1000 (CI 95% 67 fewer - 10 fewer)		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 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	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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain text summary
commencing treatment 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. [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 [21] with included studies: Steroids-SARI 2020, CAPE COVID 2020, CoDEX 2020, RECOVERY, DEXA-COVID 19 2020, COVID STEROID 2020, METCOVID 2020, REMAP-CAP 2020, RECOVERY, Edalatifard 2020. **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 [22] with included studies: Steroids-SARI 2020, REMAP-CAP 2020, CoDEX 2020, CAPE COVID 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.
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 [22] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: Serious.** Only data from one study.
8. Systematic review [21] with included studies: Edalatifard 2020, RECOVERY, RECOVERY. **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 [22] 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 [22] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Imprecision: Serious.** Only data from one study.
14. Systematic review [22] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Imprecision: Serious.** Only data from one study.
16. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
20. Systematic review [23] . **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.

The NC19CET Consumer Panel believes that informed patients 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 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 *[23]* of seven randomised trials of patients with critical COVID-19 *[27][28][29][30][31][32][33]*, one study of patients with moderate, severe and critical COVID-19 *[34]*, and one study of patients with severe COVID-19 *[35]*. 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 *[24]* and sepsis *[25]*—provided indirect evidence for serious adverse events.

We have found two new studies comparing corticosteroids with standard care (Corral-Gudino et al. (GLUCOCOVID)

Wien Klin Wochenschr doi: 10.1007/s00508-020-01805-8 and Tang et al. Respiration doi: 10.1159/000512063). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
Three studies compared dexamethasone with standard care *[32][30][34]*, three compared hydrocortisone with standard care *[31][29][27]* and three compared methylprednisolone with standard care *[28][33][35]*.

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**	**Absolute effect estimates** Standard care	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)	**Moderate** Due to some inconsistency [2]	Corticosteroids probably decrease death at day 28 in adults who require oxygen.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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)	**Moderate** Due to serious inconsistency [4]	Corticosteroids probably have little impact on serious adverse events in adults who require oxygen.
9 Critical **Invasive mechanical ventilation or death [adults requiring oxygen]** [5] Within 28 days of commencing treatment	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.
6 Important **Discharge from hospital [adults requiring oxygen]** Within 28 days of commencing treatment	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.
9 Critical **All-cause mortality [adults not requiring oxygen]** Within 28 days of commencing treatment	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**	**Absolute effect estimates** Standard care	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	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	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important		(CI 95% 10 fewer - 27 more)		
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 [21] with included studies: Steroids-SARI 2020, CAPE COVID 2020, CoDEX 2020, RECOVERY, DEXA-COVID 19 2020, COVID STEROID 2020, METCOVID 2020, REMAP-CAP 2020, RECOVERY, Edalatifard 2020. **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 [22] with included studies: Steroids-SARI 2020, REMAP-CAP 2020, CoDEX 2020, CAPE COVID 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.
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 [22] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: Serious.** Only data from one study.
8. Systematic review [21] with included studies: Edalatifard 2020, RECOVERY, RECOVERY. **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 [22] 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 [22] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Imprecision: Serious.** Only data from one study.
14. Systematic review [22] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Imprecision: Serious.** Only data from one study.
16. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
20. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.

6.1.2 - 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 panel believes that since there are mortality benefits most women would opt for dexamethasone.

The NC19CET Consumer Panel believes that most informed pregnant or breastfeeding women would agree with the recommendation.

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 *[23]* of seven randomised trials of patients with critical COVID-19 *[27][28][29][30][31][32][33]*, one study of patients with moderate, severe and critical COVID-19 *[34]* and one study of patients with severe COVID-19 *[35]*. 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 *[24]* and sepsis *[25]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[32][30][34]*, three compared hydrocortisone with standard care *[31][29][27]* and three compared methylprednisolone with standard care *[28][33][35]*.

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**	**Absolute effect estimates** Standard care	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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care — Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain text summary
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 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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain text summary
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 [36] with included studies: Steroids-SARI 2020, RECOVERY, RECOVERY, DEXA-COVID 19 2020, COVID STEROID 2020, CoDEX 2020, REMAP-CAP 2020, CAPE COVID 2020, Edalatifard 2020, METCOVID 2020. **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 [22] with included studies: COVID STEROID 2020, Steroids-SARI 2020, DEXA-COVID 19 2020, CoDEX 2020, REMAP-CAP 2020, CAPE COVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
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5. The number of patients with severe illness (i.e. who do not require mechanical ventilation at enrolment) that progress to requiring invasive mechanical ventilation or death within 28 days
6. Systematic review [22] 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 [22] 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.
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16. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
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18. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [36] with included studies: RECOVERY, Edalatifard 2020, RECOVERY. **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 NC19CET Consumer Panel also 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 *[23]* of seven randomised trials of patients with critical COVID-19 *[27][28][29][30][31][32][33]*, one study of patients with moderate, severe and critical COVID-19 *[34]* and one study of patients with severe COVID-19 *[35]*. 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 *[24]* and sepsis *[25]*—provided indirect evidence for serious adverse events.

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Three studies compared dexamethasone with standard care *[32][30][34]*, three compared hydrocortisone with standard care *[31][29][27]* and three compared methylprednisolone with standard care *[28][33][35]*.

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.

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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**	**Absolute effect estimates** Standard care Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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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 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care — Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 [36] with included studies: Steroids-SARI 2020, RECOVERY, RECOVERY, DEXA-COVID 19 2020, COVID STEROID 2020, CoDEX 2020, REMAP-CAP 2020, CAPE COVID 2020, Edalatifard 2020, METCOVID 2020.
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 [22] with included studies: COVID STEROID 2020, Steroids-SARI 2020, DEXA-COVID 19 2020, CoDEX 2020, REMAP-CAP 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. **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 [22] 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 [22] 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.
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11. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
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19. Systematic review [36] with included studies: RECOVERY, Edalatifard 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied.

6.1.3 - 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 panel believes that since there are mortality benefits most patients would opt for corticosteroids.

The NC19CET Consumer Panel believes that some informed patients (and their parents, carers, families and guardians) may prefer to wait until the available evidence is clearer, but most informed patients (and their parents/carers/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 *[23]* of seven randomised trials of patients with critical COVID-19 *[27][28][29][30][31][32][33]*, one study of patients with moderate, severe and critical COVID-19 *[34]* and one study of patients with severe COVID-19 *[35]*. 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 *[24]* and sepsis *[25]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[32][30][34]*, three compared hydrocortisone with standard care *[31][29][27]* and three compared methylprednisolone with standard care *[28][33][35]*.

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.

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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	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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Absolute effect estimates Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain text summary
after commencing treatment 9 Critical					
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 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 [36] with included studies: Steroids-SARI 2020, RECOVERY, RECOVERY, DEXA-COVID 19 2020, COVID STEROID 2020, CoDEX 2020, REMAP-CAP 2020, CAPE COVID 2020, Edalatifard 2020, METCOVID 2020. **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 [22] with included studies: COVID STEROID 2020, Steroids-SARI 2020, DEXA-COVID 19 2020, CoDEX 2020, REMAP-CAP 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. **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 [22] 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 [22] 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 [22] 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 [22] 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 [23] . **Baseline/comparator:** Control arm of reference used for intervention.
15. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [36] with included studies: RECOVERY, Edalatifard 2020, RECOVERY. **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 NC19CET 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 *[23]* of seven randomised trials of patients with critical COVID-19 *[27][28][29][30][31][32][33]*, one study of patients with moderate, severe and critical COVID-19 *[34]* and one study of patients with severe COVID-19 *[35]*. 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 *[24]* and sepsis *[25]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[32][30][34]*, three compared hydrocortisone with standard care *[31][29][27]* and three compared methylprednisolone with standard care *[28][33][35]*.

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**	**Absolute effect estimates** Standard care	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**	**Absolute effect estimates** Standard care 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 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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.
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	Relative risk 1.1 (CI 95% 1.06 - 1.15) Based on data from	582	640	**Low** Due to serious inconsistency	Corticosteroids may increase discharge from hospital in patients who

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
oxygen] Within 28 days of commencing treatment 6 Important	4,952 patients in 2 studies. [19] (Randomized controlled)	per 1000	per 1000 Difference: **58 more** per 1000 (CI 95% 35 more - 87 more)	and serious indirectness [20]	require oxygen.

1. Systematic review [36] with included studies: Steroids-SARI 2020, RECOVERY, RECOVERY, DEXA-COVID 19 2020, COVID STEROID 2020, CoDEX 2020, REMAP-CAP 2020, CAPE COVID 2020, Edalatifard 2020, METCOVID 2020. **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 [22] with included studies: COVID STEROID 2020, Steroids-SARI 2020, DEXA-COVID 19 2020, CoDEX 2020, REMAP-CAP 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. **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 [22] 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 [22] 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 [22] 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 [22] 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 [23] . **Baseline/comparator:** Control arm of reference used for intervention.
15. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [23] . **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [36] with included studies: RECOVERY, Edalatifard 2020, RECOVERY. **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 - Remdesivir

6.2.1 - 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 [47]. 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 panel believes that since there are probable mortality benefits most patients with COVID-19 who do not require ventilation would opt for remdesivir.

The Consumer Panel believes that most informed patients would agree with the recommendation and opt for this treatment.

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 *[47]*. 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 four randomised trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 *[39][40][43][46]*. 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 *[46][39]*.

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	584	*[43]*
Moderate-Critical	6513	*[39][46]*
Severe-Critical	236	*[40]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (25 fewer deaths per 1000 patients (RR 0.72, CI 95% 0.52 to 1.01; 6318 patients in 4 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 4 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 *[39]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[43]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[43]* or 6-point ordinal scale *[40]*.

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 was 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 *[42]*.

Pregnant and breastfeeding women
An additional observational study *[54]* was identified but did not meet inclusion criteria due to study design. The study included 86 pregnant and postpartum women in the USA with severe COVID-19 who received compassionate-use remdesivir. Median age of the women was 33 years (range 20 to 43) and the median gestational age was 29 weeks (range 14 to 39). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%, with the remaining 3% on room air at baseline. All postpartum women were in the ICU, as well as 67% of pregnant women.

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 (AE) were experienced by 29% of women and 16% had a serious AE. Examples of AEs experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to AEs, of which five had elevated liver enzymes concentrations, one had nausea and the other had haemoptysis.

The additional observational study is in line with the currently included 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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 0.72 (CI 95% 0.52 - 1.01) Based on data from 6,318 patients in 6 studies. [1] (Randomized controlled)	90 per 1000	65 per 1000 Difference: 25 fewer per 1000 (CI 95% 43 fewer - 1 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	Relative risk 1.2 (CI 95% 0.98 - 1.47) Based on data from 1,004 patients in 4 studies. [3] (Randomized	248 per 1000	298 per 1000 Difference: 50 more per 1000	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
treatment 9 Critical	controlled)	(CI 95% 5 fewer - 117 more)			
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).
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 - 1.2) Based on data from 4,964 patients in 1 studies. [9] (Randomized controlled)	115 per 1000	118 per 1000 Difference: **3 more** per 1000 (CI 95% 13 fewer - 23 more)	**Moderate** Only one study [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
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. [11] (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 [12]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Septic shock Within 28 days of commencing treatment	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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important					
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 5,451 patients in 1 studies. [21] (Randomized controlled)	720 per 1000	713 per 1000 Difference: **7 fewer** per 1000 (CI 95% 29 fewer - 22 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 [52] with included studies: Beigel 2020 lo-flow, Wang 2020, Beigel 2020 no O2, Spinner 2020, SOLIDARITY 2020 no O2, SOLIDARITY 2020 low/hi flow. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [52] with included studies: Wang 2020, Beigel 2020 Inv vent, SOLIDARITY 2020 ventilation, Beigel 2020 hi flow or NIV. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [48] with included studies: Wang 2020, Beigel 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 [48] 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 [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Serious.** Only data from one study.
11. Systematic review [48] with included studies: Wang 2020, Beigel 2020, Spinner 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. **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.
13. Systematic review [48] with included studies: Wang 2020, Beigel 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 [48] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 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 [48] with included studies: Beigel 2020, Spinner 2020, Spinner 2020, Wang 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 [48] with included studies: Spinner 2020, Spinner 2020, Beigel 2020, Wang 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 [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Imprecision: Serious.** Only data from one study.
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 *[41][43]*.

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 *[41]*, 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) *[41]*. 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 *[42]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Up to 10 days' treatment	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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Up to 10 days' treatment	5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Up to 10 days' treatment	5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 [45] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** due to few events.
3. Systematic review [45] 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 [45] 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 [45] 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 [45] 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 [45] with included studies: Spinner 2020, Goldman 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 [45] 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 [45] 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 [45] 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 [45] 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. Since there is a risk of harm to the patients, the panel believes most patients would not want this treatment.

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 four randomised trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 *[39][40][43][46]*. 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 *[46][39]*.

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	584	*[43]*
Moderate-Critical	6513	*[39][46]*
Severe-Critical	236	*[40]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (25 fewer deaths per 1000 patients (RR 0.72, CI 95% 0.52 to 1.01; 6318 patients in 4 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 4 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 *[39]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[43]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[43]* or 6-point ordinal scale *[40]*.

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 was 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 *[42]*.

Pregnant and breastfeeding women
An additional observational study *[54]* was identified but did not meet inclusion criteria due to study design. The study included 86 pregnant and postpartum women in the USA with severe COVID-19 who received compassionate-use remdesivir. Median age of the women was 33 years (range 20 to 43) and the median gestational age was 29 weeks (range 14 to 39). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%, with the remaining 3% on room air at baseline. All postpartum women were in the ICU, as well as 67% of pregnant women.

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 (AE) were experienced by 29% of women and 16% had a serious AE. Examples of AEs experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to AEs, of which five had elevated liver enzymes concentrations, one had nausea and the other had haemoptysis.

The additional observational study is in line with the currently included 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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 0.72 (CI 95% 0.52 - 1.01) Based on data from 6,318 patients in 6 studies. [1] (Randomized controlled)	90 per 1000	65 per 1000 Difference: **25 fewer** per 1000 (CI 95% 43 fewer - 1 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	Relative risk 0.57 (CI 95% 0.42 - 0.79) Based on data from 766 patients in 1 studies. [7]	225 per 1000	128 per 1000 Difference: **97 fewer** per 1000	**Low** Due to serious risk of bias and serious	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Within 28 days of commencing treatment 9 Critical	(Randomized controlled)	(CI 95% 131 fewer - 47 fewer)		imprecision [8]	
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 - 1.2) Based on data from 4,964 patients in 1 studies. [9] (Randomized controlled)	115 per 1000	118 per 1000 Difference: 3 more per 1000 (CI 95% 13 fewer - 23 more)	**Moderate** Only one study [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
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. [11] (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 [12]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 5,451 patients in 1 studies. [21] (Randomized controlled)	720 per 1000	713 per 1000 Difference: **7 fewer** per 1000 (CI 95% 29 fewer - 22 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 [52] with included studies: Beigel 2020 lo-flow, Wang 2020, Beigel 2020 no O2, Spinner 2020, SOLIDARITY 2020 no O2, SOLIDARITY 2020 low/hi flow. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [52] with included studies: Wang 2020, Beigel 2020 Inv vent, SOLIDARITY 2020 ventilation, Beigel 2020 hi flow or NIV. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [48] with included studies: Wang 2020, Beigel 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 [48] 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 [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference

used for intervention.
10. **Imprecision: Serious.** Only data from one study.
11. Systematic review [48] with included studies: Wang 2020, Beigel 2020, Spinner 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. **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.
13. Systematic review [48] with included studies: Wang 2020, Beigel 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 [48] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 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 [48] with included studies: Beigel 2020, Spinner 2020, Spinner 2020, Wang 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 [48] with included studies: Spinner 2020, Spinner 2020, Beigel 2020, Wang 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 [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Imprecision: Serious.** Only data from one study.
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.

6.2.2 - 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 [47]. 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 to 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 [42].

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 *[54]*.

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. 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.

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 the 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 *[47]*. 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 four randomised trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 *[39][40][43][46]*. 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 *[46][39]*.

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	584	*[43]*
Moderate-Critical	6513	*[39][46]*
Severe-Critical	236	*[40]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (25 fewer deaths per 1000 patients (RR 0.72, CI 95% 0.52 to 1.01; 6318 patients in 4 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 4 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 *[39]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[43]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[43]* or 6-point ordinal scale *[40]*.

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 was 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 *[42]*.

Pregnant and breastfeeding women
An additional observational study *[54]* was identified but did not meet inclusion criteria due to study design. The study included 86 pregnant and postpartum women in the USA with severe COVID-19 who received compassionate-use remdesivir. Median age of the women was 33 years (range 20 to 43) and the median gestational age was 29 weeks (range 14 to 39). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%, with the remaining 3% on room air at baseline. All postpartum women were in the ICU, as well as 67% of pregnant women.

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 (AE) were experienced by 29% of women and 16% had a serious AE. Examples of AEs experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to AEs, of which five had elevated liver enzymes concentrations, one had nausea and the other had haemoptysis.

The additional observational study is in line with the currently included 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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 0.72 (CI 95% 0.52 - 1.01) Based on data from 6,318 patients in 6 studies. [1] (Randomized controlled)	90 per 1000	65 per 1000 Difference: 25 fewer per 1000 (CI 95% 43 fewer - 1 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**	**Absolute effect estimates** Standard care	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).
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 - 1.2) Based on data from 4,964 patients in 1 studies. [9] (Randomized controlled)	115 per 1000	118 per 1000 Difference: 3 more per 1000 (CI 95% 13 fewer - 23 more)	**Moderate** Only one study [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
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. [11] (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 [12]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
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	Relative risk 0.75 (CI 95% 0.63 - 0.89) Based on data from	253	190	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	1,865 patients in 3 studies. [15] (Randomized controlled)	per 1000	per 1000 Difference: **63 fewer** per 1000 (CI 95% 94 fewer - 28 fewer)		(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 5,451 patients in 1 studies. [21] (Randomized controlled)	720 per 1000	713 per 1000 Difference: **7 fewer** per 1000 (CI 95% 29 fewer - 22 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 [52] with included studies: Beigel 2020 lo-flow, Wang 2020, Beigel 2020 no O2, Spinner 2020, SOLIDARITY 2020 no O2, SOLIDARITY 2020 low/hi flow. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [52] with included studies: Wang 2020, Beigel 2020 Inv vent, SOLIDARITY 2020 ventilation,

Beigel 2020 hi flow or NIV. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [48] with included studies: Wang 2020, Beigel 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 [48] 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 [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Serious.** Only data from one study.
11. Systematic review [48] with included studies: Wang 2020, Beigel 2020, Spinner 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. **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.
13. Systematic review [48] with included studies: Wang 2020, Beigel 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 [48] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 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 [48] with included studies: Beigel 2020, Spinner 2020, Spinner 2020, Wang 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 [48] with included studies: Spinner 2020, Spinner 2020, Beigel 2020, Wang 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 [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Imprecision: Serious.** Only data from one study.
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: Special populations with COVID-19 [adapted from general adult population]
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 *[41][43]*.

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 low for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is very low for death within 28 days, acute respiratory failure or ARDS, clinical recovery within 14 days, septic shock and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation *[41]*, lack of blinding), serious imprecision (too few who died), serious indirectness (exclusion or absence of children, adolescents and pregnant women) 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) *[41]*. 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 *[42]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Up to 10 days' treatment	5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 14 days of commencing treatment	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)	**Low** Due to serious imprecision and indirectness [2]	Remdesivir 5-day treatment probably has little impact on death (40 events).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Up to 10 days' treatment	5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical					
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)			**Very Low** Due to very serious imprecision and serious indirectness [4]	We are uncertain whether remdesivir 5-day treatment increases or decreases death at 28 days (5 events).
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)			**Very Low** Due to very serious imprecision and serious indirectness [6]	We are uncertain whether remdesivir 5-day treatment decreases acute respiratory failure or ARDS (34 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 and serious indirectness [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)			**Very Low** Due to serious risk of bias, imprecision and indirectness [10]	We are uncertain whether remdesivir 5-day treatment improves clinical recovery (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)	**Low** Due to serious risk of bias and indirectness [12]	Remdesivir 5-day treatment may decrease serious adverse events slightly (129 events).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Up to 10 days' treatment	5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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)	**Low** Due to serious risk of bias and indirectness [14]	Remdesivir 5-day treatment may have little impact on 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)			**Very Low** Due to serious risk of bias, imprecision and indirectness [16]	We are uncertain whether remdesivir 5-day treatment has any impact impact on discontinuation due to adverse event (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)	**Low** Due to serious risk of bias and indirectness [18]	Remdesivir 5-day treatment may have little impact on 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)			**Very Low** Due to very serious imprecision and indirectness [20]	We are uncertain whether remdesivir 5-day treatment has any impact on number of patients discharged from hospital at day 28 (344 events).

1. Systematic review [45] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** due to few events.
3. Systematic review [45] with included studies: Spinner 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 [45] with included studies: Goldman 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 [45] with included studies: Goldman 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 [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
11. Systematic review [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied.
13. Systematic review [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied.
15. Systematic review [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** due to few events.
17. Systematic review [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied.
19. Systematic review [45] with included studies: Spinner 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.** 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. Since there is a risk of harm, the panel believes most pregnant and breastfeeding women would not want this treatment.

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 four randomised trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 *[39][40][43][46]*. 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 *[46][39]*.

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	584	*[43]*
Moderate-Critical	6513	*[39][46]*
Severe-Critical	236	*[40]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (25 fewer deaths per 1000 patients (RR 0.72, CI 95% 0.52 to 1.01; 6318 patients in 4 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 4 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 *[39]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[43]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[43]* or 6-point ordinal scale *[40]*.

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 was 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 *[42]*.

Pregnant and breastfeeding women
An additional observational study *[54]* was identified but did not meet inclusion criteria due to study design. The study included 86 pregnant and postpartum women in the USA with severe COVID-19 who received compassionate-use remdesivir. Median age of the women was 33 years (range 20 to 43) and the median gestational age was 29 weeks (range 14 to 39). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%, with the remaining 3% on room air at baseline. All postpartum women were in the ICU, as well as 67% of pregnant women.

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 (AE) were experienced by 29% of women and 16% had a serious AE. Examples of AEs experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to AEs, of which five had elevated liver enzymes concentrations, one had nausea and the other had haemoptysis.

The additional observational study is in line with the currently included 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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 0.72 (CI 95% 0.52 - 1.01) Based on data from 6,318 patients in 6 studies. [1] (Randomized controlled)	90 per 1000	65 per 1000 Difference: 25 fewer per 1000 (CI 95% 43 fewer - 1 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 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).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain text summary
9 Critical **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).
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 - 1.2) Based on data from 4,964 patients in 1 studies. [9] (Randomized controlled)	115 per 1000	118 per 1000 Difference: **3 more** per 1000 (CI 95% 13 fewer - 23 more)	**Moderate** Only one study [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
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. [11] (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 [12]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
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	Absolute effect estimates Standard care	 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 5,451 patients in 1 studies. [21] (Randomized controlled)	720 per 1000	713 per 1000 Difference: **7 fewer** per 1000 (CI 95% 29 fewer - 22 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 [52] with included studies: Beigel 2020 lo-flow, Wang 2020, Beigel 2020 no O2, Spinner 2020, SOLIDARITY 2020 no O2, SOLIDARITY 2020 low/hi flow. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Wide confidence intervals.
3. Systematic review [52] with included studies: Wang 2020, Beigel 2020 Inv vent, SOLIDARITY 2020 ventilation, Beigel 2020 hi flow or NIV. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [48] with included studies: Wang 2020, Beigel 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 [48] 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 [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Serious.** Only data from one study.
11. Systematic review [48] with included studies: Wang 2020, Beigel 2020, Spinner 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. **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.
13. Systematic review [48] with included studies: Wang 2020, Beigel 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 [48] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 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 [48] with included studies: Beigel 2020, Spinner 2020, Spinner 2020, Wang 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 [48] with included studies: Spinner 2020, Spinner 2020, Beigel 2020, Wang 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 [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Imprecision: Serious.** Only data from one study.
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.

6.2.3 - 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 [42].

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 *[55]*:

- 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.
[39][41][43]

Clinical Question/ PICO

Population: Special populations with COVID-19 [adapted from general adult population]
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 *[41][43]*.

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 low for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is very low for death within 28 days, acute respiratory failure or ARDS, clinical recovery within 14 days, septic shock and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation *[41]*, lack of blinding), serious imprecision (too few who died), serious indirectness (exclusion or absence of children, adolescents and pregnant women) 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) *[41]*. 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 *[42]*.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Up to 10 days' treatment	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)	**Low** Due to serious imprecision and indirectness [2]	Remdesivir 5-day treatment probably has little impact on death (40 events).
All-cause	Relative risk 0.67			**Very Low**	We are uncertain

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Up to 10 days' treatment	5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
mortality Within 28 days of commencing treatment 9 Critical	(CI 95% 0.11 - 3.99) Based on data from 384 patients in 1 studies. [3] (Randomized controlled)			Due to very serious imprecision and serious indirectness [4]	whether remdesivir 5-day treatment increases or decreases death at 28 days (5 events).
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)			**Very Low** Due to very serious imprecision and serious indirectness [6]	We are uncertain whether remdesivir 5-day treatment decreases acute respiratory failure or ARDS (34 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 and serious indirectness [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)			**Very Low** Due to serious risk of bias, imprecision and indirectness [10]	We are uncertain whether remdesivir 5-day treatment improves clinical recovery (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)	**Low** Due to serious risk of bias and indirectness [12]	Remdesivir 5-day treatment may decrease 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)	**Low** Due to serious risk of bias and indirectness [14]	Remdesivir 5-day treatment may have little impact on adverse events (503 events).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Up to 10 days' treatment	5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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)			**Very Low** Due to serious risk of bias, imprecision and indirectness [16]	We are uncertain whether remdesivir 5-day treatment has any impact impact on discontinuation due to adverse event (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)	**Low** Due to serious risk of bias and indirectness [18]	Remdesivir 5-day treatment may have little impact on 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)			**Very Low** Due to very serious imprecision and indirectness [20]	We are uncertain whether remdesivir 5-day treatment has any impact on number of patients discharged from hospital at day 28 (344 events).

1. Systematic review [45] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** due to few events.
3. Systematic review [45] with included studies: Spinner 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 [45] with included studies: Goldman 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 [45] with included studies: Goldman 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 [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.

11. Systematic review [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied.
13. Systematic review [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied.
15. Systematic review [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** due to few events.
17. Systematic review [45] 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. **Indirectness: Serious.** Differences between the population of interest and those studied.
19. Systematic review [45] with included studies: Spinner 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.** Low number of patients, Only data from one study.

Clinical Question/ PICO

Population: Children and adolescents with COVID-19 (based on adult population)
Intervention: Remdesivir
Comparator: Standard care

Summary

Evidence indicates that remdesivir probably reduces the incidence of death in hospitalised adults not requiring ventilation and increases the incidence of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?
Evidence comes from four randomised trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 *[39][40][43][46]*. 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 *[46][39]*.

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	584	*[43]*
Moderate-Critical	6513	*[39][46]*

Severe-Critical	236	*[40]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (25 fewer deaths per 1000 patients (RR 0.72, CI 95% 0.72 (CI 95% 0.52 to 1.01; 6318 patients in 4 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 4 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 *[39]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[43]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[43]* or 6-point ordinal scale *[40]*.

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 was 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 *[42]*.

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 recruting children.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality [hospital, no ventilation]	Relative risk 0.72 (CI 95% 0.52 - 1.01) Based on data from 6,318 patients in 6 studies. [1] (Randomized	90 per 1000	65 per 1000 Difference: **25 fewer** per 1000	**Low** Due to serious imprecision, Due to serious	Remdesivir may decrease all-cause mortality slightly in hospitalised patients who do not require

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Within 28 days after commencing treatment 9 Critical	controlled)	(CI 95% 43 fewer - 1 more)		indirectness [2]	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)	**Low** Due to serious imprecision, Due to serious indirectness [4]	Remdesivir may increase all-cause mortality 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)	**Very Low** Due to serious inconsistency and serious imprecision, Due to serious indirectness [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)	**Very Low** Due to serious risk of bias and serious imprecision, Due to serious indirectness [8]	We are uncertain whether remdesivir improves or worsen invasive mechanical ventilation or ECMO (134 events).
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 - 1.2) Based on data from 4,964 patients in 1 studies. [9] (Randomized controlled)	115 per 1000	118 per 1000 Difference: **3 more** per 1000 (CI 95% 13 fewer - 23 more)	**Low** Only one study, Due to serious indirectness [10]	Remdesivir may have little or no difference on number patients requiring ventilation.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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. [11] (Randomized controlled)	711 per 1000	704 per 1000 Difference: 7 fewer per 1000 (CI 95% 100 fewer - 100 more)	Very Low Due to serious risk of bias and serious inconsistency, Due to serious indirectness [12]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
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)	Very Low Due to serious risk of bias and serious inconsistency, Due to serious indirectness [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)	Low Due to serious risk of bias, Due to serious indirectness [16]	Remdesivir may decrease 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)	Very Low Due to serious risk of bias and serious inconsistency, Due to serious indirectness [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)	Very Low Due to serious risk of bias and serious imprecision, Due to serious indirectness [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 5,451 patients in 1 studies. [21] (Randomized controlled)	720 per 1000	713 per 1000 Difference: 7 fewer per 1000 (CI 95% 29 fewer - 22 more)	Low Due to serious imprecision, Due to serious indirectness [22]	Remdesivir may have little or no difference on discharge from hospital.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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)			**Low** Due to serious risk of bias, Due to serious indirectness [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)			**Low** Due to serious risk of bias, Due to serious indirectness [24]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [52] with included studies: Wang 2020, Spinner 2020, Beigel 2020 no O2, SOLIDARITY 2020 no O2, SOLIDARITY 2020 low/hi flow, Beigel 2020 lo-flow. **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 [52] with included studies: SOLIDARITY 2020 ventilation, Beigel 2020 hi flow or NIV, Wang 2020, Beigel 2020 Inv vent. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [48] 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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [48] 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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Low number of patients, Only data from one study.
9. Systematic review [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
11. Systematic review [48] with included studies: Beigel 2020, Wang 2020, Spinner 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. **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. **Indirectness: Serious.** Differences between the population of interest and those studied.
13. Systematic review [48] with included studies: Wang 2020, Beigel 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. **Indirectness: Serious.** Differences between the population of interest and those studied.
15. Systematic review [48] with included studies: Spinner 2020, Wang 2020, Spinner 2020, Beigel 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.
17. Systematic review [48] with included studies: Beigel 2020, Wang 2020, Spinner 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. **Indirectness: Serious.** Differences between the population of interest and those studied.
19. Systematic review [48] with included studies: Spinner 2020, Spinner 2020, Wang 2020, Beigel 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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.
21. Systematic review [48] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
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. **Indirectness: Serious.** Differences between the population of interest and those studied.
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. **Indirectness: Serious.** Differences between the population of interest and those studied.

6.3 - Tocilizumab

Conditional recommendation

New

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 *[77]*.

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

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 (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).

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: 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 nine randomised trials that compared tocilizumab with standard care in 6390 adults hospitalised with COVID-19 *[58][61][62][64][65][74][76][78][79]*. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate to critical COVID-19 *[76]*. 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 *[78]*. 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 *[79]*, 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. *[74]*, 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.

Publication status
Two studies are only available as preprints (Wang et al. posted to SSRN on 29 August 2020 *[58]* and Horby et al. (RECOVERY) posted to medRxiv on 11 February 2021 *[76]*) and have therefore not been peer reviewed.

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	*[58][61][62][64][65]*
Moderate-Critical	4683	*[74][76][79]*
Critical	755	*[78]*

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 (26 fewer deaths per 1000 patients; RR 0.80, 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 *[59]*. 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**	**Absolute effect estimates** Standard care	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)	**Moderate** Due to serious inconsistency [2]	Tocilizumab probably decreases death slightly.
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)	**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 0.88 (CI 95% 0.74 - 1.05) Based on data from 2,129 patients in 7 studies. [6] (Randomized controlled)	161 per 1000	142 per 1000 Difference: **19 fewer** per 1000 (CI 95% 42 fewer - 8 more)	**Moderate** Due to serious imprecision [7]	Tocilizumab probably has little impact on serious adverse events (366 events).
Adverse events End of follow-up	Relative risk 1.03 (CI 95% 0.82 - 1.28)	504	519	**Moderate** Due to serious	Tocilizumab probably has little impact on adverse

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	 Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	Based on data from 1,382 patients in 6 studies. [8] (Randomized controlled)	per 1000	per 1000 Difference: **15 more** per 1000 (CI 95% 91 fewer - 141 more)	imprecision [9]	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 0.68 (CI 95% 0.51 - 0.9) Based on data from 520 patients in 3 studies. [12] (Randomized controlled)	**300** per 1000	**204** per 1000 Difference: **96 fewer** per 1000 (CI 95% 147 fewer - 30 fewer)	**Moderate** Due to serious imprecision [13]	Tocilizumab probably decreases 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. [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	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**	**Absolute effect estimates** Standard care	Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important					
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 [75] with included studies: Veiga 2021, Stone 2020, RECOVERY [total], Hermine 2020, Rosas 2020, REMAP-CAP tocilizumab, Salvarini 2020, Salama 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: Serious.**

3. Systematic review [75] with included studies: Stone 2020, Rosas 2020, RECOVERY [total]. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [60] 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 [73] with included studies: Veiga 2021, Hermine 2020, Wang 2020, Stone 2020, Salama 2020, Rosas 2020, REMAP-CAP tocilizumab. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: Serious.** Wide confidence intervals.
8. Systematic review [73] with included studies: Hermine 2020, Stone 2020, Veiga 2021, Rosas 2020, Wang 2020, Salama 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Imprecision: Serious.** Wide confidence intervals.
10. Systematic review [63] 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 [63] with included studies: Rosas 2020, Salvarini 2020, Hermine 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Imprecision: Serious.** Wide confidence intervals.
14. Systematic review [75] with included studies: Hermine 2020, Salvarini 2020, RECOVERY [total], Stone 2020. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Imprecision: Serious.** Wide confidence intervals.
16. Systematic review [60] 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 [60] 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 [63] with included studies: Salvarini 2020, Stone 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 [60] . **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 [60] . **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 [73] 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.

6.4 - 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 *[83]*

Pregnant and breastfeeding women
Azithromycin has only been taken by a limited number of pregnant women and women of childbearing age, and it's 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 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 opt for the 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.

The Consumer Panel believes that as this treatment has shown no clear benefits, informed patients may 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
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

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 four randomised trials that compared azithromycin with standard care in over 8600 adults hospitalised with COVID-19 *[81][82][86][104]*. The vast majority of data are from the RECOVERY trial, which included 7763 adults hospitalised with moderate-to-critical COVID-19 *[86]*. Two other trials compared azithromycin plus hydroxychloroquine with hydroxychloroquine alone in 397 adults hospitalised with severe or critical COVID-19 *[81]* and 331 with moderate COVID-19 *[104]*, and a further trial compared azithromycin plus hydroxychloroquine and lopinavir-ritonavir with hydroxychloroquine and lopinavir-ritonavir alone in 111 adults hospitalised with severe COVID-19 *[82]*.

We have found one new study comparing azithromycin with standard care (Rashad et al. Res Sq doi: 10.21203/rs.3.rs-181996/v1). This study is currently under review and an updated recommendation will be included 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; 8272 patients in 3 studies)) and probably has little impact on the number of patients requiring mechanical ventilation or ECMO (3 fewer per 1000 patients (RR 0.95, CI 95% 0.79 to 1.15; 7312 patients in 1 study)).

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 *[83]*.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care — 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 8,272 patients in 3 studies. [1] (Randomized controlled)	198 per 1000 — 200 per 1000 Difference: 2 more per 1000 (CI 95% 16 fewer - 20 more)	High	Azithromycin has no impact on death.
Mechanical ventilation or ECMO [2] Within 28 days of commencing treatment 9 Critical	Relative risk 0.95 (CI 95% 0.79 - 1.15) Based on data from 7,312 patients in 1 studies. [3] (Randomized controlled)	67 per 1000 — 64 per 1000 Difference: 3 fewer per 1000 (CI 95% 14 fewer - 10 more)	Moderate Due to serious imprecision [4]	Azithromycin probably has little impact on number of patients requiring mechanical ventilation or ECMO (479 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. [5] (Randomized controlled)	194 per 1000 — 219 per 1000 Difference: 25 more per 1000 (CI 95% 19 fewer - 81 more)	Moderate Due to serious imprecision [6]	Azithromycin probably increases number of patients experiencing serious adverse events.
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. [7] (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 [8]	Azithromycin may increase number of patients experiencing adverse events slightly (161 events).
Clinical progression (ICU admission) Within 15 days of commencing treatment 6 Important	Relative risk 0.28 (CI 95% 0.06 - 1.29) Based on data from 111 patients in 1 studies. [9] (Randomized controlled)	127 per 1000 — 36 per 1000 Difference: 91 fewer per 1000 (CI 95% 119 fewer - 37 more)	Low Due to very serious imprecision [10]	We are uncertain whether azithromycin increases or decreases clinical progression (ICU admission) (9 events).
Discharge from hospital Within 28 days of commencing treatment	Relative risk 0.92 (CI 95% 0.71 - 1.19) Based on data from 8,161 patients in 2 studies. [11] (Randomized controlled)	586 per 1000 — 539 per 1000 Difference: 47 fewer per 1000 (CI 95% 170 fewer - 111 more)	Moderate Due to serious imprecision [12]	Azithromycin probably decreases discharge from hospital slightly (4765 events).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important					
Duration of hospital stay Mean 6 Important	Based on data from: 442 patients in 2 studies. [13] (Randomized controlled)	Difference: MD 0.41 lower (CI 95% 2.42 lower - 1.59 higher)		**Low** Due to serious inconsistency and imprecision [14]	Azithromycin may have little impact on duration of hospital stay.
Duration of hospital stay [15] 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 [16]	Azithromycin probably makes little difference to duration of hospital stay.

1. Systematic review [85] with included studies: Furtado 2020, Horby 2020, Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Number of patients requiring mechanical ventilation or ECMO who weren't already requiring such support at enrolment.
3. Systematic review [85] with included studies: Horby 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Only data from one study.
5. Systematic review [80] with included studies: Cavalcanti 2020, Furtado 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Serious.** Wide confidence intervals.
7. Systematic review [80] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals.
9. Systematic review [80] with included studies: Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very Serious.** Low number of patients, Only data from one study, due to few events.
11. Systematic review [85] with included studies: Furtado 2020, Horby 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Serious.** Wide confidence intervals.
13. Systematic review [80] with included studies: Cavalcanti 2020, Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Imprecision: Serious.** Wide confidence intervals.
15. No IQR or 95% CI reported for Horby (2020)
16. **Imprecision: Serious.** Only data from one study.

6.5 - Hydroxychloroquine

Not recommended

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

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

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

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 panel believes that patients would not choose hydroxychloroquine because of the well-known harms (with potentially severe adverse events) and uncertainty regarding benefit.

The NC19CET 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 15 randomised trials that compared hydroxychloroquine with standard care in over 9000 patients (see table for references). The majority of evidence is from the RECOVERY trial, which randomised 4716 patients hospitalised with COVID-19 *[110]*.

We have found five new studies comparing hydroxychloroquine with placebo or standard care (Omrani et al. EClinMed doi: 10.1016/j.eclinm.2020.100645, Johnston et al. SSRN id=3745831, Ader et al. medRxiv doi: 10.1101/2021.01.08.20248149, Hernandez-Cardenas et al. medRxiv doi: 10.1101/2021.02.01.21250371 and Beltran-Gonzalez et al. medRxiv doi: 10.1101/2021.02.18.21252037v1). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

Publication status
Three studies, which contribute 339 patients to the results, are only available as preprints and have therefore not been peer reviewed *[91][97][113]*.

Study characteristics
Mean or median age across the trials ranged from 39 to 66 years, with the exception of one study in which the median age was 77 years *[113]*. The proportion of women ranged from 20 to 72%. In the two largest trials (accounting for nearly three-quarters of the data) 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	776	*[98][99]*
Mild-Moderate	612	*[104][113][116]*
Moderate	122	*[90][91][97]*
Mild-Moderate-Severe	2676	*[46][94][106][115]*

Moderate-Severe	4881	*[107][109][110]*

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, 13 more are likely to die compared with those receiving standard care (RR 1.07, CI 95% 0.98 to 1.18; 8767 patients in 11 studies) and 3 more are likely to require mechanical ventilation (RR 1.04, CI 95% 0.87 to 1.24; 5596 patients in 7 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, with 252 more patients per 1000 experiencing one or more adverse events with hydroxychloroquine compared with standard care (RR 2.02, CI 95% 1.24 to 3.28; 1752 patients in 9 studies). Since serious adverse events were rare, hydroxychloroquine may make little or no difference compared with standard care (70 events; 2126 patients in 9 studies; 2 fewer per 1000 with hydroxychloroquine (RR 0.94, CI 95% 0.59 to 1.48)).

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 *[95]*. There are several known and potential interactions with other drugs *[95]*. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms *[95]*.

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 *[100][101]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[100][101][102]*. 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**	**Absolute effect estimates** Standard care	Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk 1.07 (CI 95% 0.98 - 1.18) Based on data from	180	193	**High**	Hydroxychloroquine does not decrease death.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
End of follow-up 9 Critical	8,767 patients in 11 studies. [1] (Randomized controlled)	per 1000 per 1000 Difference: **13 more** per 1000 (CI 95% 4 fewer - 32 more)		
Invasive mechanical ventilation or ECMO End of follow-up 9 Critical	Relative risk 1.04 (CI 95% 0.87 - 1.24) Based on data from 5,596 patients in 7 studies. [2] (Randomized controlled)	**84** per 1000 **87** per 1000 Difference: **3 more** per 1000 (CI 95% 11 fewer - 20 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 0.94 (CI 95% 0.59 - 1.48) Based on data from 2,126 patients in 9 studies. [6] (Randomized controlled)	**34** per 1000 **32** per 1000 Difference: **2 fewer** per 1000 (CI 95% 14 fewer - 16 more)	**Moderate** Due to serious risk of bias [7]	Hydroxychloroquine probably has little impact on serious adverse events (70 events).
Adverse events End of follow-up 6 Important	Relative risk 2.02 (CI 95% 1.24 - 3.28) Based on data from 1,752 patients in 9 studies. [8] (Randomized controlled)	**247** per 1000 **499** per 1000 Difference: **252 more** per 1000 (CI 95% 59 more - 563 more)	**Moderate** Due to serious risk of bias [9]	Hydroxychloroquine probably increases adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.94 (CI 95% 0.36 - 10.37) Based on data from 244 patients in 1 studies. [10] (Randomized controlled)	**17** per 1000 **33** per 1000 Difference: **16 more** per 1000 (CI 95% 11 fewer - 159 more)	**Low** Due to very serious imprecision [11]	We are uncertain whether hydroxychloroquine decreases or increases treatment discontinuation due to adverse events (6 events).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care — Hydroxychloroquine	Certainty of the Evidence (Quality of evidence)	Plain text summary
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. [12] (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 [13]	We are uncertain whether hydroxychloroquine improves or worsens clinical improvement (191 events).
Clinical deterioration Within 28 days after commencing treatment 6 Important	Relative risk 0.81 (CI 95% 0.35 - 1.89) Based on data from 247 patients in 1 studies. [14] (Randomized controlled)	89 per 1000 — 72 per 1000 Difference: **17 fewer** per 1000 (CI 95% 58 fewer - 79 more)	**Low** Due to very serious imprecision [15]	We are uncertain whether hydroxychloroquine improves or worsens clinical deterioration (20 events).
Virological clearance (negative PCR) Day 7-10 of treatment 6 Important	Relative risk 0.94 (CI 95% 0.78 - 1.14) Based on data from 383 patients in 3 studies. [16] (Randomized controlled)	374 per 1000 — 352 per 1000 Difference: **22 fewer** per 1000 (CI 95% 82 fewer - 52 more)	**Low** Due to very serious imprecision [17]	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% 0.95 - 1.01) Based on data from 7,295 patients in 4 studies. [18] (Randomized controlled)	692 per 1000 — 678 per 1000 Difference: **14 fewer** per 1000 (CI 95% 35 fewer - 7 more)	**High**	Hydroxychloroquine has little impact on discharge from hospital.
Hospitalisation End of follow-up 6 Important	Relative risk 0.53 (CI 95% 0.26 - 1.07) Based on data from 716 patients in 2 studies. [19] (Randomized controlled)	61 per 1000 — 32 per 1000 Difference: **29 fewer** per 1000 (CI 95% 45 fewer - 4 more)	**Low** Due to serious imprecision and serious risk of bias [20]	We are uncertain whether hydroxychloroquine decreases or increases hospitalisation (33 events).
Duration of hospital stay Days 6 Important	Based on data from: 128 patients in 1 studies. [21] (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 [22]	We are uncertain whether hydroxychloroquine increases or decreases duration of hospital stay.

1. Systematic review [114] with included studies: Chen J 2020, Cavalcanti 2020, Mitja 2020, Abd-Elsalam 2020, Self 2020, Skipper 2020, Horby 2020, Ulrich 2020, Dubee 2020, Chen L 2020, Pan 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [114] with included studies: Ulrich 2020, Abd-Elsalam 2020, Mitja 2020, Dubee 2020, Horby 2020, Self 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 [108] 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 [114] with included studies: Mitja 2020, Cavalcanti 2020, Chen L 2020, Skipper 2020, Self 2020, Tang 2020, Dubee 2020, Chen Z 2020, Lyngbakken 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.
8. Systematic review [111] with included studies: Chen J 2020, Chen Z 2020, Tang 2020, Cavalcanti 2020, Mitja 2020, Ulrich 2020, Dubee 2020, Chen L 2020, Skipper 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.
10. Systematic review [112] with included studies: Dubee 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals.
12. Systematic review [112] with included studies: Dubee 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals.
14. Systematic review [112] with included studies: Dubee 2020. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Imprecision: Very Serious.** Low number of patients, Wide confidence intervals, Only data from one study.
16. Systematic review [111] with included studies: Tang 2020, Dubee 2020, Chen J 2020. **Baseline/comparator:** Control arm of reference used for intervention.
17. **Imprecision: Very Serious.** Low number of patients, Wide confidence intervals.
18. Systematic review [114] with included studies: Pan 2020, Self 2020, Dubee 2020, Horby 2020. **Baseline/comparator:** Control arm of reference used for intervention.
19. Systematic review [108] with included studies: Skipper 2020, Mitja 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.** due to few events.
21. Systematic review [108] with included studies: Ulrich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Imprecision: Very Serious.** Low number of patients, Only data from one study.

6.6 - 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 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 opt for the 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.

The Consumer Panel believes that as this treatment has shown no clear benefits, some patients may prefer not to use it, while other 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

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 *[46]*. The second, smaller trial randomised 81 adults hospitalised with severe COVID-19 *[120]*.

We have found one new study comparing interferon β-1a 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
In the SOLIDARITY trial, 35% of patients were under 50 years of age, 46% were aged between 50-69, 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 *[117][118]*.

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 *[119]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care — 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 6 Important	Relative risk 1.67 (CI 95% 0.7 - 3.99) Based on data from 91 patients in 1 studies. [3] (Randomized controlled)		**Very Low** Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether interferon β-1a improves or worsens septic shock (17 events).
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 [122] with included studies: Solidarity 2020, Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [123] with included studies: Solidarity 2020, Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [122] 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 [122] with included studies: Solidarity 2020, Davoudi-Monfared 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [122] 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.

6.7 - 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 *[92][93][127]*. 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 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 opt for the 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.

The Consumer Panel believes that as this treatment has shown no clear benefits, some patients may prefer to wait until the available evidence is clearer, while other 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 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
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

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 five randomised trials that compared lopinavir-ritonavir with standard care in 8121 patients with COVID-19 *[46][92][93][127][134]*. The vast majority of data come from the RECOVERY and WHO SOLIDARITY trials, which included 5040 patients *[134]* and 2771 patients *[46]* with moderate to critical illness. The SOLIDARITY trial was stopped early for reasons of futility. The remaining three trials included 199 patients with severe illness *[93]*, 60 patients with moderate or severe illness *[127]* and 51 patients with mild or moderate illness *[92]*.

We have found one new study comparing lopinavir-ritonavir with standard care (Ader et al. medRxiv doi: 10.1101/2021.01.08.20248149). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

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 between 50-69, and 20% were 70 years or older; 40% were women. For the three smaller trials, mean or median age ranged from 41 to 58 years and the proportion of women ranged from 38 to 59%. In the RECOVERY trial, six women were pregnant at randomisation—of the remaining studies, three excluded pregnant and breastfeeding women, and for one their eligibility was unclear *[127]*.

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 *[126]*.

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 *[128][129][130][132][133]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	 Lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality End of treatment 9 Critical	Relative risk 1.02 (CI 95% 0.92 - 1.12) Based on data from 8,061 patients in 4 studies. [1] (Randomized controlled)	**191** per 1000	**195** per 1000 Difference: **4 more** per 1000 (CI 95% 15 fewer - 23 more)	**High**	Lopinavir/ritonavir has no impact on mortality.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 0.59 (CI 95% 0.34 - 1.03) Based on data from 248 patients in 2 studies. [5] (Randomized controlled)	233 per 1000	137 per 1000 Difference: **96 fewer** per 1000 (CI 95% 154 fewer - 7 more)	**Low** Due to serious inconsistency and serious imprecision [6]	Lopinavir-ritonavir may decrease respiratory failure or ARDS (44 events).
Serious adverse events End of treatment 6 Important	Relative risk 0.63 (CI 95% 0.39 - 1.02) Based on data from 222 patients in 2 studies. [7] (Randomized controlled)			**Very Low** Due to serious risk of bias, serious inconsistency and serious imprecision [8]	We are uncertain whether lopinavir-ritonavir increases or decreases serious adverse events (52 events).
Adverse events End of treatment 6 Important	Relative risk 1.39 (CI 95% 0.48 - 4.05) Based on data from 287 patients in 3 studies. [9] (Randomized controlled)			**Very Low** Due to serious risk of bias, serious inconsistency and serious imprecision [10]	We are uncertain whether lopinavir-ritonavir increases or decreases adverse events.
Clinical improvement Day 14 after treatment 6 Important	Relative risk 1.26 (CI 95% 0.96 - 1.64) Based on data from 241 patients in 2 studies. [11] (Randomized controlled)	377 per 1000	475 per 1000 Difference: **98 more** per 1000 (CI 95% 15 fewer - 241 more)	**Low** Due to serious risk of bias and serious imprecision [12]	Lopinavir-ritonavir may have little impact on clinical improvement.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Discharge from hospital 28 Days after commencing treatment 6 Important	Relative risk 1 (CI 95% 0.98 - 1.03) Based on data from 7,811 patients in 2 studies. [13] (Randomized controlled)	747 per 1000	747 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.
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 [14]	Lopinavir-ritonavir may have little impact on time to discharge from hospital.

1. Systematic review [135] with included studies: Li 2020, Cao 2020, RECOVERY, Pan 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [135] with included studies: RECOVERY, Li 2020, Cao 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [135] 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 [135] with included studies: Cao 2020, Li 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, Low number of patients.
7. Systematic review [135] with included studies: Li 2020, Cao 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Selective outcome reporting, 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.** Wide confidence intervals.
9. Systematic review [135] with included studies: Zheng 2020, Cao 2020, Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: Serious.** Selective outcome reporting, 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.** Wide confidence intervals.
11. Systematic review [135] with included studies: Cao 2020, Li 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, Selective outcome reporting. **Imprecision: Serious.** Wide confidence intervals.
13. Systematic review [135] with included studies: Pan 2020, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Serious.** Only data from one study.

6.8 - 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 2600 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, such as dexamethasone, remdesivir, azithromycin, hydroxychloroquine and lopinavir-ritonavir, for most 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.

6.8.1 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[136]*.

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 *[137]*. There are several known and potential interactions with other drugs, including hormonal contraceptives *[137]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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 6 Important	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 indirectness [4]	There were too few who were discharged from hospital (2 events) to determine whether aprepitant makes a difference.

1. Systematic review [138] 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 [138] 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 *[136]*.

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 *[137]*. There are several known and potential interactions with other drugs including hormonal contraceptives *[137]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care 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 6 Important	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 indirectness [4]	There were too few who were discharged from hospital to determine whether aprepitant makes a difference (2 events).

1. Systematic review [138] 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 [138] 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.

6.8.2 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[142]*.

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 *[141]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	 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) 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 and very serious imprecision [9]	We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (11 events).

1. Systematic review [139] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [139] 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 [139] 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 [139] with included studies: [140]. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [139] with included studies: [140]. **Baseline/comparator:** Control arm of reference used for intervention.
8. Systematic review [139] 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 *[142]*.

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 *[141]*.

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**	**Absolute effect estimates** Standard care	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 During treatment (14 days)	[7]				Data for number of patients experiencing one or more events were not reported.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Baloxavir marboxil	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important **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 [139] with included studies: Lou 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [139] 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 [139] 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 [139] with included studies: [140]. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [139] with included studies: [140]. **Baseline/comparator:** Control arm of reference used for intervention.
8. Systematic review [139] 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.

6.8.3 - 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 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 opt for the 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 *[146]*, and ACTIV-3/TICO compared bamlanivimab with placebo in 314 patients with moderate to severe illness *[147]*.

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**	**Absolute effect estimates** Standard care	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	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).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Bamlanivimab	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important					
Hospitalisation Within 30 days of commencing treatment 6 Important	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 (CI 95% 52 fewer - 10 fewer)	**Low** Due to very serious imprecision [8]	We are uncertain whether bamlanivimab increases or decreases hospitalisation (14 events).
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 [145] with included studies: Gottlieb 2021, Lundgren 2020. **Baseline/comparator:** Control arm of reference used for intervention.

2. **Imprecision: Very Serious.** Wide confidence intervals, due to few events.
3. Systematic review [145] 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 [145] 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 [145] 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 [145] 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 [145] with included studies: Gottlieb 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very Serious.** Wide confidence intervals.
13. Systematic review [145] 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 [145] 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.

6.8.4 - Baricitinib

Not recommended

Do not use baricitinib 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 baricitinib for the treament 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, although preliminary evidence suggests that baricitinib does not increase the incidence of adverse or serious adverse events compared with standard care, it remains unclear if baricitinib 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 baricitinib 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 baricitinib for pregnant or breastfeeding women.

Certainty of the Evidence Low

General adult population
Certainty of the evidence for all outcomes is low due to very serious imprecision (reliance on a single study and wide confidence intervals).

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 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 opt for the 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 baricitinib 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 baricitinib 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 baricitinib 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 baricitinib to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

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

Summary

There remains significant uncertainty whether baricitinib 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 baricitinib plus remdesivir with remdesivir alone in 1033 adults hospitalised with suspected COVID-19 *[149]*.

Study characteristics
Mean age of participants was 56 years and 38% were women. Patients either received 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). Pregnant and breastfeeding women were ineligible.

What are the main results?
Baricitinib plus remdesivir may decease slightly the number of deaths and the need for invasive mechanical ventilation or ECMO. We are uncertain whether baricitinib plus remdesivir increases or decreases NIV/HFNO, clinical recovery and adverse or serious adverse events.

Our confidence in the results
Certainty of the evidence for all outcomes is low 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
As of 19 January 2021, baricitinib 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 baricitinib.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.65 (CI 95% 0.4 - 1.07) Based on data from 1,033 patients in 1 studies. [1] (Randomized controlled)	71 per 1000	46 per 1000 Difference: 25 fewer per 1000 (CI 95% 43 fewer - 5 more)	**Low** Due to very serious imprecision [2]	Baricitinib may decrease risk of death slightly (61 events).
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.54 (CI 95% 0.23 - 1.25) Based on data from 1,033 patients in 1 studies. [3] (Randomized controlled)	29 per 1000	16 per 1000 Difference: 13 fewer per 1000 (CI 95% 22 fewer - 7 more)	**Low** Due to very serious imprecision [4]	Baricitinib may decrease risk of death slightly (23 events).
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. [5] (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 [6]	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. [7] (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 [8]	We are uncertain whether baricitinib increases or decreases NIV / HFNO (152 events).
Serious adverse events End of follow-up	Relative risk 0.76 (CI 95% 0.59 - 0.99) Based on data from 1,016 patients in 1 studies. [9] (Randomized	210 per 1000	160 per 1000 Difference: 50 fewer per 1000 (CI 95% 86 fewer - 2 fewer)	**Low** Due to very serious imprecision [10]	Baricitinib may reduce serious adverse events (188 events).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	controlled)				
Adverse events End of follow-up 6 Important	Relative risk 0.87 (CI 95% 0.76 - 1.01) Based on data from 1,033 patients in 1 studies. [11] (Randomized controlled)	459 per 1000	399 per 1000 Difference: **60 fewer** per 1000 (CI 95% 110 fewer - 5 more)	**Low** Due to very serious imprecision [12]	We are uncertain whether baricitinib increases or decreases adverse events (445 events).
Clinical recovery End of follow-up 6 Important	Relative risk 1.07 (CI 95% 1.01 - 1.14) Based on data from 1,033 patients in 1 studies. [13] (Randomized controlled)	784 per 1000	839 per 1000 Difference: **55 more** per 1000 (CI 95% 8 more - 110 more)	**Low** Due to very serious imprecision [14]	We are uncertain whether baricitinib increases or decreases clinical recovery.

1. Systematic review [148] with included studies: Kalil 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **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 [148] 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 [148] 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 [148] with included studies: Kalil 2020. **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: No serious.**
9. Systematic review [148] with included studies: Kalil 2020. **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: No serious.**
11. Systematic review [148] with included studies: Kalil 2020. **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: No serious.**
13. Systematic review [148] 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.**

6.8.5 - 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 very low for all 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 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 opt for the 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 two randomised trials that compared bromhexine hydrochloride with placebo in 96 adults hospitalised with mild or moderate COVID-19 *[151][152]*.

Study characteristics
In the study by Ansarin et al. mean age was 60 years and the proportion of women was 45% *[152]*; in Li et al. mean age was 50 years and the proportion of women was 22% *[151]*.

Patients in Ansarin et al. received 8 mg bromhexine hydrochloride three times a day for 14 days; patients in Li et al. received 32 mg three times a day for 14 days. Pregnant and breastfeeding women were ineligible.

What are the main results?
There were too few who died (five deaths) or suffered adverse events to determine whether bromhexine hydrochloride makes a difference. No patients experienced serious adverse events. It is unclear whether bromhexine hydrochloride increases or decreases time to clinical improvement or viral clearance by day 28.

Our confidence in the results
Certainty of the evidence is very low for all 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 *[221]*.

Pregnant and breastfeeding women
Bromhexine hydrochloride is considered safe in pregnancy *[221]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Bromhexine hydrochloride	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of follow-up 9 Critical	Relative risk 0.09 (CI 95% 0.01 - 1.59) Based on data from 96 patients in 2 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 bromhexine hydrochloride makes a difference (5 deaths).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	 Bromhexine hydrochloride	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.11 (CI 95% 0.01 - 0.84) Based on data from 78 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 bromhexine hydrochloride makes a difference (10 events).
Serious adverse events End of follow-up 9 Critical	Based on data from 78 patients in 2 studies. [5] (Randomized controlled)			**Very Low** Due to very serious risk of bias and very serious imprecision [6]	No patients experienced serious adverse events.
Adverse events End of follow-up 6 Important	Relative risk 0.38 (CI 95% 0.12 - 1.16) 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]	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. [9] (Randomized controlled)			**Very Low** Due to very serious risk of bias and very serious imprecision [10]	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. [11] (Randomized controlled)			**Very Low** Due to very serious risk of bias and serious imprecision [12]	There were too few who required ICU admission to determine whether bromhexine hydrochloride makes a difference (13 events).
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. [13] (Randomized controlled)			**Very Low** Due to very serious risk of bias and very serious imprecision [14]	We are uncertain whether bromhexine hydrochloride increases or decreases virological clearance.
Discharge from	Relative risk 2.5			**Very Low**	We are uncertain

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Bromhexine hydrochloride	Certainty of the Evidence (Quality of evidence)	Plain text summary
hospital End of follow-up 6 Important	(CI 95% 0.78 - 7.97) Based on data from 18 patients in 1 studies. [15] (Randomized controlled)			Due to very serious risk of bias and very serious imprecision [16]	whether bromhexine hydrochloride increases discharge from hospital.

1. Systematic review [150] with included studies: Li 2020, Ansarin 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **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.** Point estimates vary widely. **Indirectness: Very Serious. Imprecision: Very Serious.** Low number of patients, only two small studies and Wide confidence intervals. **Publication bias: No serious.**
3. Systematic review [150] with included studies: Ansarin 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **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.**
5. Systematic review [150] with included studies: Ansarin 2020, Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **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/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.** Low number of patients, Low number of patients, Wide confidence intervals. **Publication bias: No serious.**
7. Systematic review [150] 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.** Low number of patients, Wide confidence intervals. **Publication bias: No serious.**
9. Systematic review [150] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **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.**
11. Systematic review [150] with included studies: Ansarin 2020, Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **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.**
13. Systematic review [150] 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.**
15. Systematic review [150] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **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.**

6.8.6 - 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 *[153]*. 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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.

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 *[97]*.

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**	**Absolute effect estimates** Standard care	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				[7]	There were no serious adverse events.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Chloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
events Within 28 days after commencing treatment 6 Important	Based on data from 30 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)	5.5 (Median) CI 95%	**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)	8.5 (Median) CI 95%	**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 [96] 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 [96] 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 [96] 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 *[97]*.

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**	**Absolute effect estimates** Standard care	 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)	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)	7.5 (Median) CI 95%	5.5 (Median)	**Very Low** Due to serious risk of bias, serious indirectness and very serious	We are uncertain whether chloroquine increases or decreases time to clinical recovery.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Chloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	Lower better (Randomized controlled)			imprecision [8]	
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)	8.5 (Median) CI 95%	**Very Low** Due to serious risk of bias, serious indirectness and very serious imprecision [9]	We are uncertain whether chloroquine increases or decreases time to termination of oxygen therapy.

1. Systematic review [96] 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 [96] 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 [96] 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.

6.8.7 - Colchicine

Not recommended

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

Colchicine 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 colchicine 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 known side effects and harms associated with colchicine including diarrhoea. Overdose of colchicine can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock.

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 colchicine has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. Studies of colchicine in pregnancy for some rheumatological conditions have shown no increase in major fetal anomalies or pregnancy loss *[156]*.

Certainty of the Evidence — Very Low

Certainty of the evidence is moderate for mortality, mechanical ventilation, adverse or serious adverse events due to serious imprecision (few events or 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).

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 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 opt for the 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 colchicine in pregnancy are unknown.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

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

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

Clinical Question/ PICO

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

Summary

There remains uncertainty whether colchicine 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 colchicine with standard care in 240 adults hospitalised with COVID-19 *[155][157][159]*, and one study (COLCORONA trial) that compared colchicine to placebo in 4488 non-hospitalised adults with confirmed COVID-19 *[161]*.

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 *[157]*, Salehzadeh et al. posted to Res Sq on 21 September 2020 *[159]* and Tardif et al. (COLCORONA) posted to medRxiv on 27 January 2021 *[161]*).

The final results of Lopes et al. *[157]* 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 the COLCORONA trial mean age of participants was ~55 years and the proportion of women was 54%. For the three smaller studies, median age ranged from 48 to 63 years in the colchicine groups and from 54 to 65 years in the control groups; the proportion of women was 49% and 52% respectively. Pregnant and breastfeeding women were ineligible.

What are the main results?
For the critical outcomes of death and mechanical ventilation, there were too few events to determine whether colchicine makes a difference. We are uncertain whether colchicine increases or decreases discharge from hospital, duration of hospital stay or the likelihood of experiencing a serious adverse event. However, colchicine may increase the incidence of adverse events (147 more adverse events per 1000 patients; RR 1.93, CI 95% 1.18 to 3.16; 4517 participants 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 moderate for mortality, mechanical ventilation and adverse or serious adverse events due to serious imprecision (few events or 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 *[154]*. There are several known and potential interactions with other drugs *[154]*.

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**	**Absolute effect estimates** Standard care	Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 21-28 days of commencing treatment 9 Critical	Relative risk 0.47 (CI 95% 0.18 - 1.23) Based on data from 4,628 patients in 3 studies. [1] (Randomized controlled)	6 per 1000	3 per 1000 Difference: 3 fewer per 1000 (CI 95% 5 fewer - 1 more)	**Moderate** Due to serious imprecision [2]	Colchicine probably has little impact on death (19 events).
Mechanical ventilation Within 21-28 days of commencing treatment 9 Critical	Relative risk 0.42 (CI 95% 0.16 - 1.09) Based on data from 4,593 patients in 2 studies. [3] (Randomized controlled)	12 per 1000	5 per 1000 Difference: 7 fewer per 1000 (CI 95% 10 fewer - 1 more)	**Moderate** Due to serious imprecision [4]	Colchicine probably has little impact on mechanical ventilation (39 events).
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. [5] (Randomized controlled)	61 per 1000	48 per 1000 Difference: 13 fewer per 1000 (CI 95% 24 fewer - 0 fewer)	**Moderate** Due to serious imprecision [6]	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. [7] (Randomized controlled)	158 per 1000	305 per 1000 Difference: 147 more per 1000 (CI 95% 28 more - 341 more)	**Moderate** Due to serious imprecision [8]	Colchicine probably increases adverse events (934 events).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Colchicine	Certainty of the Evidence (Quality of evidence)	Plain text summary
Discontinuation due to adverse events During treatment 6 Important	Based on data from 140 patients in 2 studies. [9] (Randomized controlled)			**Low** Due to very serious imprecision [10]	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. [11] (Randomized controlled)			**Low** Due to very serious imprecision [12]	There were too few who were admitted to ICU to determine whether colchicine makes a difference (2 events).
Clinical progression Increase of 2 grades on 7-grade scale; 21 days after commencing treatment 6 Important	Relative risk 0.13 (CI 95% 0.02 - 1.02) Based on data from 105 patients in 1 studies. [13] (Randomized controlled)	140 per 1000	18 per 1000 Difference: **122 fewer** per 1000 (CI 95% 137 fewer - 3 more)	**Low** Due to very serious imprecision [14]	There were too few who experienced clinical deterioration to determine whether colchicine makes a difference (8 events).
Discharge from hospital 10 days after commencing treatment 6 Important	Relative risk 1.3 (CI 95% 0.96 - 1.78) Based on data from 35 patients in 1 studies. [15] (Randomized controlled)	722 per 1000	939 per 1000 Difference: **217 more** per 1000 (CI 95% 29 fewer - 563 more)	**Low** Due to very serious imprecision [16]	We are uncertain whether colchicine increases or decreases discharge from hospital (29 events).
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 [17]	We are uncertain whether colchicine increase or decreases duration of hospital stay.

1. Systematic review [160] with included studies: Lopes 2020, Deftereos 2020, Tardif 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** due to few events.
3. Systematic review [160] with included studies: Tardif 2021, Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Imprecision: Serious.** due to few events.
5. Systematic review [160] with included studies: Tardif 2021, Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Serious.** SAEs only occurred in one study.
7. Systematic review [160] with included studies: Tardif 2021, Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Serious.** Wide confidence intervals.
9. Systematic review [160] with included studies: Lopes 2020, Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very Serious.** Low number of patients, due to few events.
11. Systematic review [160] with included studies: Lopes 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very Serious.** Low number of patients, Only data from one study, Wide confidence intervals.
13. Systematic review [160] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Very Serious.** Low number of patients, Only data from one study.
15. Systematic review [160] with included studies: Lopes 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Imprecision: Very Serious.** Low number of patients, Only data from one study.
17. **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.

6.8.8 - 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 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 opt for the 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.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
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 *[163]*.

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 *[231]*.

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 *[221]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Control	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).
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	Hazard Ratio 2.68 (CI 95% 1.57 - 4.59)			**Very Low** Due to serious	We are uncertain whether CMCS

Outcome Timeframe	Study results and measurements	Absolute effect estimates Control CMCS	Certainty of the Evidence (Quality of evidence)	Plain text summary
End of follow-up 6 Important	Based on data from 93 patients in 1 studies. (Randomized controlled)		risk of bias and very serious imprecision [5]	decreases time to recovery.

1. Systematic review [162] 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 [162] 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.**

6.8.9 - Convalescent plasma

Not recommended

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

The Taskforce notes the statement from the chief investigators of the RECOVERY trial on 11 January that found no significant difference in the primary endpoint of 28-day mortality in patients receiving convalescent plasma compared with usual care. The preliminary analysis is based on 1873 reported deaths among 10,406 randomised patients (RR 1.04 95% CI 0.95 to 1.14). Once the data have been published, an updated recommendation will be included in a future version of the guideline.

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 convalescent plasma 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 evidence suggests convalescent plasma does not result in more 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) *[165]*.

Certainty of the Evidence Very Low

General adult population
Certainty of the evidence is low for mortality, invasive mechanical ventilation, adverse or serious adverse events, admission to ICU, clinical deterioration, clinical improvement, hospital discharge, resolution of dyspnoea, time to improvement and time to discharge from hospital. These judgements are based on serious imprecision (due to reliance on a single study, low patient numbers and/or wide confidence intervals) and serious risk of bias. Certainty is very low for all other outcomes.

Certainty has been downgraded for all outcomes 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 *[166]*. Three studies did not report specific NAb titers of included patients *[171][174][176]*. The remaining studies detected NAb in 76% *[172]*, 49% *[169]*, 80% *[167]* and 54% *[175]* of patients at baseline.

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 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 opt for the 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 convalescent plasma in pregnancy are unknown.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 convalescent plasma on patient-relevant outcomes in the treatment of COVID-19 *[165]*. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that convalescent plasma 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 convalescent plasma to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

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

Summary

There remains significant uncertainty whether convalescent plasma is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from eight randomised trials that compared convalescent plasma with standard care in 160 adults with mild COVID-19 *[176]*, 631 adults with moderate COVID-19 *[167][169][172]*, and 525 adults with severe COVID-19 *[166][171][174][175]*.

The Taskforce notes the statement from the chief investigators of the RECOVERY trial on 11 January that found no significant difference in the primary endpoint of 28-day mortality in patients receiving convalescent plasma compared with usual care. The preliminary analysis is based on 1873 reported deaths among 10,406 randomised patients (18% convalescent plasma vs. 18% standard care alone; RR 1.04 95% CI 0.95 to 1.14). Once the data have been published, an updated recommendation will be included in a future version of the guideline.

We have found two new studies comparing convalescent plasma with standard care (Ray et al. medRxiv doi: 10.1101/2020.11.25.20237883 and Salman et al. Egypt J Anaesth doi: 10.1080/11101849.2020.1842087). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

Publication status
Three studies are only available as preprints (posted to medRxiv on 3 July, 29 September and 4 November) and have therefore not been peer reviewed *[167][169][174]*.

Study characteristics
For a comprehensive description, see the study characteristics table.

What are the main results?
Compared with standard care, there are no important differences in respect of death, requirement for invasive mechanical ventilation, admission to ICU, clinical improvement, hospital discharge or time to hospital discharge in patients treated with convalescent plasma. Convalescent plasma may increase the incidence of serious adverse events (42 more per 1000 patients; RR 1.24, CI 95% 0.81 to 1.90; 414 patients in 2 studies) and adverse events (252 more per 1000 patients; RR 1.47, CI 95% 0.38 to 5.74; 414 patients in 2 studies). However, convalescent plasma may also increase the rate of resolution of dyspnoea (78 more per 1000 patients; RR 1.21, CI 95% 0.87 to 1.68; 797 patients in 2 studies).

We are uncertain whether convalescent plasma makes a difference to incidence of respiratory failure or ARDS, clinical deterioration or clinical recovery, viral nucleic acid negativity at 72 hours or time to improvement.

Our confidence in the results
Certainty of the evidence is low for mortality, invasive mechanical ventilation, adverse or serious adverse events, admission to ICU, clinical deterioration, clinical improvement, hospital discharge, resolution of dyspnoea, time to improvement and time to discharge from hospital. These judgements are based on serious imprecision (due to reliance on a single study, low patient numbers and/or wide confidence intervals) and serious risk of bias. Certainty is very low for all other outcomes.

Certainty has been downgraded for all outcomes 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 *[166]*. Three studies did not report specific NAb titers of included patients *[171][174][176]*. The remaining studies detected NAb in 76% *[172]*, 49% *[169]*, 80% *[167]* and 54% *[175]* of patients at baseline.

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**	**Absolute effect estimates** Control	 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 0.83 (CI 95% 0.58 - 1.18) Based on data from 1,228 patients in 7 studies. [1] (Randomized controlled)	132 per 1000	110 per 1000 Difference: **22 fewer** per 1000 (CI 95% 55 fewer - 24 more)	**Low** Due to serious risk of bias and imprecision [2]	Convalescent plasma may have little impact on death (144 events).
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 1.04 (CI 95% 0.74 - 1.45) Based on data from 957 patients in 3 studies. [3] (Randomized controlled)	116 per 1000	121 per 1000 Difference: **5 more** per 1000 (CI 95% 30 fewer - 52 more)	**Low** Due to serious risk of bias and imprecision [4]	Convalescent plasma probably has little impact on invasive mechanical ventilation at day 28 (129 events).
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. [5] (Randomized controlled)			**Very Low** Due to serious risk of bias and very serious imprecision [6]	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. [7] (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 [8]	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. [9] (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 [10]	Convalescent plasma may increase adverse events (222 events).
ICU admission Within 28 days of commencing treatment	Relative risk 0.75 (CI 95% 0.36 - 1.59) Based on data from 493 patients in 2 studies. [11] (Randomized controlled)	373 per 1000	280 per 1000 Difference: **93 fewer** per 1000	**Low** Due to serious risk of bias and imprecision [12]	Convalescent plasma may decrease ICU admission slightly (194 events).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Control	Convalescent plasma	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important		(CI 95% 239 fewer - 220 more)			
Clinical deterioration (progression to severe/critical) [13] 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. [14] (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 [15]	Convalescent plasma may have little impact on clinical deterioration (progression to severe/ critical) at day 28 (37 events).
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. [16] (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 [17]	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. [18] (Randomized controlled)			**Very Low** Due to serious risk of bias and very serious imprecision [19]	We are uncertain whether convalescent plasma worsens clinical recovery (223 events).
Hospital discharge Within 28 days of commencing treatment 6 Important	Relative risk 1.06 (CI 95% 0.92 - 1.22) Based on data from 515 patients in 3 studies. [20] (Randomized controlled)	672 per 1000	712 per 1000 Difference: **40 more** per 1000 (CI 95% 54 fewer - 148 more)	**Low** Due to serious risk of bias and imprecision [21]	Convalescent plasma may have little imapct on hospital discharge (364 events).
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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Control	Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 discharge from hospital Days 6 Important	Based on data from: 797 patients in 2 studies. (Randomized controlled)	Agarwal 2020 (n=464) and Simonovich 2020 (n=333) both reported time to discharge from hospital. Both studies demonstrated slightly lower time to discharge in the control vs convalescent plasma group (median 13 days vs 14 days, and median 12 days vs 13 days, respectively).		**Low** Due to serious risk of bias and imprecision [27]	Convalescent plasma probably has little impact on time to discharge from hospital.

1. Systematic review [173] with included studies: AlQahtani 2020, Avendano-Sola 2020, Libster 2020, Simonovich 2020, Rasheed 2020, Li 2020, Agarwal 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **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.
3. Systematic review [173] with included studies: Libster 2020, Simonovich 2020, Agarwal 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Due to either high or unknown levels of neutralising antibodies at baseline in the majority of studies for both treatment and control groups. **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [173] with included studies: Libster 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **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.
7. Systematic review [173] with included studies: Simonovich 2020, Avendano-Sola 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **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.
9. Systematic review [173] with included studies: Simonovich 2020, AlQahtani 2020. **Baseline/comparator:** Control arm of reference used for intervention.

10. **Risk of bias: Serious.** Due to either high or unknown levels of neutralising antibodies at baseline in the majority of studies for both treatment and control groups. **Imprecision: Serious.** Wide confidence intervals.
11. Systematic review [173] with included studies: Simonovich 2020, Libster 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **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.
13. Measured by the number of patients who progressed from moderate to either severe or critical illness
14. Systematic review [164] with included studies: Agarwal 2020, Avendano-Sola 2020. **Baseline/comparator:** Control arm of reference used for intervention.
15. **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.
16. Systematic review [173] with included studies: Simonovich 2020, Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
17. **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.
18. Systematic review [173] with included studies: Simonovich 2020. **Baseline/comparator:** Control arm of reference used for intervention.
19. **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.
20. Systematic review [173] with included studies: Simonovich 2020, Li 2020, Avendano-Sola 2020. **Baseline/comparator:** Control arm of reference used for intervention.
21. **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.
22. Systematic review [173] with included studies: Simonovich 2020, Agarwal 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 [164] 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.

6.8.10 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[180]*.

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**	**Absolute effect estimates** Standard care	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	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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Darunavir-cobicistat	Certainty of the Evidence (Quality of evidence)	Plain text summary
9 Critical					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 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 and very serious imprecision [12]	We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 3 (6 events).

1. Systematic review [177] 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 [177] 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[180]. **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 [177] 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 [177] 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 [177] 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 *[180]*.

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 *[181]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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).
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	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**	**Absolute effect estimates** Standard care	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, serious indirectness and very serious imprecision [12]	cobicistat increases or decreases viral clearance at day 3 (6 events).

1. Systematic review [177] 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 [177] 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[180]. **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 [177] 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 [177] 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 [177] 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.**

6.8.11 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[184]*.

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 *[183]*.

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 *[183]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard Care	Dutasteride	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Hospitalisation End of Follow-up	Based on data from 87			2	No patients required hospitalisation.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care	 Dutasteride	Certainty of the Evidence (Quality of evidence)	Plain text summary
9 Critical	patients in 1 studies. [1]				
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 [182] 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 [182] . **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.**

6.8.12 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
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 *[142][185][189][190]*.

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**	**Absolute effect estimates** Standard care	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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Favipiravir	Certainty of the Evidence (Quality of evidence)	Plain text summary
					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 (CI 95% 50 fewer - 1,005 more)	**Low** Due to serious risk of bias and serious imprecision [12]	We are uncertain whether favipiravir increases adverse events (165 events).
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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Favipiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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	**Low** Due to serious risk of bias and very serious imprecision [20]	We are uncertain whether favipiravir increases negative PCR.
		Difference: **73 more** per 1000 (CI 95% 8 more - 146 more)			
sdfgsdfg	High better	**7.3** (Median)	**3.5** (Median)		
		CI 95%			

1. Systematic review [188] 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 [186] with included studies: Ivashchenko 2020, Lou 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 [186] 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 [186] 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 [188] with included studies: Ruzhentsova 2020, Ivashchenko 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 [188] with included studies: Ivashchenko 2020, ?, Ruzhentsova 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 [188] 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 [186] 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 [188] 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 [188] 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.

6.8.13 - 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 *[193]*.

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 *[193]*. 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
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 *[192]*.

Study characteristics
Median age was ~46 years in both groups and the proportion of women was 72%. 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 *[193]*. 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 *[193]*. 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 *[193]*.

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) *[193]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	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**	**Absolute effect estimates** Placebo	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 [191] with included studies: Lenze 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [191] 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 [191] 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 [191] 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 [191] 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 [191] 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.

6.8.14 - 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) *[194]*.

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 *[194]*.

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 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 opt for the 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.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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. 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 *[195][199]* and 24 adults with mild to severe disease *[198]*.

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 *[198][199]*; in one study their eligibility was unclear *[195]*.

Patients in the intervention groups received either: 2 x 10^6 cells/kg on day 0 *[195]*, 100 x 10^6 cells on days 0 and 3 *[198]*, or 4 x 10^7 cells on days 0, 3 and 6 *[199]*.

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 *[194]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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	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	We are uncertain whether hU-MSC increases clinical improvement.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care hU-MSC	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important			imprecision [12]	
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.
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 [197] with included studies: Lanzoni 2020, Shi 2020, Shu 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 [197] 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 [197] with included studies: Lanzoni 2020. **Baseline/comparator:** Systematic review [197] 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 [197] 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 [197] 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 [197] 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:** [195],
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:** [195],
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.

6.8.15 - Hydroxychloroquine plus azithromycin

Not recommended

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

Hydroxychloroquine plus azithromycin 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 hydroxychloroquine plus azithromycin for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

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 or azithromycin, administered individually.

Certainty of the Evidence Low

General adult population
Certainty of the evidence is low for all outcomes. This judgement is based on very serious imprecision (wide confidence intervals, reliance on a single study and few events—for death 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 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 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 opt for the 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 hydroxychloroquine plus azithromycin during pregnancy and breastfeeding are unknown in the context of COVID-19.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
Although we have no systematically collected evidence regarding acceptability, the use of hydroxychloroquine plus azithromycin in clinical trials 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 hydroxychloroquine plus azithromycin 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 hydroxychloroquine plus azithromycin 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 hydroxychloroquine plus azithromycin 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: 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 one three-armed randomised trial that compared hydroxychloroquine plus azithromycin with azithromycin alone and standard care. The comparison of hydroxychloroquine plus azithromycin with standard care included 444 hospitalised adults with moderate illness (345 with laboratory-confirmed COVID-19) *[104]*.

We have found two new studies comparing hydroxychloroquine plus azithromycin with placebo (Omrani et al. EClinMed doi: 10.1016/j.eclinm.2020.100645 and Johnston et al. SSRN id=3745831). These studies are currently

under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
Mean age of participants was 50 years in both groups and 43% were women. Pregnant women were ineligible.

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 or discharge from hospital, but it may increase slightly the duration of hospital stay 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 *[95]*.

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 *[83]*.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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).
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. [3] (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 [4]	We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases the need for invasive mechanical ventilation (31 events).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	HCQ+AZM	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Adverse events Within 15 days of commencing treatment 6 Important	Relative risk 1.74 (CI 95% 1.27 - 2.38) Based on data from 416 patients in 1 studies. [5] (Randomized controlled)	226 per 1000	393 per 1000 Difference: **167 more** per 1000 (CI 95% 61 more - 312 more)	**Low** Due to serious risk of bias and serious imprecision [6]	Hydroxychloroquine plus azithromycin may increase adverse events (134 events).
Serious adverse events Within 15 days of commencing treatment 6 Important	Relative risk 1.85 (CI 95% 0.36 - 9.43) Based on data from 416 patients in 1 studies. [7] (Randomized controlled)			**Very Low** Due to serious risk of bias and very serious imprecision [8]	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. [9] (Randomized controlled)			**Very Low** Due to serious risk of bias and very serious imprecision [10]	Hydroxychloroquine plus azithromycin may have little impact on discharge from hospital (266 events).
Duration of hospital stay Days 6 Important	Based on data from: 345 patients in 1 studies. [11] (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 [12]	We are uncertain if hydroxychloroquine plus azithromycin increases duration of hospital stay.

1. Systematic review [200] 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 [200] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very Serious.** due to few events, Only data from one study.
5. Systematic review [200] with included studies: Cavalcanti 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.** Only data from one study, Wide confidence intervals.
7. Systematic review [200] with included studies: 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: Very Serious. due to few events, Only data from one study.
9. Systematic review [200] with included studies: Cavalcanti 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.** Only data from one study, Wide confidence intervals.
11. Systematic review [200] 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.

Clinical Question/ PICO

Population:	Special populations 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 one three-armed randomised trial that compared hydroxychloroquine plus azithromycin with azithromycin alone and standard care. The comparison of hydroxychloroquine plus azithromycin with standard care included 444 hospitalised adults with moderate illness (345 with laboratory-confirmed COVID-19) *[104]*.

We have found one new study comparing hydroxychloroquine plus azithromycin with placebo (Omrani et al. EClinMed doi: 10.1016/j.eclinm.2020.100645). 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 50 years in both groups and 43% were women. Pregnant women were ineligible.

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 or discharge from hospital, but it may increase slightly the duration of hospital stay and result in more adverse events.

Our confidence in the results
Certainty of the evidence is 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), serious risk of bias (lack of blinding) and serious indirectness (limited inclusion of these populations).

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 *[95]*.

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 *[83]*.

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 *[100][101]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[100][101][102]*. 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) *[83]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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)			**Very Low** Due to very serious imprecision and serious indirectness [2]	There were too few who died to determine whether hydroxychloroquine plus azithromycin makes a difference (8 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. [3] (Randomized controlled)			**Very Low** Due to very serious imprecision and serious indirectness [4]	We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases the need for invasive mechanical ventilation (31 events).
Adverse events	Relative risk 1.74			**Very Low**	We are uncertain

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	HCQ+AZM	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Within 15 days of commencing treatment 6 Important	(CI 95% 1.27 - 2.38) Based on data from 416 patients in 1 studies. [5] (Randomized controlled)			Due to serious risk of bias, serious imprecision and serious indirectness [6]	whether hydroxychloroquine plus azithromycin increases adverse events (134 events).
Serious adverse events Within 15 days of commencing treatment 6 Important	Relative risk 1.85 (CI 95% 0.36 - 9.43) Based on data from 416 patients in 1 studies. [7] (Randomized controlled)			**Very Low** Due to serious risk of bias and very serious imprecision [8]	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. [9] (Randomized controlled)			**Very Low** Due to very serious imprecision, serious risk of bias and serious indirectness. [10]	We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases discharge from hospital (266 events).
Duration of hospital stay Days 6 Important	Based on data from: 345 patients in 1 studies. [11] (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 very serious imprecision, serious risk of bias and serious indirectness [12]	We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases duration of hospital stay

1. Systematic review [200] with included studies: Cavalcanti 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.** due to few events, Only data from one study.
3. Systematic review [200] with included studies: Cavalcanti 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.** due to few events, Only data from one study.
5. Systematic review [200] with included studies: Cavalcanti 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.** Only data from one study, Wide confidence intervals.
7. Systematic review [200] with included studies: 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: Very Serious.** due to few events, Only data from one study.
9. Systematic review [200] with included studies: Cavalcanti 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.** Only data from one study, Wide confidence intervals.
11. Systematic review [200] 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. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals.

6.8.16 - 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 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 opt for the 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.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
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 *[202]*.

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 *[117][118]*.

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 *[119]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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	Relative risk 1.1 (CI 95% 0.85 - 1.44) Based on data from 98 patients in 1 studies. [5]	660 per 1000	726 per 1000	**Low** Due to very serious imprecision [6]	We are uncertain whether inhaled interferon β-1a increases discharge

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Inhaled interferon β-1a	Certainty of the Evidence (Quality of evidence)	Plain text summary
treatment 6 Important	(Randomized controlled)	Difference: **66 more** per 1000 (CI 95% 99 fewer - 290 more)			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).
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 [201] 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 [201] 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 [201] 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 [201] 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 [201] 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 [201] 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 [201] 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.

6.8.17 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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

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 *[203]*.

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.

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 *[206]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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).
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	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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care Interferon β-1b	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important				
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 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 and serious risk of bias [16]	We are uncertain if interferon β-1b decreases clinical deterioration (based on admission to ICU; 36 events).
Time to discharge from hospital Days	Based on data from: 66 patients in 1 studies. [17]	**13** (Median) **11** (Median) CI 95%	**Very Low** Due to very serious imprecision and	We are uncertain whether interferon β-1b increases or decreases time to discharge from hospital.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Interferon β-1b	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important	(Randomized controlled)		serious risk of bias [18]	

1. Systematic review [205] 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 [205] 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 [205] 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 [205] 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 [205] . **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [205] . **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [205] 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 [205] 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 [204] 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[203]. **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 *[203]*.

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 *[206]*.

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 *[119]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care 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 and serious indirectness [2]	We are uncertain whether interferon β-1b increases or decreases death at 14 days (4 events).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care Interferon β-1b	**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% 0.07 - 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).
Discharge from	Relative risk 1.15 (CI 95% 0.96 - 1.38)		**Very Low**	We are uncertain whether interferon β-1b

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Interferon β-1b	Certainty of the Evidence (Quality of evidence)	Plain text summary
hospital Within 28 days of commencing treatment 6 Important	Based on data from 66 patients in 1 studies. [13] (Randomized controlled)		Due to very serious imprecision, serious risk of bias and serious indirectness [14]	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 [205] 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 [205] 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 [205] 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 [205] 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 [205] . **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [205] . **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [205] 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 [205] 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 [204] 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[203]. **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.

6.8.18 - 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 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 opt for the treatment.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[208]*.

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 *[209]*.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 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	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).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Interferon gamma	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important					

1. Systematic review [207] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [207] 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 [207] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [207] 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 [207] 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 [207] 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 *[208]*.

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 *[209]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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	Relative risk 1.84 (CI 95% 1.04 - 3.25) Based on data from 59			**Very Low** Due to serious risk of bias, very	We are uncertain whether interferon gamma increases the number of patients with

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	 Interferon gamma	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
commencing treatment 6 Important	patients in 1 studies. [5] (Randomized controlled)			serious imprecision and serious indirectness [6]	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, very serious imprecision and serious indirectness [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, very serious imprecision and serious indirectness [10]	We are uncertain whether interferon gamma increases discharge from hospital (60 events).

1. Systematic review [207] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [207] 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 [207] with included studies: Moynelo 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [207] 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 [207] 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 [207] 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.

6.8.19 - 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 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 opt for the 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 *[211]*.

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**	**Absolute effect estimates** Standard care	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]	Relative risk 1.21 (CI 95% 0.96 - 1.51) Based on data from 80			**Very Low** Due to serious risk of bias and	We are uncertain whether IFN-κ plus TFF2 increases or

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	IFN-κ plus TFF2	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Within 12 days of commencing treatment 6 Important	patients in 1 studies. [4] (Randomized controlled)			very serious imprecision [5]	decreases clinical improvement based on chest CT scan (64 events).
Time to discharge from hospital Days 6 Important	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.
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 [210] with included studies: Fu 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [210] 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 [210] 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.

6.8.20 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[213]*.

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 *[215]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Immunoglobulin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk 0.47 (CI 95% 0.24 - 0.93)			Very Low Due to very	We are uncertain whether

Outcome Timeframe	Study results and measurements	Absolute effect estimates Placebo	 Immunoglobulin	Certainty of the Evidence (Quality of evidence)	Plain text summary
End of treatment 9 Critical	Based on data from 64 patients in 1 studies. [1]			serious risk of bias and very serious imprecision [2]	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 [212] 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.

6.8.21 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[216]*.

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 *[215]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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 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 [4]	There were too few who experienced invasive mechanical ventilation to determine whether combination immunoglobulin plus methylprednisolone makes a difference (9 events).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Absolute effect estimates Immunoglobulin plus methylprednisolone	Certainty of the Evidence (Quality of evidence)	Plain text summary
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 [214] 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 [214] 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 [214] with included studies: Sakoulas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [214] . **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 *[216]*.

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 *[215]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	 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 commencing	6				No studies were found that looked at serious adverse events.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Immunoglobulin plus methylprednisolone	Certainty of the Evidence (Quality of evidence)	Plain text summary
treatment 6 Important					

1. Systematic review [214] 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 [214] 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 [214] with included studies: Sakoulas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [214] . **Baseline/comparator:** Control arm of reference used for intervention.

6.8.22 - 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 *[220]*.

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 *[220]*.

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 *[221]*.

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 and admission to ICU, 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 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 opt for the 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 seven randomised trials that compared ivermectin with standard care in 518 adults with COVID-19 *[217][218][219][224][225][226][227]*.

We have found three new studies comparing ivermectin with standard care (Mohan et al. Res Sq doi: 10.21203/rs.3.rs-191648/v1, Shah Bukhari et al. medRxiv doi: 10.1101/2021.02.02.21250840 and Beltran-Gonzalez et al. medRxiv doi: 10.1101/2021.02.18.21252037v1). These studies are currently under review and an updated recommendation will be included in a future version of the guideline. One other study (Okumus et al. Res Sq doi: 10.21203/rs.3.rs-224203/v1) has been reviewed and excluded because assignment to groups was not truly random.

Publication status
Three studies are only available as preprints and have therefore not been peer reviewed (Krolewiecki et al. posted to SSRN on 11 November 2020 *[219]*, Niaee et al. posted to Res Sq on 24 November 2020 *[218]* and Kirti et al. posted

to medRxiv on 9 January 2021 *[226]*).

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 58%. Pregnant and breastfeeding women were ineligible in all trials.

What are the main results?
We are uncertain whether ivermectin increases or decreases mortality, patients requiring invasive mechanical ventilation or oxygen, adverse or serious adverse events, admission to ICU, rate of viral clearance, discharge from hospital, 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 and admission to ICU, 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 *[220]*.

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 *[221]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.05 - 6.33) Based on data from 292 patients in 2 studies. [1] (Randomized controlled)	68 per 1000	39 per 1000 Difference: 29 fewer per 1000 (CI 95% 65 fewer - 362 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether ivermectin impacts death (19 events).
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.21 (CI 95% 0.03 - 1.72) Based on data from 112 patients in 1 studies. [3] (Randomized controlled)	88 per 1000	18 per 1000 Difference: 70 fewer per 1000 (CI 95% 85 fewer - 63 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether ivermectin increases or decreases need for invasive mechanical ventilation (6 events).
Adverse events End of follow-up	Relative risk 1.16 (CI 95% 0.62 - 2.16) Based on data from 69 patients in 2 studies. [5]	370 per 1000	429 per 1000	**Low** Due to very serious imprecision [6]	We are uncertain whether ivermectin increases or decreases adverse events (28

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important	(Randomized controlled)	Difference: 59 more per 1000 (CI 95% 141 fewer - 429 more)			events).
Serious adverse events End of follow-up 6 Important	Based on data from 114 patients in 3 studies. [7] (Randomized controlled)			**Low** Due to very serious imprecision [8]	We are uncertain whether ivermectin increases or decreases serious adverse events (1 event).
Viral clearance 10 days after commencing treatment 6 Important	Relative risk 0.95 (CI 95% 0.79 - 1.13) Based on data from 40 patients in 1 studies. [9] (Randomized controlled)			**Very Low** Due to serious risk of bias and very serious imprecision [10]	We are uncertain whether ivermectin increases or decreases viral clearance at day 10 (37 events).
Discharge from hospital Within 10 days of commencing treatment 6 Important	Relative risk 1.07 (CI 95% 0.99 - 1.16) Based on data from 112 patients in 1 studies. [11] (Randomized controlled)	930 per 1000 Difference: 65 more per 1000 (CI 95% 9 fewer - 149 more)	995 per 1000	**Low** Due to very serious imprecision [12]	We are uncertain whether ivermectin improves discharge from hospital (108 events).
ICU admission End of follow-up 6 Important	Relative risk 0.86 (CI 95% 0.28 - 2.67) Based on data from 112 patients in 1 studies. [13] (Randomized controlled)	105 per 1000 Difference: 15 fewer per 1000 (CI 95% 76 fewer - 175 more)	90 per 1000	**Low** Due to very serious imprecision [14]	We are uncertain whether ivermectin increases or decreases ICU admission (11 events).
No. participants requiring 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Time to clinical recovery [onset to resolution] [18] 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 [19]	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 [20]	We are uncertain whether ivermectin increases or decreases time to clinical recovery (from randomisation).
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 [21]	We are uncertain whether ivermectin increases or decreases duration of hospital stay.

1. Systematic review [223] with included studies: Niaee 2020, Ravikirti 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, due to few events..
3. Systematic review [223] with included studies: Ravikirti 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, due to few events.
5. Systematic review [223] with included studies: Chaccour 2020, Krolewiecki 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients.
7. Systematic review [223] with included studies: Chaccour 2020, Krolewiecki 2020, Ahmed 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.
9. Systematic review [270] with included studies: Podder 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: Serious.** Inadequate sequence generation (odd-even method) resulting in potential for selection bias; concealment of allocation during randomization process not reported, resulting in potential for selection bias; no protocol, analysis plan or trial registration record available.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study.
11. Systematic review [223] with included studies: Ravikirti 2021. **Baseline/comparator:** Control arm of reference used for intervention.

12. **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients.
13. Systematic review [223] with included studies: Ravikirti 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Very Serious.** Low number of patients, Wide confidence intervals, Only data from one study, due to few events.
15. Systematic review [223] with included studies: Ahmed 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [223] 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. Measured as time to clinical recovery from onset of illness to complete resolution of symptoms
19. **Risk of bias: Very Serious. Imprecision: Very Serious.** Low number of patients, Only data from one study, Wide confidence intervals.
20. **Risk of bias: Very Serious. Imprecision: Very Serious.** Low number of patients, Only data from one study.
21. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Very Serious.** Only data from one study.

6.8.23 - 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 *[231]*.

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 *[221]*.

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 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 opt for the 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

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 *[230]*.

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 *[231]*.

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 *[221]*.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Placebo	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.
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 [229] 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 [229] 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 [229] 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 [229] 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 [229] 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.**

6.8.24 - 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 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 opt for the 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.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
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:	Peginterferon lambda for 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 *[233][234]*.

Publication status
One study is only available as a preprint (Jagannathan et al. posted to medRxiv on 23 November 2020 *[233]*) and has therefore not been peer reviewed.

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**	**Absolute effect estimates** Standard care	 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 6 Important	Relative risk 1 (CI 95% 0.21 - 4.82) Based on data from 180 patients in 2 studies. [2] (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 [3]	We are uncertain whether peginterferon lambda increases or decreases serious adverse events (6 events).
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 [232] with included studies: Feld 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [232] with included studies: Feld 2020, Jagannathan 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 [232] 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 [232] with included studies: Jagannathan 2020, Feld 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.

6.8.25 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
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 *[235]*.

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 *[236]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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).
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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	rhG-CSF	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 [131] 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 [131] 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 [131] 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 [131] 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 [131] 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 *[235]*.

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 *[236]*.

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 *[236]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care 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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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)			**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 [131] 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 [131] 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 [131] 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 [131] 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 [131] 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.**

6.8.26 - 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 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 opt for the 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.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[239]*.

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**	**Absolute effect estimates** Placebo	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 [238] 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 [238] 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.

6.8.27 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[242]*.

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 *[241]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	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	Odds Ratio 0.22			**Very Low**	There were too few

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
mechanical ventilation Within 28 days of commencing treatment 9 Critical	(CI 95% 0.04 - 1.24) Based on data from 41 patients in 1 studies. [3] (Randomized controlled)			Due to serious risk of bias and very serious imprecision [4]	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 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 very serious imprecision [8]	We are uncertain whether ruxolitinib improves or worsens clinical improvement (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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Time to improvement Median days to improvement 6 Important	Lower better [15] (Randomized controlled)	15 (Median)	12 (Median) CI 95%	**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)	17 (Median) CI 95%	**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 [240] 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 [240] 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 [240] 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 [240] 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 [240] 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 [240] 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 [240] 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: [242]. **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: [242]. **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 *[242]*.

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 *[241]*.

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**	**Absolute effect estimates** Placebo	Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality (Day 28) Within 28 days of	Odds Ratio 0.13 (CI 95% 0.01 - 2.67) Based on data from 41 patients in 1 studies. [1]			**Very Low** Due to serious indirectness and very serious	There were too few who died to determine whether ruxolitinib makes a difference (3

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
commencing treatment 9 Critical	(Randomized controlled)			imprecision [2]	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).
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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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)	12 (Median) CI 95%	**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)	17 (Median) CI 95%	**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 [240] 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 [240] 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 [240] 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 [240] 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 [240] 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 [240] 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 [240] 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: [242]. **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: [242]. **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.

6.8.28 - Sarilumab

Not recommended

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

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

The Taskforce notes the preprint of the adaptive, multicentre trial by Lescure et al., posted to medRxiv on 3 February, which randomised 420 patients with severe or critical COVID-19 to sarilumab (200 mg or 400 mg) or placebo. This study is currently under review and an updated recommendation will be included in a future version of the guideline.

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 sarilumab 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 and harms associated with sarilumab, including upper respiratory tract infections, neutropenia and injection site reactions *[243]*.

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

Certainty of the Evidence Low

Certainty of the evidence is low for both 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 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 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 opt for the 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.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
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 sarilumab 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 sarilumab 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 sarilumab to treat COVID-19 in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

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

Summary

There remains significant uncertainty whether sarilumab 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 sarilumab with standard care in 450 adults hospitalised with critical COVID-19 requiring organ support (48 received sarilumab and 402 received standard care) *[78]*.

Study characteristics
Mean age of participants was 63 and 61 years, and the proportion of women was 19% and 30% in the sarilumab and standard care arms, respectively. 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. The majority of patients (68% before and 93% after publication of the dexamethasone results from the RECOVERY trial) concomitantly received corticosteroids either at or within 48 hours of enrolment. Pregnant and breastfeeding women were ineligible.

What are the main results?
Most results were presented as adjusted odds ratios or hazard ratios. There was a non-significant reduction in proportion of deaths in the sarilumab arm compared with standard care, and no difference in incidence of serious adverse events.

Our confidence in the results
Certainty of the evidence is low for both 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 studies).

Additional information
According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropenia, increased alanine aminotransferase (ALT) and injection site redness *[243]*.

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Sarilumab	Certainty of the Evidence (Quality of evidence)	Plain text summary
All-cause mortality 21 days after commencing treatment 9 Critical	Relative risk 0.62 (CI 95% 0.35 - 1.09) Based on data from 442 patients in 1 studies. [1] (Randomized controlled)	358 per 1000	222 per 1000 Difference: **136 fewer** per 1000 (CI 95% 233 fewer - 32 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether sarilumab reduces risk of death in critical patients (152 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.36 (CI 95% 0.02 - 5.97) Based on data from 450 patients in 1 studies. [3] (Randomized controlled)	27 per 1000	10 per 1000 Difference: **17 fewer** per 1000 (CI 95% 26 fewer - 134 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether sarilumab increases or decreases serious adverse events in critical patients (11 events).

1. Systematic review [71] with included studies: REMAP-CAP sarilumab. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study.
3. Systematic review [71] with included studies: REMAP-CAP sarilumab. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals, due to few events.

6.8.29 - Sofosbuvir-daclatasvir

Not recommended

Updated

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 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 opt for the treatment.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 *[246]* and 89 adults hospitalised with mild to severe COVID-19 *[251]*. A third study compared sofosbovir-daclatasvir plus hydroxychloroquine with hydroxychloroquine alone in 55 adult outpatients with confirmed COVID-19 *[253]*.

Publication status
One study is only available as a preprint (Yakoot et al. posted to SSRN on 6 October 2020 *[251]*) 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 *[247]*, and known acute harms for daclatasvir include fatigue, diarrhoea, nausea and headache. There are several known and potential interactions with other drugs *[248]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	 Sofosbuvir-daclatasvir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.41 (CI 95% 0.08 - 2) Based on data from 89 patients in 1 studies. [1] (Randomized controlled)			**Very Low** Due to very serious imprecision [2]	We are uncertain whether sofosbuvir-daclatasvir increases or 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	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).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Sofosbuvir-daclatasvir	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important					
Hospitalisation End of follow-up 6 Important	Relative risk 0.26 (CI 95% 0.03 - 2.17) Based on data from 55 patients in 1 studies. [13] (Randomized controlled)	143 per 1000	37 per 1000 Difference: **106 fewer** per 1000 (CI 95% 139 fewer - 167 more)	**Low** Due to very serious imprecision [14]	We are uncertain whether sofosbuvir-daclatasvir decreases incidence of 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	149 per 1000 Difference: **244 fewer** per 1000 (CI 95% 338 fewer - 16 more)	**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 [250] 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 [250] 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 [250] 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 [250] 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 [250] 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 [250] with included studies: Yakoot 2020, Sadeghi 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very Serious.** Low number of patients, Wide confidence intervals.
13. Systematic review [252] 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 [252] 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.

6.8.30 - Sulodexide

Not recommended

New

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 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 opt for the 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 *[255]*.

Publication status
The study is only available as a preprint paper (posted to medRxiv on 7 December 2020) and has therefore not been peer reviewed.

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**	**Absolute effect estimates** Placebo	Sulodexide	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 21 days of commencing treatment	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).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Placebo	Sulodexide	Certainty of the Evidence (Quality of evidence)	Plain text summary
9 Critical					
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 treatment 6 Important	Relative risk 0.6 (CI 95% 0.38 - 0.97) Based on data from 243 patients in 1 studies. [7] (Randomized controlled)	294 per 1000	176 per 1000 Difference: **118 fewer** per 1000 (CI 95% 182 fewer - 9 fewer)	**Very Low** Due to very serious imprecision and serious risk of bias [8]	We are uncertain whether sulodexide increases or decreases 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).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Placebo	Sulodexide	Certainty of the Evidence (Quality of evidence)	Plain text summary
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 [254] 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 [254] 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 [254] 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 [254] 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 [254] 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 [254] 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 [254] 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 [254] 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.

6.8.31 - 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 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 opt for the treatment.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 *[256]*.

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 *[257]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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).
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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Telmisartan	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 [258] 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 [258] 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 [258] 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 [258] 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 [258] 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 [258] 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 [258] . **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 *[256]*.

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 *[257]*.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	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	Relative risk 1.43			**Very Low**	We are uncertain

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Telmisartan	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
hospital 15 days after commencing treatment 6 Important	(CI 95% 1.01 - 2.02) Based on data from 68 patients in 1 studies. [11] (Randomized controlled)			Due to very serious imprecision and serious indirectness [12]	whether 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%	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 [258] 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 [258] 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 [258] 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 [258] 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 [258] 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 [258] 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 [258] . **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.

6.8.32 - 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 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 opt for the 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 *[260]*.

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**	**Absolute effect estimates** Placebo	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					Data for patients

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Triazavirin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
mechanical ventilation Within 28 days of commencing treatment 9 Critical					requiring mechanical ventilation were not reported.
Serious adverse events Within 28 days of commencing treatment 9 Critical	Relative risk 0.8 (CI 95% 0.24 - 2.65) Based on data from 52 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 experienced one or more serious adverse 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)	**7** Days (Median) CI 95%	**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 [259] 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 [259] 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 [259] 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 [259] 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: [260]. **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.**

6.8.33 - 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 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 opt for the 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.

The NC19CET Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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
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 *[92][261][263]*.

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**	**Absolute effect estimates** Standard care	Umifenovir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality Within 21 days of commencing treatment 9 Critical	Based on data from 52 patients in 1 studies. [1]				No patients died.
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	Based on data from 82 patients in 2 studies. [4]				No patients experienced a serious adverse event.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Umifenovir	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important					
Clinical deterioration (mild/mod to sev/crit) [5] Within 21 days of commencing treatment	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).
6 Important					
Clinical improvement [8] Based on chest CT scan 14 days after commencing treatment	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).
6 Important					
Negative PCR Within 14 days of commencing treatment	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).
6 Important					
Discharge from hospital Within 21 days of commencing treatment	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).
6 Important					

1. Systematic review [262] with included studies: Li 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [262] with included studies: [263], Li 2020, Yethindra 2020. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision: Very Serious.** Low number of patients, due to few events.
4. Systematic review [262] 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 [262] with included studies: Yethindra 2020, Li 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 [262] 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 [262] 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 [262] 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.

6.8.34 - 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 panel believes that since there is uncertainty about the benefits, some patients would be willing to opt for the treatment while others may prefer to wait.

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.

The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, informed patients may 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 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 *[264][267][268]*.

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**	**Absolute effect estimates** Standard care	Vitamin D analogues	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality End of follow-up 9 Critical	Relative risk 0.58 (CI 95% 0.05 - 7.18) Based on data from 313 patients in 2 studies. [1] (Randomized controlled)	56 per 1000	32 per 1000 Difference: 24 fewer per 1000 (CI 95% 53 fewer - 346 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether vitamin D analogues decrease death (16 deaths).
Invasive mechanical ventilation End of follow-up	Relative risk 0.47 (CI 95% 0.21 - 1.04) Based on data from 237 patients in 1 studies. [3]	144 per 1000	68 per 1000	**Low** Due to very serious imprecision [4]	We are uncertain whether vitamin D analogues decrease the requirement of invasive

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	 Vitamin D analogues	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	(Randomized controlled)	Difference: **76 fewer** per 1000 (CI 95% 114 fewer - 6 more)			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 [266] 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 [266] 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 [266] 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 [266] 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.

6.8.35 - 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][88][89]*, 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.

6.9 - 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.

6.9.1 - Anakinra

6.9.2 - Ivermectin plus doxycycline

We have found four new studies: one comparing ivermectin plus doxycycline with standard care (Hashim et al. medRxiv doi: 110.1101/2020.10.26.20219345) and three comparing ivermectin plus docxycycline with placebo (Reaz et al. clinicaltrials.gov: NCT04523831, Spoorthi et al. Int Arch Integr Med 2020;7(10)177-82 and Ahmed et al. Int J Infect Dis doi: 10.1016/j.ijid.2020.11.191). These studies are currently under review and a recommendation will be included in a future version of the guideline.

6.9.3 - Nitazoxanide

6.9.4 - Zinc

We have found one study comparing zinc supplementation in addition to hydroxychloroquine with hydroxychloroquine alone (Abd-Elsalam et al. Biol Trace Elem Res doi: 10.1007/s12011-020-02512-1), and two studies comparing zinc with placebo or standard care (Thomas et al. JAMA Netw Open doi: 10.1001/jamanetworkopen.2021.0369 and Patel et al. J Med Virol doi: 10.1002/jmv.26895). These studies are 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 *[281][282][283]*.

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 *[283]*. Participants in Grau-Pujol et al. were given 400 mg hydroxychloroquine daily for four days, followed by 400 mg once weekly for one month *[281]*. In the study by Abella et al. participants received 600 mg of hydroxychloroquine daily for eight weeks *[282]*.

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 *[281]*, one study did not specify whether pregnant or breastfeeding women were eligible *[282]*, and no pregnant women enrolled in the third study, although 30 women reported breastfeeding at baseline *[283]*.

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**	**Absolute effect estimates** Placebo	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	Relative risk 0.75 (CI 95% 0.5 - 1.11)	77	58	**Low** Due to serious	Hydroxychloroquine pre-exposure prophylaxis

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Pre-exp HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
COVID-19 12 weeks 6 Important	Based on data from 1,483 patients in 1 studies. [8] (Randomized controlled)	per 1000	per 1000 Difference: **19 fewer** per 1000 (CI 95% 39 fewer - 8 more)	risk of bias and serious imprecision [9]	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).
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 [280] 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 [280] with included studies: Rajasingham 2020, Abella 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [280] with included studies: Rajasingham 2020, Grau-Pujol 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 [280] with included studies: Grau-Pujol 2020, Abella 2020, Rajasingham 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 [280] 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 [280] 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 [280] 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 NC19CET Consumer Panel believes that as there is evidence of harm with using hydroxychloroquine, informed patients would not choose this treatment.

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 *[284][286]*. 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 *[284]*. In the second trial of 2314 people, mean age was 49 years and 73% were women *[286]*.

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 *[95]*. There are several known and potential interactions with other drugs *[95]*. 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 *[95]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	 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 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)	**Low** Due to serious risk of bias and imprecision [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)	**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	Relative risk 0.68 (CI 95% 0.22 - 2.07) Based on data from 3,318 patients in 2 studies. [7] (Randomized	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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	controlled)				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 [285] 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 [285] 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 [285] 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 [285] with included studies: Boulware 2020, Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Very Serious.** Only 13 events.
9. Systematic review [285] with included studies: Mitja 2020. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Very Serious.** Only 31 events.

11. Systematic review [285] with included studies: Mitja 2020, Boulware 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 [285] with included studies: Boulware 2020, Mitja 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 *[284][286]*. 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 *[284]*. In the second trial of 2314 people, mean age was 49 years and 73% were women *[286]*.

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 *[95]*. There are several known and potential interactions with other drugs *[95]*. 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 *[95]*.

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 *[100][101]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[100][101][102]*. 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**	**Absolute effect estimates** Placebo	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 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)	**Very Low** Due to very serious imprecision and serious indirectness [8]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis improves or worsens all-cause mortality (13 events).
Serious adverse events End of treatment	Relative risk 0.89 (CI 95% 0.44 - 1.81) Based on data from 2,497 patients in 1	13 per 1000	12 per 1000	**Very Low** Due to very serious imprecision and	We are uncertain whether hydroxychloroquine post-exposure

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
6 Important	studies. [9] (Randomized controlled)	Difference: **1 fewer** per 1000 (CI 95% 7 fewer - 11 more)		serious indirectness [10]	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 [285] 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 [285] 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 [285] 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 [285] 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 [285] 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 [285] 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 [285] with included studies: Boulware 2020, Mitja 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 *[287]*. 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

Recommendations are reviewed by the Guidelines Leadership Group and Steering Committee before being published.

The remaining panels review recommendations when relevant to their sp group. In addition, all our recommendations are reviewed by the Consum

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 *[294]*.

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**	**Absolute effect estimates** Conventional therapy	 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 controlled) Follow up: 7 to 90 days.	272 per 1000	256 per 1000 Difference: **16 fewer** per 1000 (CI 95% 90 fewer - 84 more)	**Low** Due to serious imprecision and indirectness [2]	HFNO may have little or no difference on mortality.
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)	Based on data from: 1,247 patients in 4	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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Conventional therapy	HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical	studies.				
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 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).		**Very Low** Due to serious risk of bias and indirectness [11]	We are uncertain whether HFNO increases or decreases dispersal of droplets and aerosols.

1. Systematic reviewwith included studies: [292]. **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: [292]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious. Indirectness: Serious. Imprecision: Serious.**
5. Systematic reviewwith included studies: [292]. **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 *[297]*. 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 *[297]*. 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**	**Absolute effect estimates** HFNO or SOT	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**	**Absolute effect estimates** HFNO or SOT	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**	**Absolute effect estimates** HFNO or SOT	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.

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 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 *[287]*. 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 *[302]*. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation *[307]*.

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 *[300][301][303][304][305][306]*. (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 *[299]*. 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 comp

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**	**Absolute effect estimates** Direct laryngoscopy	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	50	20	Low Due to serious risk of bias and	Videolaryngoscopy may decrease oesophageal intubation.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Direct laryngoscopy	Videolaryngoscopy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
	patients in 4 studies. [3] (Randomized controlled)	per 1000	per 1000 Difference: **30 fewer** per 1000 (CI 95% 41 fewer - 3 fewer)	indirectness [4]	
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 [298] with included studies: Lascarrou 2017, Sulser 2016, Driver 2016, Janz 2016, Gao 2018, Griesdale 2012, Silverberg 2015. **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 [298] 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[307]. **Baseline/comparator:** Control arm of reference used for intervention[307].
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 [302].
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 *[309][310][311][312][313]*.

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 *[310]*. 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**	**Absolute effect estimates** No NMBA	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).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No NMBA	NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 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	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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates No NMBA NMBA	Certainty of the Evidence (Quality of evidence)	Plain text summary
	studies. [15] (Randomized controlled) Follow up: 28 days.			

1. Systematic review [308] with included studies: Forel 2006, Gainnier 2004, Moss 2019, 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 [308] with included studies: Forel 2006, Moss 2019, Papazian 2010, Gainnier 2004, Guervilly 2017. **Baseline/comparator:** Control arm of reference used for intervention.
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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 [308] 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 [308] with included studies: Gainnier 2004, Guervilly 2017, Papazian 2010, Moss 2019. **Baseline/comparator:** Control arm of reference used for intervention.
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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 [308] with included studies: Forel 2006, Guervilly 2017, Gainnier 2004, Papazian 2010, Moss 2019. **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.**
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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 *[309][310][311][312][313]*.

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 *[310]*. 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**	**Absolute effect estimates** No NMBA	NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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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	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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates No NMBA NMBA	Certainty of the Evidence (Quality of evidence)	Plain text summary
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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 [308] 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 [308] with included studies: Gainnier 2004, Guervilly 2017, Papazian 2010, Moss 2019. **Baseline/comparator:** Control arm of reference used for intervention.
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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 [308] with included studies: Moss 2019, Papazian 2010. **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 *[287]*.

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 *[287]*. 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 *[314]*. 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**	**Absolute effect estimates** Not proning	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 *[287]*. 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 *[287]*. 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 *[315]* and the other included 83 patients *[316]*.

Study characteristics
The Extracorporeal Life Support Organization (ELSO) Registry included 1035 patients (median age of 49 years) from

213 hospitals in 36 countries *[315]*. 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% *[316]*. 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	Absolute effect estimates No ECMO 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 *[287]*. 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 *[309][310][311][312][313]*.

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 *[310]*. 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**	**Absolute effect estimates** No NMBA	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).

Outcome Timeframe	Study results and measurements	Absolute effect estimates No NMBA	 NMBA	Certainty of the Evidence (Quality of evidence)	Plain text summary
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 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 [308] with included studies: Gainnier 2004, Guervilly 2017, Moss 2019, Papazian 2010, Forel 2006. **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 [308] with included studies: Forel 2006, Moss 2019, Gainnier 2004, Guervilly 2017, Papazian 2010. **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 [308] with included studies: Guervilly 2017, Forel 2006, 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 [308] with included studies: Papazian 2010, Moss 2019, 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 [308] with included studies: Guervilly 2017, Moss 2019, Papazian 2010, 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 [308] 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 [308] with included studies: Moss 2019, Gainnier 2004, Papazian 2010, Forel 2006, Guervilly 2017. **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 [308] 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 *[302]*. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation *[307]*.

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 *[300][301][303][304][305][306]*. (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 *[299]*. 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 c

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**	**Absolute effect estimates** Direct laryngoscopy	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	50	20	**Very Low** Due to serious risk of bias and	Videolaryngoscopy may decrease oesophageal intubation.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Direct laryngoscopy	 Videolaryngoscopy	Certainty of the Evidence (Quality of evidence)	Plain text summary
	patients in 4 studies. [3] (Randomized controlled)	per 1000	per 1000 Difference: 30 fewer per 1000 (CI 95% 41 fewer - 3 fewer)	indirectness [4]	
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 [298] with included studies: Lascarrou 2017, Griesdale 2012, Silverberg 2015, Gao 2018, Driver 2016, Janz 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 [298] with included studies: Gao 2018, Janz 2016, Silverberg 2015, 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[307]. **Baseline/comparator:** Control arm of reference used for intervention[307].
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 [302].

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 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

Substantial net benefits of the recommended alternative

There is uncertainty around benefits and harms for patients with COVID-19, but 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

There is no available evidence regarding outcomes for the use of LMW heparin or other anticoagulants in patients with COVID-19.

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.

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 No important issues with the recommended alternative

There are no identified equity issues.

Acceptability Important issues, or potential issues not investigated

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 *[317]*, University of Miami *[318]* and British Haematological Society *[319]*. Wording has been adapted for clarity and applicability to the Australian context.

Clinical Question/ PICO

Population: People with moderate COVID-19
Intervention: VTE prophylaxis
Comparator: Standard care

Summary

At present there are no randomised trials that have investigated the benefits of using anticoagulants in patients with moderate COVID-19. There is variability in existing COVID-19-specific recommendations regarding the use of anticoagulants in COVID-19 patients, such that the use of anticoagulants should be considered in all patients *[317][318]*, all immobilised or severely ill patients *[319]* or used based on best existing data and best current local practices *[320]*.

Heparin is contraindicated in individuals with ulcerative conditions showing a tendency to haemorrhage (e.g. gastrointestinal ulcer, ulcerative colitis), cerebral haemorrhage, severe thrombocytopaenia or other severe coagulation disorders, and individuals with an uncontrollable active bleeding state. The use of heparin can result in side effects such as haemorrhage, thrombocytopaenia, skin necrosis or irritation at the injection site, and suppression of aldosterone synthesis with hyperkalaemia and/or metabolic acidosis *[321][322]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
See summary					

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**

Consensus recommendation

Consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) in **adults with severe or critical COVID-19 or other indications**, unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 10^9/L. Where 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 40 mg once daily or dalteparin 5000 IU once daily).

For body weights outside 50-90 kg or heights outside 150-180 cm, calculate the 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

Substantial net benefits of the recommended alternative

There is uncertainty around the benefits and harms for patients with COVID-19. However, there are well-known benefits as well as harms associated with the use of LMW heparin and other anticoagulants in other patient groups.

Certainty of the Evidence

There is currently no evidence relating to increased prophylactic doses of anticoagulants in patients with COVID-19.

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 benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.

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 treatments by patients currently using them for other indications.

Equity — No important issues with the recommended alternative

There are no identified equity issues.

Acceptability — Important issues, or potential issues not investigated

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

Conventional prophylactic doses of anticoagulants seem less effective in preventing VTE in severe or critically ill COVID-19 patients. It is unclear whether higher doses will improve outcomes but the risk-benefit ratio seems acceptable.

Clinical Question/ PICO

Population: Patients with severe COVID-19
Intervention: Therapeutic dose thromboprophylaxis
Comparator: Prophylactic dose thromboprophylaxis

Summary

There remains significant uncertainty whether therapeutic dosage is more effective and safer than prophylactic dosage of thromboprophylaxis in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared therapeutic dosage with prophylactic dosage of thromboprophylaxis in 20 adults hospitalised with severe COVID-19 *[337]*. We are aware of 20 ongoing randomised trials that will include over 14,000 people hospitalised with COVID-19 *[339]*.

Study characteristics
Mean age was 57 years and the proportion of women was 20%. Patients in the therapeutic dose group received subcutaneous enoxaparin with dose according to age and adjusted daily by creatinine clearance estimated by the CKD-EPI equation for two weeks. The maximum dose allowed was 140 mg twice a day. Patients in the prophylactic dosage group received either: a) subcutaneous unfractionated heparin at a dose of 5000 IU TID (if < 120 kg) and 7500 IU TID (if > 120 kg), or b) enoxaparin 40 mg once daily (if < 120 kg) and 40 mg twice daily (if > 120 Kg) according to the doctor's judgment.

Standard care included norepinephrine, neuromuscular blockers, prone positioning and lung-protective ventilation strategy. Patients aged over 85 years, patients with a creatinine clearance (CrCl) < 10 mL/min, severe circulatory shock with a dose of norepinephrine higher than 1.0 µg/kg/min, chronic renal failure in renal replacement therapy, Child B and C chronic liver disease, advanced diseases, such as active cancer, heart failure with functional class III and IV (New York Heart Failure Association), COPD using home oxygen, advanced dementia, significant disability from stroke or severe head injury, cardiorespiratory arrest, recent major surgery or severe trauma in the last 3 weeks, recent stroke in the last 3 months, active bleeding, blood dyscrasia such as hemophilia, Von Willebrand factor deficiency, participation in another clinical investigation, indication for therapeutic anticoagulation due to pulmonary embolism, and acute coronary syndrome were excluded from the study. Pregnant and breastfeeding women were ineligible.

What are the main results?
No patients experienced serious adverse events or major bleeding. There were too few who died to determine whether

therapeutic dose thromboprophylaxis makes a difference to mortality at 28 days (4 deaths) or in-hospital mortality (7 deaths). We are uncertain if therapeutic dose thromboprophylaxis has any impact on the PaO2/FiO2 ratio at day 14, number of ventilator-free days or duration of hospital stay.

Our confidence in the results
Certainty of the evidence is very low for mortality at 28 days, in-hospital mortality, minor bleeding, day 14 PaO2/FiO2 ratio and duration of hospital stay (due to serious risk of bias and very serious imprecision) and low for serious adverse events, major bleeding and ventilator-free days (due to very serious imprecision).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence of these populations in the included study).

Additional information
Common adverse effects of enoxaparin are bleeding, bruising and pain at injection site, nausea, diarrhoea, confusion and mild reversible thrombocytopenia *[338]*.

Heparin is contraindicated in individuals with ulcerative conditions showing a tendency to haemorrhage (e.g. gastrointestinal ulcer, ulcerative colitis), cerebral haemorrhage, severe thrombocytopaenia or other severe coagulation disorders, and individuals with an uncontrollable active bleeding state. The use of heparin can result in side effects such as haemorrhage, thrombocytopaenia, skin necrosis or irritation at the injection site, and suppression of aldosterone synthesis with hyperkalaemia and/or metabolic acidosis *[321][322]*.

Pregnant and breastfeeding women
Enoxaparin is considered safe for use during pregnancy and for women who are breastfeeding *[221]*.

Children
The safety and efficacy of enoxaparin has not been established in children *[338]*.

Older people living with frailty or cognitive impairment
Older people (especially 80 years or older) may be at an increased risk for bleeding complications with therapeutic dosage ranges *[338]*.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prophylactic dose Therapeutic dose	**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% 0.04 - 2.69) Based on data from 20 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 therapeutic dose thromboprophylaxis makes a difference (4 deaths).
In-hospital mortality 9 Critical	Relative risk 0.4 (CI 95% 0.1 - 1.6) Based on data from 20 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 died in hospital to determine whether therapeutic dose thromboprophylaxis makes a difference (7 deaths).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prophylactic dose Therapeutic dose	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Serious adverse events [5] End of follow-up 9 Critical	Based on data from 20 patients in 1 studies. [6] (Randomized controlled)		**Low** Due to very serious imprecision [7]	No patients experienced serious adverse events.
Major bleeding End of follow-up 9 Critical	Based on data from 20 patients in 1 studies. [8] (Randomized controlled)		**Low** Due to very serious imprecision [9]	No patients experienced major bleeding.
Minor bleeding End of follow-up 6 Important	Relative risk 5 (CI 95% 0.27 - 92.62) Based on data from 20 patients in 1 studies. [10] (Randomized controlled)		**Very Low** Due to serious risk of bias and very serious imprecision [11]	There were too few who experienced minor bleeding to determine whether therapeutic dose thromboprophylaxis makes a difference (2 patients).
PaO2/FiO2 ratio Day 14 6 Important	Based on data from: 20 patients in 1 studies. [12] (Randomized controlled)	The mean (SD) PaO2/FiO2 ratio at day 14 was 195 mmHg (108) in the group receiving a prophylactic dose and 261 mmHg (50) in the group receiving a therapeutic dose.	**Very Low** Due to serious risk of bias and very serious imprecision [13]	We are uncertain whether therapeutic dose thromboprophylaxis has any impact on the PaO2/FiO2 ratio at day 14.
Ventilator-free days End of follow-up 6 Important	Based on data from: 20 patients in 1 studies. [14] (Randomized controlled)	The median (IQR) ventilator-free days was 0 (0 to 11) in the prophylactic dose group and 15 (6 to 16) in the therapeutic dose group.	**Low** Due to very serious imprecision [15]	It is unclear if therapeutic dose thromboprophylaxis has any impact on the number of ventilator-free days.
Duration of hospital stay 6 Important	Based on data from: 20 patients in 1 studies. [16] (Randomized controlled)	The median (IQR) duration of hospital stay was 30 (23 to 38) in the prophylactic dose group and 31 (22 to 35) in the therapeutic dose group.	**Very Low** Due to serious risk of bias and very serious imprecision. [17]	We are uncertain whether therapeutic dose thromboprophylaxis has any impact on the duration of hospital stay.

1. Systematic review [323] with included studies: Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Selective outcome reporting: The statistical analysis plan was not available. The protocol specifies the outcome of 28-day mortality but this was probably not before unblinded data were available for analysis.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study, few

events. **Publication bias: No serious.**
3. Systematic review [323] with included studies: Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Selective outcome reporting: The trial registration/protocol did not specify the outcome of in-hospital mortality.. **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. No. of patients experiencing one or more serious adverse events
6. Systematic review [323] with included studies: Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Risk of bias: No serious.** Assessment of serious adverse events not considered to be at risk of bias for unblinded trials.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study, no events. **Publication bias: No serious.**
8. Systematic review [323] with included studies: Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Risk of bias: No serious.** Assessment of major bleeding not considered to be at risk of bias for unblinded trials.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study, no events. **Publication bias: No serious.**
10. Systematic review [323] with included studies: Lemos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Risk of bias: Serious.** 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, few events. **Publication bias: No serious.**
12. Primary study **Supporting references:** [337],
13. **Risk of bias: Serious.** Lack of blinding of participants and personnel, resulting in potential for performance bias (P/F ratio can be augmented with ventilation strategies)., Selective outcome reporting: Analysed change from baseline for P/F rather than comparison of values. The statistical analysis plan was not available.. **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.**
14. Primary study **Supporting references:** [337],
15. **Risk of bias: No serious.** Lack of blinding of outcome assessors unlikely to lead to detection bias for the assessment of ventilator-free days.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
16. Primary study **Supporting references:** [337],
17. **Risk of bias: Serious.** Lack of blinding may result in bias for length of hospital stay, Selective outcome reporting: no statistical analysis plan available, this outcome not pre-specified in trial registry or protocol.. **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: Patients with severe or critical COVID-19
Intervention: Increased-dose thromboprophylaxis
Comparator: Conventional treatment

Summary

There are no randomised trials comparing increased-dose thromboprophylaxis to conventional treatment in patients with COVID-19. There is currently one small 20-patient randomised trial comparing therapeutic dose

thromboprophylaxis with a prophylactic dose thromboprophylaxis in patients with COVID-19 *[337]*. There are 20 ongoing RCTs that will include over 1400 people hospitalised with COVID-19. Additionally, a Cochrane rapid review identified seven retrospective non-randomised studies (5929 participants) but determined that there is insufficient evidence to determine the benefits and harms of thromboprophylaxis in patients hospitalised with COVID-19 *[339]*.

The evidence considered in developing this consensus recommendation included 10 studies reporting on the prevalence of venous thromboembolic (VTE) events in patients with critical or severe COVID-19, ranging from 3.3% to 69% (see Table).

Table Prevalence of VTE events (lowest to highest)

Study	Severity of illnes	VTE events
Goyal 2020 *[335]*	Moderate / Critical	13/393 (3.3%)*
Lodigani 2020 *[327]*	Severe / Critical	28/362 (7.7%)
Helms 2020 *[331]*	Severe / Critical	28/150 (18.7%)
Middeldorp 2020 *[326]*	Severe / Critical	39/198 (20%)
Poissy 2020 *[325]*	Severe / Critical	22/107 (20.6%)
Cui 2020 *[330]*	Severe / Critical	20/81 (25%)
Klok 2020 *[329]*	Severe / Critica	l75/184 (40.8%)
Zhang 2020 *[332]*	Critical	66/143 (46.1%)
Wichmann 2020 *[324]*	Critical	7/12 (58%)
Llitjos 2020 *[328]*	Severe / Critical	18/26 (69%)

*prevalence was 7.7% and 1.1% in patients receiving and not receiving mechanical ventilation, respectively.

Eight studies were assessed as moderate risk of bias due to low external validity—cohort not representative of the target population and lack of random selection/census. One was at high risk of bias *[324]* and one was unclear due to limited reporting of methods *[335]*.

One study reported outcomes in patients with moderate to critical COVID-19 who received systemic anticoagulants versus those who did not *[334]*. Mortality was similar between the groups (22.5% systemic vs 22.8% control). Although more patients receiving systemic anticoagulants required mechanical ventilation (29.8% vs 8.1%), mortality was lower in this group (29.1% vs 62.7%). Major bleeding events were slightly higher in the control group (3.0% vs 1.9%).

A meta-analysis on platelet count in patients with COVID-19 included nine studies (1779 participants) *[333]*. Platelet count was significantly lower in patients with more severe compared to less severe COVID-19 (mean -31 x 109/L), with the lowest platelet counts linked to mortality (mean -48 x 109/L). The authors concluded that low platelet count is associated with increased risk of severe disease and mortality in patients with COVID-19.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** control	prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
See summary					

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 Taskforce awaits publication of the relevant trial results to consider changes to the recommendations above.

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 NC19CET 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 *[341][342][343][344][345][346][347][348][349][350][351][352][353][354]*. 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 *[355][356][357][358]*. 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**	**Absolute effect estimates** Stopping concomitant ACEIs/ARBs	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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Stopping concomitant ACEIs/ARBs	 Continued use of concomitant ACEIs/ARBs	Certainty of the Evidence (Quality of evidence)	Plain text summary
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.
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 [357] . **Baseline/comparator:** Systematic review [356] .
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 [356] . **Baseline/comparator:** Systematic review [356] .
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 [355].
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 *[359]*. 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 NC19CET 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 NC19CET 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 *[360]*, NICE [NG168] *[361]* and NICE [NG 166] *[362]*. 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) *[360]*. 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 *[362]*.

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 *[361]*. 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 *[363][364]*.

Abrupt withdrawal of corticosteroids can lead to acute adrenal insufficiency or exacerbation of symptoms of asthma or COPD.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	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 - 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.

12.1 - 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 *[365]*. 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.

12.2 - 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) *[366]*. 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% (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 *[367]* (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 *[375]*. 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Vaginal birth	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.**

12.3 - 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 *[368][369]*.

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.

12.4 - 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 *[370][371]*. 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 for the risk of transmission of COVID-19 with skin-to-skin contact is available. However, important indirect evidence is available from an observational cohort study in the US of newborns whose mothers had confirmed COVID-19 *[375]*. While the number of newborns who received skin-to-skin care was not reported, the standard of care at all participating institutions was to initiate newborn skin-to-skin contact with mothers in the first hour of life if medically appropriate.

The Salvatore study reported on 106 newborns born to 116 mothers who were positive for COVID-19. Mothers could practice skin-to-skin care in the delivery room, during their hospital stay and after discharge, provided they were wearing a surgical mask and with proper hand hygiene. 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. All newborns returned negative test results for SARS-CoV-2 at all timepoints. There was no evidence that skin-to-skin contact increased the newborn infection risk for COVID-19.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No skin-to-skin contact	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.**

12.5 - 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 *[373]*. 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 37 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 *[374]*. 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.

Additional evidence is available from an observational cohort study in the US of newborns whose mothers had confirmed COVID-19 *[375]*. 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.

Publication status
Update searches are planned as needed to keep the living systematic review current. In addition to our daily evidence surveillance processes, we follow up with the corresponding author every two months to request information on the review's status.

Study characteristics
Living systematic review: SARS-CoV-2 infection status by feeding type was available from 37 studies for 77 newborns and infants where breast milk samples were available. Breast milk samples were tested for SARS-CoV-2 RNA using RT-PCR analysis. No studies 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.

Cohort study: 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: of the 37 included studies where breast milk samples were available, 14 out of 72 newborns

had confirmed COVID-19, diagnosed either by viral RNA detection or by serology (Table 1).

Of the 27 newborns who were breastfed (n=23) or received mixed feeding (n=4), 10 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).

Nine out of 68 breast milk samples collected from COVID-19 positive mothers tested positive for SARS-CoV-2 via RT-PCR assay. Of the six newborns and infants who were known to be exposed to breast milk with detectable viral RNA, four tested positive and two tested negative for SARS-CoV-2.

The authors make note of 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.

Additional cohort study: for 82 newborns with follow-up data, 64/82 (78%) were breastfed at 5-7 days and 45/53 (85%) were breastfed at 1 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 living systematic review 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 where breast milk samples were available (N=37)

Feeding type	Confirmed COVID-19	Negative COVID-19	Total
Newborns ≤ 28 days			
Breast milk	8	15	23
Mixed feeding	2	2	4
Formula	2	16	18
Not reported feeding practice	2	25	27
Subtotal	**14**	**58**	**72**
Infants > 28 days			
Breast milk	2	0	2
Mixed feeding	3	0	3
Formula	0	0	0
Not reported feeding practice	0	0	0
Subtotal	**5**	**0**	**5**

Table 2 Studies where breast milk samples were not available (N=303)

Feeding type	Confirmed COVID-19	Negative COVID-19	Total
Newborns ≤ 28 days			
Breast milk	16	137	153
Mixed feeding	3	7	10
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**

Outcome Timeframe	Study results and measurements	Absolute effect estimates No breastfeeding or breast milk	 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: 72 patients in 37 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 [374]. **Supporting references:** [375], 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 [374].
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.

12.6 - 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 *[376]* as well as duration of breastfeeding *[377]*. 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 *[366]*. 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 newborns	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 *[375]*. 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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No rooming-in Rooming-in	**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: 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 their mother, six were cared for in the same room as their mother and for 16 newborns the approach taken was not reported.	**Very Low** Due to very serious risk of bias, and serious imprecision, indirectness and inconsistency [2]	We are uncertain whether rooming-in increases or decreases the number of infected newborns.

1. Number of infected neonates within 30 days of breastfeeding or receiving expressed breast milk
2. **Risk of bias: Very Serious.** Evidence is derived from case studies and case reports.. **Inconsistency: Serious.** Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities.. **Indirectness: Serious.** Differences between the outcomes of interest and those reported. Testing of breast milk not reported.. **Imprecision: Serious.** Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities.. **Publication bias: No serious.**

13 - 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.

13.1 - 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 *[381]*. The US Centers for Disease Control and Prevention has named it multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) *[379]*. WHO has also defined this condition and used the label MIS-C *[380]*.

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 *[378]*. 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) *[381]* 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 *[382]*).

Royal College of Paediatrics and Child Health (PIMS-TS) case definition *[381]*

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 *[379]*

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 *[380]*

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) *[381]*.

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 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.

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.

13.1.1 - Intravenous immunoglobulin

Consensus recommendation

Consider using intravenous immunoglobulin (2 g/kg per dose) in children and adolescents who meet PIMS-TS criteria or have features of Kawasaki disease related to COVID-19.

Practical Info

Primary classification of PIMS-TS should be based on the presenting phenotype (adapted from Harwood *[383]*:

1. Kawasaki disease-like: complete and incomplete, classified using the American Heart Association criteria *[384]*
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 intravenous immunoglobulin in children and adolescents for other diseases, particularly in Kawasaki disease, which shares common characteristics and partially overlaps with PIMS-TS. Benefits outweigh the risks for using intravenous immunoglobulin in this population.

Certainty of the Evidence

No randomised trials have been identified assessing the use of intravenous immunoglobulin 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. As intravenous immunoglobulin is a blood-derived product, some may decline this intervention.

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 is generally a well-accepted intervention, and there are no important issues regarding acceptability. However, some groups may decline this intervention as it is a blood-derived product.

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. Initial reports show it has been used to treat PIMS-TS patients. No randomised trials have been identified.

13.1.2 - Corticosteroids

Consensus recommendation

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

Intravenous 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.

In certain cases, Intravenous corticosteroids may be indicated as a first-line option in combination with intravenous immunoglobulin.

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 common 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

No randomised trials have been identified assessing the use of corticosteroids for the treatment of PIMS-TS.

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.

13.1.3 - 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 *[385][386]*.

13.1.4 - 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.

14 - 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
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
PaO2	Partial pressure of arterial oxygen
PCR	Polymerase chain reaction
PEEP	Positive end-expiratory pressure
PIMS-TS	Paediatric multisystem inflammatory syndrome - temporally associated with SARS-CoV-2
PPE	Personal protective equipment
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

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