COVID-19 rapid guideline: Managing COVID-19

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The National Institute for Health and Care Excellence (NICE)

Contact

Sections

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Consensus recommendation

Communicate with people with COVID-19, and their families and carers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups (including NHS Volunteer Responders), to UK government guidance on the mental health and wellbeing aspects of COVID-19 and UK government guidance on supporting children and young people's mental health and wellbeing, and to Royal College of Paediatrics and Child Health resources for parents and carers.

Remark: Give people information in a way that they can use and understand, to help them take part in decisions about their care. Follow relevant national guidance on communication, providing information (including in different formats and languages) and shared decision making, for example, NICE's guideline on patient experience in adult NHS services.

The Royal College of Obstetricians and Gynaecologists has produced information on COVID-19 and pregnancy for pregnant women and their families.

Consensus recommendation

For adults with COVID-19, explain:

- that the typical symptoms are cough, fever, and loss of sense of smell or taste, but that they may also have breathlessness (which may cause anxiety), delirium (which may cause agitation), fatigue, headache, muscle aches and sore throat
- that other symptoms may be drowsiness (particularly in older people), poor appetite, and chest discomfort or pain
- that they and people in close contact with them or in the same household (including those caring for them) should follow the UK guidance on self-isolation and the UK guidance on protecting vulnerable people
- that they are likely to feel much better in a week if their symptoms are mild
- who to contact if their symptoms get worse, for example, NHS 111 online.

Consensus recommendation

For carers of people with COVID-19 who should isolate but are unable to (for example, people with dementia), signpost to relevant support and resources.

Remark: For example, the Alzheimer's Society has information on staying safe from coronavirus and reducing the risk of infection.

Consensus recommendation

For children and young people under 18 years with COVID-19, explain:

- that additional symptoms (to those found in adults) may include grunting, nasal flare, nasal congestion, poor appetite, gastrointestinal symptoms, skin rash and conjunctivitis
- that they and people in close contact with them or in the same household (including those caring for them) should follow the UK guidance on self-isolation and the UK guidance on protecting vulnerable people
- that they are likely to feel much better in a week if their symptoms are mild
- who to contact if their symptoms get worse, for example, NHS 111 online
- that the presence of fever, rash, abdominal pain, diarrhoea or vomiting may indicate paediatric inflammatory multisystem syndrome (PIMS)
- how and when to seek medical help if PIMS is suspected.

Consensus recommendation

In the community, consider the risks and benefits of face-to-face and remote care for each person. Where the risks of face-to-face care outweigh the benefits, remote care can be optimised by:

- offering telephone or video consultations (see BMJ guidance on Covid-19: a remote assessment in primary care for a useful guide, including a visual summary for remote consultation)
- cutting non-essential face-to-face follow up
- using electronic prescriptions rather than paper
- using different methods to deliver medicines to people, for example, pharmacy deliveries, postal services and NHS volunteers, or introducing drive-through pick-up points for medicines.

Consensus recommendation

When possible, discuss the risks, benefits and possible likely outcomes of the treatment options with people with COVID-19, and their families and carers. Use decision support tools (when available).

Remark: This will help people express their preferences about their treatment and escalation plans. Bear in mind that these discussions may need to take place remotely.

Consensus recommendation

For people with pre-existing advanced comorbidities, find out if they have advance care plans or advance decisions to refuse treatment, including do not attempt cardiopulmonary resuscitation decisions. Document this clearly and take account of these in planning care.

5 - Assessment

5.1 - In the community

Consensus recommendation

5.1.1 Identifying severe COVID-19

Use the following signs and symptoms to help identify people with COVID-19 with the most severe illness:

- severe shortness of breath at rest or difficulty breathing
- reduced oxygen saturation levels measured by pulse oximetry (see the recommendation on pulse oximetry levels that indicate serious illness)
- coughing up blood
- blue lips or face
- feeling cold and clammy with pale or mottled skin
- collapse or fainting (syncope)
- new confusion
- becoming difficult to rouse
- reduced urine output.

Remark: For signs and symptoms to help identify paediatric inflammatory multisystem syndrome (PIMS) temporarily associated with COVID-19, see the guidance on PIMS from the Royal College of Paediatrics and Child Health.

Consensus recommendation

When pulse oximetry is available, use oxygen saturation levels below 94% for adults (or below 88% for adults with known type 2 respiratory failure) and below 91% for children in room air at rest to identify people who are seriously ill. See NHS England's guide to pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings.

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

Info Box

Assessing shortness of breath (dyspnoea) is important, but may be difficult via remote consultation. Tools such as the Medical Research Council's dyspnoea scale or the Centre for Evidence Based Medicine's review of ways of assessing dyspnoea (breathlessness) by telephone or video can be useful.

The NEWS2 tool may be used in adults in addition to clinical judgment to assess a person's risk of deterioration. Note that use of NEWS2 is not advised in children or pregnant women. Although the NEWS2 tool is not validated for predicting the risk of clinical deterioration in prehospital settings, it may be a helpful adjunct to clinical judgement in adults. A face-to-face consultation should not be arranged solely to calculate a NEWS2 score.

Locally approved Paediatric Early Warning Scores should be used for children. When using early warning scores, ensure that readings are based on calibrated machines. Be aware that readings may be incomplete when doing remote consultations.

Consensus recommendation

For people with severe respiratory symptoms associated with COVID-19 (for example, suspected pneumonia) being managed in the community, see the recommendation on venous thromboembolism in hospital-led acute care in the community.

Consensus recommendation

5.1.2 Care planning

Discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (for example, virtual wards or hospital at home teams).

Remark: Some benefits and risks may be similar for all patients (for example, improved diagnostic tests and access to treatments, or better contact with families in the community), but others may be personal to the individual (such as loss of access to carers who can anticipate needs well in someone unable to communicate themselves, or risks of spreading COVID-19).

Consensus recommendation

Explain that people with COVID-19 may deteriorate rapidly. Discuss future care preferences at the first assessment to give people who do not have existing advance care plans an opportunity to express their preferences.

5.2 - In hospital

Consensus recommendation

When a person is admitted to hospital with COVID-19, ensure a holistic assessment is done, including discussion about their treatment expectations and care goals:

- Document and assess the stability of underlying health conditions, involving relevant specialists as needed.
- Use the Clinical Frailty Scale (CFS) when appropriate, available from the NHS Specialised Clinical Frailty Network, to assess baseline health and inform discussions on treatment expectations.
- Use the CFS within an individualised assessment of frailty.
- Do not use the CFS for younger people, people with stable long-term disabilities (for example, cerebral palsy), learning disabilities or autism. Make an individualised assessment of frailty in these people, using clinical assessment and alternative scoring methods.
- Record the assessment and discussion in the person's medical records.

Remark: For assessment of paediatric inflammatory multisystem syndrome (PIMS), follow the guidance on PIMS from the Royal College of Paediatrics and Child Health.

Consensus recommendation

When making decisions about the care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, for example, people with advanced dementia, see the NICE guideline on decision-making and mental capacity.

Ensure discussions on significant care interventions involve families and carers as appropriate, and local experts or advocates.

6 - Management

6.1 - In the community

6.1.1 - Care planning

Consensus recommendation

Put treatment escalation plans in place in the community after sensitively discussing treatment expectations and care goals with people with COVID-19, and their families and carers.

Remark: People with COVID-19 may deteriorate rapidly. If it is agreed that the next step is a move to secondary care, ensure that they and their families understand how to access this with the urgency needed. If the next step is other community-based support (whether virtual wards, hospital at home services or palliative care), ensure that they and their families understand how to access these services, both in and out of hours.

6.1.2 - Managing cough

Consensus recommendation

Encourage people with cough to avoid lying on their backs, if possible, because this may make coughing less effective.

Remark: Be aware that older people or those with comorbidities, frailty, impaired immunity or a reduced ability to cough and clear secretions are more likely to develop severe pneumonia. This could lead to respiratory failure and death.

Consensus recommendation

Use simple measures first, including advising people over 1 year with cough to take honey.

Remark: The dose is 1 teaspoon of honey.

Consensus recommendation

Consider short-term use of codeine linctus, codeine phosphate tablets or morphine sulfate oral solution in people 18 years and over to suppress coughing if it is distressing. Seek specialist advice for people under 18 years.

Remark: See practical info for dosages for treatments to manage cough in people 18 years and over.

6.1.3 - Managing fever

Consensus recommendation

Advise people with COVID-19 and fever to drink fluids regularly to avoid dehydration. Support their families and carers to help when appropriate. Communicate that fluid intake needs can be higher than usual because of fever.

Consensus recommendation

Advise people to take paracetamol or ibuprofen if they have fever and other symptoms that antipyretics would help treat. Tell them to continue only while both the symptoms of fever and the other symptoms are present.

Remark: People can take paracetamol or ibuprofen when self-medicating for symptoms of COVID-19, such as fever (see the Central Alerting System: novel coronavirus - anti-inflammatory medications for further details of ibuprofen including dosage).

For people 18 years and over, the paracetamol dosage is 1 g orally every 4 to 6 hours (maximum 4 g per day). See the BNF and Medicines and Healthcare products Regulatory Agency advice for appropriate use and dosage in specific adult populations.

For children and young people over 1 month and under 18 years, see the dosing information on the pack or the BNF for children.

Rectal paracetamol, if available, can be used as an alternative. For rectal dosage information, see the BNF and BNF for children.

6.1.4 - Managing breathlessness

Consensus recommendation

Identify and treat reversible causes of breathlessness, for example, pulmonary oedema, pulmonary embolism, chronic obstructive pulmonary disorder and asthma.

Remark: For further information on identifying and managing pulmonary embolism, see the NICE guideline on venous thromboembolic diseases: diagnosis, management and thrombophilia testing.

Consensus recommendation

When significant medical pathology has been excluded or further investigation is inappropriate, the following may help to manage breathlessness as part of supportive care:

- keeping the room cool
- encouraging relaxation and breathing techniques, and changing body positioning
- encouraging people who are self-isolating alone to improve air circulation by opening a window or door.

If hypoxia is the likely cause of breathlessness:

- consider a trial of oxygen therapy
- discuss with the person, their family or carer possible transfer to and evaluation in secondary care.

Remark: Breathlessness with or without hypoxia often causes anxiety, which can then increase breathlessness further.

6.1.5 - Managing anxiety, delirium and agitation

Consensus recommendation

Assess reversible causes of delirium. See the NICE guidance on delirium: prevention, diagnosis and management.

Consensus recommendation

Address reversible causes of anxiety by:

- exploring the person's concerns and anxieties
- explaining to people providing care how they can help.

Consensus recommendation

Consider trying a benzodiazepine to manage anxiety or agitation. See practical info for treatments for managing anxiety, delirium and agitation in people 18 years and over. Seek specialist advice for people under 18 years.

6.1.6 - Managing medicines

Consensus recommendation

When supporting people with symptoms of COVID-19 who are having care in the community delivered by social care, follow the NICE guideline on managing medicines for adults receiving social care in the community. This includes processes for ordering and supplying medicines, and transporting, storing and disposing of medicines.

Consensus recommendation

When prescribing, handling, administering and disposing of medicines in care homes and hospices follow the NICE guideline on managing medicines in care homes and the UK government COVID-19 standard operating procedure for running a medicines re-use scheme in a care home or hospice setting.

6.2 - In hospital

6.2.1 - Deciding when to escalate treatment

Consensus recommendation

Base decisions about escalating treatment within the hospital on the likelihood of a person's recovery. Take into account their treatment expectations, goals of care and the likelihood that they will recover to an outcome that is acceptable to them.

Remark: For support with decision making, see advice on ethics from the British Medical Association, ethical guidance from the Royal College of Physicians and the General Medical Council advice on decision-making and consent.

Consensus recommendation

Ensure healthcare professionals have access to resources to support discussions about treatment plans (see, for example, decision-making for escalation of treatment and referring for critical care support, and an example decision support form).

Consensus recommendation

Document referral to and advice from critical care services and respiratory support units in a standard format. When telephone advice from critical care or respiratory support units is appropriate, this should still be documented in a standard format (see an example of a tool for documentation).

6.2.2 - Escalating and de-escalating treatment

Consensus recommendation

Start all advanced respiratory support or organ support with a clear plan of how it will address the diagnosis and lead to agreed treatment goals (outcomes).

Stop advanced respiratory support or organ support when it is considered that it will no longer result in the desired overall goals (outcomes). Record the decision and the discussion with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate).

Info Box

NICE is reviewing evidence on respiratory support and further recommendations will be added in a future version of this guideline.

6.2.3 - Delivering services in critical care and respiratory support units

Consensus recommendation

Trusts should review their management for people who are deteriorating strategy, and use of the track-and-trigger system (NEWS2 has been endorsed by NHS England and Improvement), to allow for telephone advice rather than face-to-face review from critical care or respiratory support units when clinically appropriate. See the NICE guideline on acutely ill adults in hospital for recommendations on identifying patients whose clinical condition is deteriorating or is at risk of deterioration.

Remark: See the Royal College of Physician's information on the place of NEWS2 in managing patients with COVID-19.

7 - Therapeutics for COVID-19

7.1 - Antibiotics

Consensus recommendation

Do not use antibiotics for preventing or treating COVID-19.

Remark: Only use antibiotics if there is strong clinical suspicion of additional bacterial infection.

7.2 - Corticosteroids

Strong recommendation New

Offer dexamethasone, or either hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable, to people with COVID-19 who:

- need supplemental oxygen to meet their prescribed oxygen saturation levels or
- have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

Continue corticosteroids for up to 10 days unless there is a clear indication to stop early, which includes discharge from hospital or a hospital-supervised virtual COVID ward.

Remark: Being on a hospital-supervised virtual COVID ward is not classed as being discharged from hospital.

See Practical info for dosage information.

For full details of adverse events and contraindications, see the summaries of product characteristics.

For children with a greater than 44-week corrected gestational age, follow the risk criteria set out in Royal College of Paediatric and Child Health guidance for assessing children admitted to hospital with COVID-19. For preterm babies with a corrected gestational age of less than 44 weeks, seek specialist advice.

Weak recommendation against New

Do not routinely use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen, unless there is another medical indication to do so.

7.3 - Remdesivir

Info Box

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'

Weak recommendation

Consider remdesivir for 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, who are in hospital and on supplemental oxygen but not on invasive mechanical ventilation.

Complete the 5-day course of treatment if remdesivir has been started and there is subsequent progression to invasive mechanical ventilation.

Remark:

It is unclear whether the 5-day or the 10-day regimen of remdesivir is the optimal treatment duration.

The criteria for accessing remdesivir in the UK are outlined in NHS England's Interim Clinical Commissioning Policy on remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older).

Only in research settings

Do not use remdesivir for COVID-19 pneumonia in adults, young people and children who are in hospital and on invasive mechanical ventilation, except within the context of a clinical trial setting.

7.4 - Tocilizumab

Info Box New

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'.

Strong recommendation New

Offer tocilizumab to adults in hospital with COVID-19 if all of the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.

And they either:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Remark: In April 2021, the marketing authorisations for tocilizumab do not cover use in COVID-19. See NICE's information on prescribing medicines for more about off-label and unlicensed use of medicines.

The recommended dosage for tocilizumab is a single dose of 8 mg/kg by intravenous infusion. The total dose should not exceed 800 mg.

For tocilizumab use in pregnancy, follow the Royal College of Obstetrics and Gynaecology guidance on coronavirus (COVID-19) infection and pregnancy.

For full details of adverse events and contraindications, see the summaries of product characteristics for tocilizumab.

See NHS England's Interim Clinical Commissioning Policy on tocilizumab for hospitalised patients with COVID-19 pneumonia (adults) for further information.

Only in research settings New

Consider tocilizumab for children and young people who have severe COVID-19 or paediatric inflammatory multisystem syndrome only if they are 1 year and over, and only in the context of a clinical trial.

7.5 - Sarilumab

Info Box New

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'.

Weak recommendation New

Consider sarilumab for adults in hospital with COVID-19 only if tocilizumab cannot be used or is unavailable. Use the same eligibility criteria as those for tocilizumab. That is, if all of the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by sarilumab.

And they either:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Remark: In April 2021, the marketing authorisations for sarilumab do not cover use in COVID-19. See NICE's information on prescribing medicines for more about off-label and unlicensed use of medicines.

The recommended dosage for sarilumab is a single dose of 400 mg by intravenous infusion.

For sarilumab use in pregnancy, follow the Royal College of Obstetrics and Gynaecology guidance on coronavirus (COVID-19) infection and pregnancy.

For full details of adverse events and contraindications, see the summaries of product characteristics.

See NHS England's Interim Clinical Commissioning Policy on sarilumab for critically ill patients with COVID-19 pneumonia (adults) for further information.

7.6 - Colchicine

Info Box New

NICE is reviewing the evidence for colchicine.

7.7 - Low molecular weight heparins

Info Box

For recommendations on the therapeutic use of low molecular weight heparins, see the section on venous thromboembolism (VTE) prophylaxis.

7.8 - Vitamin D supplementation

Info Box

For recommendations on vitamin D, see the NICE COVID-19 rapid guideline on vitamin D.

8 - Preventing and managing acute complications

8.1 - Acute kidney injury (AKI)

Info Box

In people with COVID-19, AKI:

- may be common, but prevalence is uncertain and depends on clinical setting (the Intensive Care National Audit and Research Centre's report on COVID-19 in critical care provides information on people in critical care who need renal replacement therapy for AKI)
- is associated with an increased risk of dying
- can develop at any time (before, during or after hospital admission)
- may be caused by volume depletion (hypovolaemia), haemodynamic changes, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology or rhabdomyolysis
- may be associated with haematuria, proteinuria and abnormal serum electrolyte levels (both increased and decreased serum sodium and potassium).

Info Box

In people with COVID-19:

- maintaining optimal fluid status (euvolaemia) is difficult but critical to reducing the incidence of AKI
- treatments for COVID-19 may increase the risk of AKI
- treatments for pre-existing conditions may increase the risk of AKI
- fever and increased respiratory rate increase insensible fluid loss.

8.1.1 - Assessing and managing acute kidney injury (AKI)

Info Box

The potassium binders patiromer and sodium zirconium cyclosilicate can be used as options alongside standard care for the emergency management of acute life-threatening hyperkalaemia (see NICE's technology appraisal guidance on patiromer and sodium zirconium cyclosilicate for treating hyperkalaemia).

Info Box

For information on assessing and managing AKI, see the NICE guideline on acute kidney injury: prevention, detection and management.

For information on using intravenous fluids, see the NICE guideline on intravenous fluid therapy in adults in hospital and NICE guideline on intravenous fluid therapy in children and young people in hospital.

8.1.2 - Follow up

Consensus recommendation

Monitor people with chronic kidney disease for at least 2 years after AKI, in line with the NICE guideline on chronic kidney disease in adults: assessment and management.

Remark: See guidance on care after hospital discharge in the Royal College of General Practitioners AKI toolkit.

8.2 - Acute myocardial injury

8.2.1 - Diagnosing acute myocardial injury

Consensus recommendation

For people in hospital with COVID-19 with signs or symptoms that suggest acute myocardial injury, measure high sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro B-type natriuretic peptide, and do an ECG.

Use the following test results to help inform a diagnosis:

- evolving ECG changes suggesting myocardial ischaemia
- an NT-proBNP level above 400 ng/litre
- high levels of hs-cTnI or hs-cTnT, particularly levels increasing over time.

Info Box

Elevated troponin levels may reflect cardiac inflammatory response to severe COVID-19 rather than acute coronary syndrome.

8.2.2 - Managing myocardial injury

Consensus recommendation

For all people with COVID-19 and suspected or confirmed acute myocardial injury:

- monitor in a setting where cardiac or respiratory deterioration can be rapidly identified
- do continuous ECG monitoring
- monitor blood pressure, heart rate and fluid balance.

Consensus recommendation

For people with a clear diagnosis of myocardial injury:

- seek specialist cardiology advice on treatment, further tests and imaging
- follow local treatment protocols.

Consensus recommendation

For people with a high clinical suspicion of myocardial injury, but without a clear diagnosis:

- repeat high sensitivity troponin (hs-cTnI or hs-cTnT) measurements and ECG monitoring daily, because dynamic change may help to monitor the course of the illness and establish a clear diagnosis
- seek specialist cardiology advice on further investigations such as transthoracic echocardiography and their frequency.

Remark: See also the management section for recommendations on care planning and recommendations on escalating and de-escalating treatment.

Info Box

See the Medicines and Healthcare products Regulatory Agency's Drug Safety Update on erythromycin: caution required due to cardiac risks (QT interval prolongation); drug interaction with rivaroxaban.

8.3 - Venous thromboembolism (VTE) prophylaxis

Info Box

Definitions

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'

Hospital-led acute care in the community is defined as a setting in which people who would otherwise be admitted to hospital have acute medical care provided by members of the hospital team, often working with the person's GP team. They include hospital at home services and COVID-19 virtual wards.

Intermediate dose VTE prophylaxis is defined as the standard prophylactic dose of anticoagulant for people who are acutely ill and having medical care, given twice daily instead of once daily (and doubling of the usual daily dose).

Treatment dose is defined as the licensed dose of anticoagulation used to treat confirmed VTE.

8.3.1 - In hospital

Consensus recommendation

For young people and adults with COVID-19 that is being managed in hospital, assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review. Use a risk assessment tool published by a national UK body, professional network or peer-reviewed journal.

Consensus recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH), unless contraindicated, for young people and adults with COVID-19 who:

- are likely to be in hospital for the next 3 days
- need supplemental oxygen and who are not yet receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Treatment should be for a minimum of 14 days or until discharge. Dose reduction may be needed to respond to any changes in a person's clinical circumstances. See the recommendation on people with COVID-19 who need high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation or palliative care.

Remark: For people with COVID-19 who do not need supplemental oxygen, follow the recommendations in the NICE guideline on venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism.

In March 2021, the use of a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See NICE's information on prescribing medicines.

Consensus recommendation

For young people and adults with COVID-19 who are having supplemental oxygen and a treatment dose of a low molecular weight heparin (LMWH), and now need high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation or palliative care:

- reduce the dose of the LMWH to a locally agreed intermediate or standard dose
- reassess VTE and bleeding risks daily.

Remark: In March 2021, the use of intermediate or treatment doses of a LMWH for VTE prophylaxis were off-label uses of parenteral anticoagulants. See NICE's information on prescribing medicines.

Consensus recommendation

For young people and adults who are already receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation and are on a standard prophylactic dose of a low molecular weight heparin (LMWH) for VTE prophylaxis:

- consider increasing anticoagulation to an intermediate dose
- reassess VTE and bleeding risks daily.

Remark: In March 2021, the use of an intermediate dose of a LMWH for VTE prophylaxis was an off-label use of parenteral anticoagulants. See NICE's information on prescribing medicines.

Consensus recommendation

Do not base prophylactic dosing of heparin on levels of D-dimer.

Consensus recommendation

For young people and adults with COVID-19 who need supplemental oxygen and who progress onto high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, only offer continuing a treatment dose of a low molecular weight heparin as part of a nationally approved clinical trial.

Consensus recommendation

For people at extremes of body weight or with impaired renal function, consider adjusting the dose of low molecular weight heparins in line with the summary of product characteristics and locally agreed protocols.

Consensus recommendation

For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).

Remark: In March 2021, LMWHs, fondaparinux sodium and UFH were off label for people under 18 years. See NICE's information on prescribing medicines.

Consensus recommendation

Start VTE prophylaxis as soon as possible and within 14 hours of admission.

Consensus recommendation

For people who are already having anticoagulation treatment for another condition when admitted to hospital:

- continue their current treatment dose of anticoagulant unless contraindicated by a change in clinical circumstances
- consider switching to a low molecular weight heparin (LMWH) if their current anticoagulant is not an LMWH and their clinical condition is deteriorating.

Consensus recommendation

If a person's clinical condition changes, assess the risk of VTE, reassess bleeding risk and review VTE prophylaxis.

Consensus recommendation

Organisations should collect and regularly review information on bleeding and other adverse events in people with COVID-19 having treatment or intermediate doses of pharmacological VTE prophylaxis.

Consensus recommendation

Ensure that people who will be completing pharmacological VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.

8.3.2 - In hospital-led acute care in the community

Consensus recommendation

For people with COVID-19 managed in hospital-led acute care in the community settings:

- assess the risks of VTE and bleeding
- consider pharmacological prophylaxis if the risk of VTE outweighs the risk of bleeding.

8.3.3 - People with COVID-19 and additional risk factors

Consensus recommendation

For women with COVID-19 who are pregnant or have given birth within the past 6 weeks, follow the advice on VTE prevention in the Royal College of Obstetricians and Gynaecologists guidance on coronavirus (COVID-19) in pregnancy.

Consensus recommendation

For children with COVID-19 admitted into hospital, follow the advice on COVID-19 guidance for management of children admitted to hospital in the Royal College of Paediatrics and Child Health guidance.

8.3.4 - Information and support

Consensus recommendation

Give people with COVID-19, and their families or carers if appropriate, information about the benefits and risks of VTE prophylaxis.

Remark: See the recommendations on giving information and planning for discharge in the NICE guideline on venous thromboembolism in over 16s, including information on alternatives to heparin for people who have concerns about using animal products.

Consensus recommendation

Offer people the opportunity to take part in ongoing clinical trials on COVID-19.

8.4 - Suspected or confirmed co-infection

Consensus recommendation

Do not offer an antibiotic for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.

Remark: Antibiotics do not work on viruses, and inappropriate antibiotic use may reduce availability. Also, inappropriate use may lead to *Clostridioides difficile* infection and antimicrobial resistance, particularly with broad-spectrum antibiotics.

Info Box

Evidence as of March 2021 suggests that bacterial co-infection occurs in less than about 8% of people with COVID-19, and could be as low as 0.1% in people in hospital with COVID-19. Viral and fungal co-infections occur at lower rates than bacterial co-infections.

Secondary infection or co-infection (bacterial, viral or fungal) is more likely the longer a person is in hospital and the more they are immunosuppressed (for example, because of certain types of treatment).

The type and number of secondary infections or co-infections will vary depending on the season and any restrictions in place (for example, lockdowns).

8.4.1 - Identifying secondary bacterial pneumonia

Consensus recommendation

In hospitals or other acute delivery settings (for example, virtual wards), to help identify non-SARS-CoV-2 viral, fungal or bacterial pneumonia, and to inform decision making about using antibiotics, consider the following tests:

- a full blood count
- chest imaging (X-ray, CT or ultrasound)
- respiratory and blood samples (for example, sputum or a tracheal aspirate sample, blood culture; see Public Health England's COVID-19: guidance for sampling and for diagnostic laboratories)
- urine samples for legionella and pneumococcal antigen testing
- throat samples for respiratory viral (and atypical pathogen) polymerase chain reaction testing.

Info Box

High C-reactive protein levels do not necessarily indicate whether pneumonia is due to bacteria or SARS-COV-2.

Low C-reactive protein level indicates that a secondary bacterial infection is less likely.

Consensus recommendation

Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.

Info Box

There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about antibiotics. Centres already using procalcitonin tests are encouraged to participate in research and data collection.

Procalcitonin tests could be useful in identifying whether there is a bacterial infection. However, it is not clear whether they add benefit beyond what is suggested in the recommendation on tests to help differentiate between viral and bacterial pneumonia to guide decisions about antibiotics. The most appropriate threshold for procalcitonin is also uncertain.

8.4.2 - Antibiotic treatment in the community

Consensus recommendation

Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.

Consensus recommendation

If a person has suspected or confirmed secondary bacterial pneumonia, start antibiotic treatment as soon as possible. Take into account any different methods needed to deliver medicines during the COVID-19 pandemic (see the recommendation on minimising face-to-face contact in communication and shared decision making).

Info Box

For antibiotic choices to treat community-acquired pneumonia caused by a secondary bacterial infection, see the recommendations on choice of antibiotic in the NICE antimicrobial prescribing guideline on community-acquired pneumonia.

Consensus recommendation

Advise people to seek medical help without delay if their symptoms do not improve as expected, or worsen rapidly or significantly, whether they are taking an antibiotic or not.

Consensus recommendation

On reassessment, reconsider whether the person has signs and symptoms of more severe illness (see the recommendation on signs and symptoms to help identify people with COVID-19 with the most severe illness) and whether to refer them to hospital, other acute community support services or palliative care services.

8.4.3 - Starting antibiotics in hospital

Consensus recommendation

Start empirical antibiotics if there is clinical suspicion of a secondary bacterial infection in people with COVID-19. When a decision to start antibiotics has been made:

- start empirical antibiotic treatment as soon as possible after establishing a diagnosis of secondary bacterial pneumonia, and certainly within 4 hours
- start treatment within 1 hour if the person has suspected sepsis and meets any of the high-risk criteria for this outlined in the NICE guideline on sepsis.

8.4.4 - Choice of antibiotics in hospital

Info Box

To guide decision making about antibiotics for secondary bacterial pneumonia in people with COVID-19, see the NICE guideline on pneumonia (hospital acquired): antimicrobial prescribing.

Consensus recommendation

When choosing antibiotics, take account of:

- local antimicrobial resistance data and
- other factors such as their availability.

Consensus recommendation

Give oral antibiotics if the person can take oral medicines and their condition is not severe enough to need intravenous antibiotics.

Consensus recommendation

Consider seeking specialist advice on antibiotic treatment for people who:

- are immunocompromised
- have a history of infection with resistant organisms
- have a history of repeated infective exacerbations of lung disease
- are pregnant
- are receiving advanced respiratory support or organ support.

Consensus recommendation

Seek specialist advice if:

- there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic or
- there is clinical or microbiological evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.

8.4.5 - Reviewing antibiotic treatment in hospital

Consensus recommendation

Review all antibiotics at 24 to 48 hours, or as soon as test results are available. If appropriate, switch to a narrower spectrum antibiotic, based on microbiological results.

For intravenous antibiotics, review within 48 hours and think about switching to oral antibiotics (in line with the NICE guideline on pneumonia (hospital-acquired): antimicrobial prescribing)

Give antibiotics for 5 days, and then stop them unless there is a clear indication to continue (see the recommendation on when to seek specialist advice).

Consensus recommendation

Reassess people if their symptoms do not improve as expected, or worsen rapidly or significantly.

9 - Discharge, follow up and rehabilitation

Info Box

NICE is reviewing evidence on follow up, discharge and rehabilitation. More recommendations will be added in a future version of the guideline.

Info Box

For follow up and rehabilitation for people who have either ongoing symptomatic COVID-19 or post-COVID-19 syndrome, see the NICE guideline on the long-term effects of COVID-19.

10 - Palliative care

10.1 - Principles of care

Info Box

For people who are nearing the end of their life, see:

- The NICE guideline on care of dying adults in the last days of life: this includes recommendations on recognising when a person may be in the last days of life, communication and shared decision making.
- The NICE guideline on end of life care for adults: service delivery: this includes recommendations for service providers on systems to help identify adults who may be at the end of their life, providing information and advanced care planning.
- The NICE guideline on care and support of people growing older with learning disabilities: this includes recommendations on accessing end-of-life care services, person-centred care, and involving families and support networks in end-of-life care planning.

10.2 - Medicines for end-of-life care

Consensus recommendation

Consider an opioid and benzodiazepine combination. See the table in practical info for managing breathlessness in the last days and hours of life for people 18 years and over with COVID-19 who:

- are at the end of life and
- have moderate to severe breathlessness and
- are distressed.

Consider concomitant use of an antiemetic and a regular stimulant laxative. Seek specialist advice for children and young people under 18 years.

Info Box

For more recommendations on pharmacological interventions and anticipatory prescribing, see the NICE guideline on care of dying adults in the last days of life and prescribing information in the BNF's prescribing in palliative care.

Consensus recommendation

For people with COVID-19 who are out of hospital, when prescribing and supplying anticipatory medicines at the end of life:

- Take into account potential waste, medicines shortages and lack of administration equipment by prescribing smaller quantities or by prescribing a different medicine, formulation or route of administration when appropriate.
- If there are fewer health and care staff, you may need to prescribe subcutaneous, rectal or long-acting formulations. Family members could be considered as an alternative option to administer medications if they so wish and have been provided with appropriate training.

Consensus recommendation

For people with COVID-19 who are out of hospital, consider different routes for administering medicines if the person is unable to take or tolerate oral medicines, such as sublingual or rectal routes, subcutaneous injections or continual subcutaneous infusions.

11 - Research recommendations

What is the effectiveness and safety of standard-dose compared with intermediate-dose pharmacological venous thromboembolism (VTE) prophylaxis for people with COVID-19, with or without additional risk factors for VTE?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over being treated for COVID-19 pneumonia in hospital or the community who have:

- no additional risk factors for VTE
- additional risk factors for VTE

I: intermediate dose:

- low molecular weight heparins (LMWH)
- unfractionated heparin (UFH)
- fondaparinux sodium
- direct-acting anticoagulant
- vitamin K antagonists

C: Standard-dose:

- LMWH
- UFH
- fondaparinux sodium
- direct-acting anticoagulants
- vitamin K antagonists
- antiplatelets

O:

- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- admission to critical care (including use of advanced organ support)
- serious adverse events such as major bleeding or admission to hospital

What is the effectiveness and safety of extended pharmacological venous thromboembolism (VTE) prophylaxis for people who have been discharged after treatment for COVID-19?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over who have been discharged after treatment for COVID-19 pneumonia

I: extended (2 to 6 weeks) pharmacological VTE prophylaxis with standard-dose:

- low molecular weight heparins
- unfractionated heparins
- fondaparinux sodium
- direct-acting anticoagulant
- vitamin K antagonists

C: No extended pharmacological VTE prophylaxis

O:

- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- serious adverse events such as major bleeding or admission to hospital

What is the effectiveness and safety of a treatment dose with a low molecular weight heparin (LMWHs) compared with a standard prophylactic dose for venous thromboembolism (VTE) prophylaxis in young people under 18 years with COVID-19?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 18 years and under who have COVID-19 pneumonia

I: treatment-dose LMWH

C: standard prophylaxis with LMWH

O:

- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- admission to critical care (including use of advanced organ support)
- serious adverse events such as major bleeding or admission to hospital

Does early review and referral to specialist palliative care services improve outcomes for adults with COVID-19 thought to be approaching the end of their life?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients with a confirmed diagnosis of COVID-19 in hospital or community approaching the last days of life

I: early referral to specialist palliative care services (for example, in the last days of life)

C: late referral (for example, within the final day of life) or no referral

O:

- quality of life
- changes to clinical care
- patient or carer satisfaction (feeling supported)
- identification and/or achievement of patient wishes such as preferred place of death

12 - Equality considerations

12.1 - Equalities impact assessment during scoping - draft scope

12.2 - Equalities impact assessment during scoping - final scope

12.3 - Equalities impact assessment during guideline development

13 - Methods and processes

1 - How to use this guideline

In response to the COVID-19 pandemic, NICE produced multiple rapid guidelines to support the health and social care system. We know that having different products can make it difficult for people trying to find guidance, so we have brought together NICE's published recommendations on managing COVID-19 into this single guideline. We hope users will find the content easier to find and use.

Many of the recommendations made early in the pandemic were based on the consensus of the guideline expert panels, so supporting information is limited. We have reviewed all content, using topic expert input and more recent evidence, and updated the recommendations where needed.

We aim to update these recommendations frequently in line with new evidence and will produce new recommendations where gaps are identified. We search and sift the evidence weekly to produce living recommendations that reflect the latest best available evidence.

We have developed this guideline using our methods and processes for guidelines developed during health and social care emergencies. For more details of the methods and processes used for this guideline, including details of the expert advisory panel members, see the methods and processes section.

Your responsibility
When using this guideline, follow the usual professional guidelines, standards and laws (including those on equalities, safeguarding, communication and mental capacity), as described in making decisions using NICE guidelines.

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian. All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Using the guideline in MAGICapp
The guideline consists of 2 layers: recommendations and supporting information.

Click on the recommendation to learn more about the basis of the recommendation. As stated, supporting information is limited for recommendations created early in the pandemic. Additional information will be added as recommendations are updated in light of new evidence.

Recommendations will have supporting information in some or all of the following areas:

Research evidence: The overall effect estimates and references to the studies.

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 statistically significantly different.
- **Low**: We have limited confidence in the estimated effect. The true effect may be statistically significantly different from the estimated effect.

- **Very low**: We have very little confidence in the estimated effect. The true effect is likely to be statistically significantly different from the 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 panel reached its decision.

Practical information: Practical information about the treatment and information on any special patient considerations.

Adaption: If a recommendation has been adapted from another guideline, this will provide further details.

Feedback: If you are logged in as a user, you can use the 'Feedback' option to comment on specific recommendations.

References: Reference list for the recommendation.

2 - Introduction

Scope and purpose

This guideline is for health and care practitioners, and those involved in planning and delivering services. It provides guidance on managing COVID-19. The guideline makes recommendations about care in all settings for adults, children and young people with clinically diagnosed or laboratory-confirmed COVID-19.

Key questions

This section lists the key questions that the guideline addresses. These are a broad set of overarching review questions. Through our living approach, we will review the scope, and develop more specific review questions to address gaps in content and, where needed, additional review questions.

- What investigations should be carried out, and when, to determine the appropriate management of COVID-19 and any complications?
- What is the clinical effectiveness and safety of pharmacological and non-pharmacological treatments for acute symptoms and complications of COVID-19?
- How should symptoms and complications be managed?
- How, and how often, should people with COVID-19 be followed up?
- What palliative and end-of-life strategies are effective for people with COVID-19?

Areas to be excluded

The following areas are outside of the scope of this guideline and we will not look at evidence in these areas:

- procuring and distributing medicines and technologies, including vaccines
- procuring, distributing and using personal protective equipment
- procuring and distributing COVID-19 tests
- frequency of staff testing for COVID-19.

Acknowledgement

This work was done by NICE. The views expressed in this publication are those of the authors. We collaborated with the Australian National COVID-19 Clinical Evidence Taskforce based at Cochrane Australia, in the School of Population Health and Preventive Medicine at Monash University, to ensure appropriate development of the guideline, and acknowledge their contribution to identifying and reviewing the evidence for therapeutics.

3 - Definition of disease severity

COVID-19 disease severity definitions according to the World Health Organization (WHO COVID-19 clinical management: living guidance).

Mild disease		Patients with symptoms meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. See the WHO website for the most up-to-date case definitions. Presenting signs and symptoms of COVID-19 vary: • Most people experience fever (8% to 99%), cough (59% to 82%), fatigue (44% to 70%), anorexia (40% to 84%), shortness of breath (31% to 40%), myalgias (11% to 35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported. • Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms have also been reported. • Additional neurological manifestations reported include dizziness, agitation, weakness, seizures or findings suggestive of stroke including trouble with speech or vision, sensory loss, or problems with balance when standing or walking. • Older people and people who are immunosuppressed in particular may present with atypical symptoms such as reduced alertness, reduced mobility, diarrhoea, loss of appetite, confusion and absence of fever. • Symptoms such as dyspnoea, fever, gastrointestinal symptoms or fatigue because of physiological adaptations in women who are pregnant, adverse pregnancy events or other diseases such as malaria, may overlap with symptoms of COVID-19. • Children may report fever or cough less frequently than adults.
Moderate disease	Pneumonia	**Adolescents or adults** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 90% or more on room air. **Children** with clinical signs of non-severe pneumonia (cough or difficulty breathing plus fast breathing or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths per minute): under 2 months: 60 or more; 2 months to 11 months: 50 or more; 1 year to 5 years: 40 or more. While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan or ultrasound) may assist in diagnosis, and may identify or exclude pulmonary complications.
Severe disease	Severe pneumonia	**Adolescents or adults** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus 1 of the following: respiratory rate more than 30 breaths per minute; severe respiratory distress; or SpO_2 less than 90% on room air. **Children** with clinical signs of pneumonia (cough or difficulty in breathing) plus at least 1 of the following: • Central cyanosis or SpO_2 less than 90%; severe respiratory distress (for example, fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. • Fast breathing (in breaths per minute): less than 2 months: 60 or more; 2 months to 11 months: 50 or more; 1 year to 5 years: 40 or more. While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan or ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Critical	Acute	**Onset**: within 1 week of a known clinical insult (that is, pneumonia) or new or worsening

disease	respiratory distress syndrome (ARDS)	respiratory symptoms. **Chest imaging** (radiograph, CT scan or ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (for example, echocardiography) to exclude hydrostatic cause of infiltrate or oedema if no risk factor present. **Oxygenation impairment in adults:** • Mild ARDS: 200 mmHg less than PaO_2/FiO_2[1] 300 mmHg or less (with PEEP or CPAP 5 cmH_2O or more)[2]. • Moderate ARDS: 100 mmHg less than PaO_2/FiO_2 200 mmHg or less (with PEEP 5 cmH_2O or more)[2]. • Severe ARDS: PaO_2/FiO_2 100 mmHg or less (with PEEP 5 cmH_2O or more)[2]. **Oxygen impairment in children:** note OI and OSI[3]. Use OI when available. If PaO_2 is not available, wean FiO_2 to maintain SpO_2 97% or less to calculate OSI or SpO_2/FiO_2 ratio: • Bi-level (NIV or CPAP) more than or equal to 5 cmH_2O via full face mask: PaO_2/FiO_2 300 mmHg or less or SpO_2/FiO_2 264 or less. • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5. (OI greater than or equal to 4 and less than 8, or OSI greater than or equal to 5 and less than 7.5). • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3. (OI greater than or equal to 8 and less than 16, or OSI greater than or equal to 7.5 and less than 12.3). • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3. (OI greater than or equal to 16, or OSI greater than or equal to 12.3).
Critical disease	Sepsis	**Adults** with acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopaenia, acidosis, high lactate and hyperbilirubinaemia. **Children** with suspected or proven infection and 2 or more age-based systemic inflammatory response syndrome (SIRS) criteria[4], of which 1 must be abnormal temperature or white blood cell count.
Critical disease	Septic shock	**Adults** with persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP 65 mmHg or more and serum lactate level of more than 2 mmol/litre. **Children** with any hypotension (SBP below fifth centile or more than 22 SD below normal for age) or 2 or 3 of the following: altered mental status; bradycardia or tachycardia (HR less than 90 bpm or more than 160 bpm in babies and heart rate less than 70 bpm or more than 150 bpm in children); prolonged capillary refill (more than 2 seconds) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia.

[1] If altitude is higher than 1000 m, then the correction factor should be calculated as follows: PaO_2/FiO_2 x barometric pressure/760.
[2] When PaO_2 is not available, SpO_2/FiO_2 315 or less suggests ARDS (including in non-ventilated patients).
[3] Oxygenation index (OI) is an invasive measurement of the severity of hypoxaemic respiratory failure and may be used to predict

outcomes in children. It is calculated as follows: percentage of fraction of inhaled oxygen multiplied by the mean airway pressure (in mmHg), divided by the partial pressure of arterial oxygen (in mmHG). Oxygen saturation index (OSI) is a non-invasive measurement and has been shown to be a reliable surrogate marker of OI in children and adults with respiratory failure. OSI replaces PaO_2 with oxygen saturation as measured by pulse oximetry (SpO_2) in the OI equation.

[4] SIRS criteria: abnormal temperature (more than 38.5°C or less than 36°C); tachycardia for age or bradycardia for age if less than 1 year; tachypnoea for age or need for mechanical ventilation; abnormal white blood cell count for age or more than 10% bands.

4 - Communication and shared decision making

Consensus recommendation

Communicate with people with COVID-19, and their families and carers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups (including NHS Volunteer Responders), to UK government guidance on the mental health and wellbeing aspects of COVID-19 and UK government guidance on supporting children and young people's mental health and wellbeing, and to Royal College of Paediatrics and Child Health resources for parents and carers.

Give people information in a way that they can use and understand, to help them take part in decisions about their care. Follow relevant national guidance on communication, providing information (including in different formats and languages) and shared decision making, for example, NICE's guideline on patient experience in adult NHS services.

The Royal College of Obstetricians and Gynaecologists has produced information on COVID-19 and pregnancy for pregnant women and their families.

Consensus recommendation

For adults with COVID-19, explain:

- that the typical symptoms are cough, fever, and loss of sense of smell or taste, but that they may also have breathlessness (which may cause anxiety), delirium (which may cause agitation), fatigue, headache, muscle aches and sore throat
- that other symptoms may be drowsiness (particularly in older people), poor appetite, and chest discomfort or pain
- that they and people in close contact with them or in the same household (including those caring for them) should follow the UK guidance on self-isolation and the UK guidance on protecting vulnerable people
- that they are likely to feel much better in a week if their symptoms are mild
- who to contact if their symptoms get worse, for example, NHS 111 online.

Consensus recommendation

For carers of people with COVID-19 who should isolate but are unable to (for example, people with dementia), signpost to relevant support and resources.

For example, the Alzheimer's Society has information on staying safe from coronavirus and reducing the risk of infection.

Consensus recommendation

For children and young people under 18 years with COVID-19, explain:

- that additional symptoms (to those found in adults) may include grunting, nasal flare, nasal congestion, poor appetite, gastrointestinal symptoms, skin rash and conjunctivitis
- that they and people in close contact with them or in the same household (including those caring for them) should follow the UK guidance on self-isolation and the UK guidance on protecting vulnerable people
- that they are likely to feel much better in a week if their symptoms are mild
- who to contact if their symptoms get worse, for example, NHS 111 online
- that the presence of fever, rash, abdominal pain, diarrhoea or vomiting may indicate paediatric inflammatory multisystem syndrome (PIMS)
- how and when to seek medical help if PIMS is suspected.

Consensus recommendation

In the community, consider the risks and benefits of face-to-face and remote care for each person. Where the risks of face-to-face care outweigh the benefits, remote care can be optimised by:

- offering telephone or video consultations (see BMJ guidance on Covid-19: a remote assessment in primary care for a useful guide, including a visual summary for remote consultation)
- cutting non-essential face-to-face follow up
- using electronic prescriptions rather than paper
- using different methods to deliver medicines to people, for example, pharmacy deliveries, postal services and NHS volunteers, or introducing drive-through pick-up points for medicines.

Consensus recommendation

When possible, discuss the risks, benefits and possible likely outcomes of the treatment options with people with COVID-19, and their families and carers. Use decision support tools (when available).

This will help people express their preferences about their treatment and escalation plans. Bear in mind that these discussions may need to take place remotely.

Consensus recommendation

For people with pre-existing advanced comorbidities, find out if they have advance care plans or advance decisions to refuse treatment, including do not attempt cardiopulmonary resuscitation decisions. Document this clearly and take account of these in planning care.

5 - Assessment

5.1 - In the community

5.1.1 Identifying severe COVID-19

Consensus recommendation

Use the following signs and symptoms to help identify people with COVID-19 with the most severe illness:

- severe shortness of breath at rest or difficulty breathing
- reduced oxygen saturation levels measured by pulse oximetry (see the recommendation on pulse oximetry levels that indicate serious illness)
- coughing up blood
- blue lips or face
- feeling cold and clammy with pale or mottled skin
- collapse or fainting (syncope)
- new confusion
- becoming difficult to rouse
- reduced urine output.

For signs and symptoms to help identify paediatric inflammatory multisystem syndrome (PIMS) temporarily associated with COVID-19, see the guidance on PIMS from the Royal College of Paediatrics and Child Health.

Consensus recommendation

When pulse oximetry is available, use oxygen saturation levels below 94% for adults (or below 88% for adults with known type 2 respiratory failure) and below 91% for children in room air at rest to identify people who are seriously ill. See NHS England's guide to pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings.

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

Info Box

Assessing shortness of breath (dyspnoea) is important, but may be difficult via remote consultation. Tools such as the Medical Research Council's dyspnoea scale or the Centre for Evidence Based Medicine's review of ways of assessing dyspnoea (breathlessness) by telephone or video can be useful.

The NEWS2 tool may be used in adults in addition to clinical judgment to assess a person's risk of deterioration. Note that use of NEWS2 is not advised in children or pregnant women. Although the NEWS2 tool is not validated for predicting the risk of clinical deterioration in prehospital settings, it may be a helpful adjunct to clinical judgement in adults. A face-to-face consultation should not be arranged solely to calculate a NEWS2 score.

Locally approved Paediatric Early Warning Scores should be used for children. When using early warning scores, ensure that readings are based on calibrated machines. Be aware that readings may be incomplete when doing remote consultations.

Consensus recommendation

For people with severe respiratory symptoms associated with COVID-19 (for example, suspected pneumonia) being managed in the community, see the recommendation on venous thromboembolism in hospital-led acute care in the community.

5.1.2 Care planning

Consensus recommendation

Discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (for example, virtual wards or hospital at home teams).

Some benefits and risks may be similar for all patients (for example, improved diagnostic tests and access to treatments, or better contact with families in the community), but others may be personal to the individual (such as loss of access to carers who can anticipate needs well in someone unable to communicate themselves, or risks of spreading COVID-19).

Consensus recommendation

Explain that people with COVID-19 may deteriorate rapidly. Discuss future care preferences at the first assessment to give people who do not have existing advance care plans an opportunity to express their preferences.

5.2 - In hospital

Consensus recommendation

When a person is admitted to hospital with COVID-19, ensure a holistic assessment is done, including discussion about their treatment expectations and care goals:

- Document and assess the stability of underlying health conditions, involving relevant specialists as needed.
- Use the Clinical Frailty Scale (CFS) when appropriate, available from the NHS Specialised Clinical Frailty Network, to assess baseline health and inform discussions on treatment expectations.
- Use the CFS within an individualised assessment of frailty.
- Do not use the CFS for younger people, people with stable long-term disabilities (for example, cerebral palsy), learning disabilities or autism. Make an individualised assessment of frailty in these people, using clinical assessment and alternative scoring methods.
- Record the assessment and discussion in the person's medical records.

For assessment of paediatric inflammatory multisystem syndrome (PIMS), follow the guidance on PIMS from the Royal College of Paediatrics and Child Health.

Consensus recommendation

When making decisions about the care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, for example, people with advanced dementia, see the NICE guideline on decision-making and mental capacity.

Ensure discussions on significant care interventions involve families and carers as appropriate, and local experts or advocates.

6 - Management

6.1 - In the community

6.1.1 - Care planning

Consensus recommendation

Put treatment escalation plans in place in the community after sensitively discussing treatment expectations and care goals with people with COVID-19, and their families and carers.

People with COVID-19 may deteriorate rapidly. If it is agreed that the next step is a move to secondary care, ensure that they and their families understand how to access this with the urgency needed. If the next step is other community-based support (whether virtual wards, hospital at home services or palliative care), ensure that they and their families understand how to access these services, both in and out of hours.

6.1.2 - Managing cough

Consensus recommendation

Encourage people with cough to avoid lying on their backs, if possible, because this may make coughing less effective.

Be aware that older people or those with comorbidities, frailty, impaired immunity or a reduced ability to cough and clear secretions are more likely to develop severe pneumonia. This could lead to respiratory failure and death.

Consensus recommendation

Use simple measures first, including advising people over 1 year with cough to take honey.

The dose is 1 teaspoon of honey.

Consensus recommendation

Consider short-term use of codeine linctus, codeine phosphate tablets or morphine sulfate oral solution in people 18 years and over to suppress coughing if it is distressing. Seek specialist advice for people under 18 years.

See practical info for dosages for treatments to manage cough in people 18 years and over.

Practical Info

Treatments for managing cough in people 18 years and over

Treatment	Dosage
Initial management: use simple non-drug measures, for example, taking honey	A teaspoon of honey
First choice, only if cough is distressing: codeine linctus (15 mg/5 ml) or codeine phosphate tablets (15 mg, 30 mg)	15 mg to 30 mg every 4 hours as required, up to 4 doses in 24 hours If necessary, increase dose to a maximum of 30 mg to 60 mg four times a day (maximum 240 mg in 24 hours)
Second choice, only if cough is distressing: morphine sulfate oral solution (10 mg/5 ml)	2.5 mg to 5 mg when required every 4 hours Increase up to 5 mg to 10 mg every 4 hours as required If the person is already taking regular morphine increase the regular dose by a third

Notes: See the BNF and MHRA advice for appropriate use and dosage in specific populations.
All doses are for oral administration.
Consider the addiction potential of codeine linctus, codeine phosphate and morphine sulfate. Issue as an 'acute' prescription with a limited supply. Advise the person of the risks of constipation and consider prescribing a regular stimulant laxative.
Avoid cough suppressants in chronic bronchitis and bronchiectasis because they can cause sputum retention.

6.1.3 - Managing fever

Consensus recommendation

Advise people with COVID-19 and fever to drink fluids regularly to avoid dehydration. Support their families and carers to help when appropriate. Communicate that fluid intake needs can be higher than usual because of fever.

Consensus recommendation

Advise people to take paracetamol or ibuprofen if they have fever and other symptoms that antipyretics would help treat. Tell them to continue only while both the symptoms of fever and the other symptoms are present.

People can take paracetamol or ibuprofen when self-medicating for symptoms of COVID-19, such as fever (see the Central Alerting System: novel coronavirus - anti-inflammatory medications for further details of ibuprofen including dosage).

For people 18 years and over, the paracetamol dosage is 1 g orally every 4 to 6 hours (maximum 4 g per day). See the BNF and Medicines and Healthcare products Regulatory Agency advice for appropriate use and dosage in specific adult populations.

For children and young people over 1 month and under 18 years, see the dosing information on the pack or the BNF for children.

Rectal paracetamol, if available, can be used as an alternative. For rectal dosage information, see the BNF and BNF for children.

6.1.4 - Managing breathlessness

Consensus recommendation

Identify and treat reversible causes of breathlessness, for example, pulmonary oedema, pulmonary embolism, chronic obstructive pulmonary disorder and asthma.

For further information on identifying and managing pulmonary embolism, see the NICE guideline on venous thromboembolic diseases: diagnosis, management and thrombophilia testing.

Consensus recommendation

When significant medical pathology has been excluded or further investigation is inappropriate, the following may help to manage breathlessness as part of supportive care:

- keeping the room cool
- encouraging relaxation and breathing techniques, and changing body positioning
- encouraging people who are self-isolating alone to improve air circulation by opening a window or door.

If hypoxia is the likely cause of breathlessness:

- consider a trial of oxygen therapy
- discuss with the person, their family or carer possible transfer to and evaluation in secondary care.

Breathlessness with or without hypoxia often causes anxiety, which can then increase breathlessness further.

6.1.5 - Managing anxiety, delirium and agitation

Consensus recommendation

Assess reversible causes of delirium. See the NICE guidance on delirium: prevention, diagnosis and management.

Consensus recommendation

Address reversible causes of anxiety by:

- exploring the person's concerns and anxieties
- explaining to people providing care how they can help.

Consensus recommendation

Consider trying a benzodiazepine to manage anxiety or agitation. See practical info for treatments for managing anxiety, delirium and agitation in people 18 years and over. Seek specialist advice for people under 18 years.

Practical Info

Treatments for managing anxiety, delirium and agitation in people 18 years and over

Treatment	Dosage
	Higher doses may be needed for symptom relief in people with COVID-19. Lower doses may be needed because of the person's size or frailty The doses are based on the BNF and the Palliative care formulary
Anxiety or agitation and able to swallow: lorazepam tablets	Lorazepam 0.5 mg to 1 mg four times a day as required (maximum 4 mg in 24 hours) Reduce the dose to 0.25 mg to 0.5 mg in older people or those who are debilitated (maximum 2 mg in 24 hours) Oral tablets can be used sublingually (off-label use)
Anxiety or agitation and unable to swallow: midazolam injection	Midazolam 2.5 mg to 5 mg by subcutaneous injection every 2 to 4 hours as required If needed frequently (more than twice daily), a subcutaneous infusion via a syringe driver may be considered (if available) starting with midazolam 10 mg over 24 hours Reduce dosage to 5 mg over 24 hours if estimated glomerular filtration rate is less than 30 ml per minute
Delirium and able to swallow: haloperidol tablets	Haloperidol 0.5 mg to 1 mg at night and every 2 hours when required. Increase dose in 0.5 mg to 1 mg increments as required (maximum 10 mg daily, or 5 mg daily in older people) The same dose of haloperidol may be administered by subcutaneous injection as required rather than orally, or as a subcutaneous infusion of 2.5 mg to 10 mg over 24 hours Consider a higher starting dose (1.5 mg to 3 mg) if the person is severely distressed or causing immediate danger to others Consider adding a benzodiazepine such as lorazepam or midazolam if the person remains agitated (see dosages above)
Delirium and unable to swallow: levomepromazine injection	Levomepromazine 12.5 mg to 25 mg as a subcutaneous injection as a starting dose and then hourly as required (use 6.25 mg to 12.5 mg in older people) Maintain with a subcutaneous infusion of 50 mg to 200 mg over 24 hours, increased according to response (doses greater than 100 mg over 24 hours should be given under specialist supervision) Consider midazolam alone or in combination with levomepromazine if the person also has anxiety (see dosages above)
	Special considerations Seek specialist advice for people under 18 years old

Notes: At the time of publication (March 2021), midazolam and levomepromazine did not have a UK marketing authorisation for this indication or route of administration (see the General Medical Council's guidance on prescribing unlicensed medicines for further information).
See the BNF and MHRA advice for appropriate use and dosing in specific populations.

6.1.6 - Managing medicines

Consensus recommendation

When supporting people with symptoms of COVID-19 who are having care in the community delivered by social care, follow the NICE guideline on managing medicines for adults receiving social care in the community. This includes processes for ordering and supplying medicines, and transporting, storing and disposing of medicines.

Consensus recommendation

When prescribing, handling, administering and disposing of medicines in care homes and hospices follow the NICE guideline on managing medicines in care homes and the UK government COVID-19 standard operating procedure for running a medicines re-use scheme in a care home or hospice setting.

6.2 - In hospital

6.2.1 - Deciding when to escalate treatment

Consensus recommendation

Base decisions about escalating treatment within the hospital on the likelihood of a person's recovery. Take into account their treatment expectations, goals of care and the likelihood that they will recover to an outcome that is acceptable to them.

For support with decision making, see advice on ethics from the British Medical Association, ethical guidance from the Royal College of Physicians and the General Medical Council advice on decision-making and consent.

Consensus recommendation

Ensure healthcare professionals have access to resources to support discussions about treatment plans (see, for example, decision-making for escalation of treatment and referring for critical care support, and an example decision support form).

Consensus recommendation

Document referral to and advice from critical care services and respiratory support units in a standard format. When telephone advice from critical care or respiratory support units is appropriate, this should still be documented in a standard format (see an example of a tool for documentation).

6.2.2 - Escalating and de-escalating treatment

Consensus recommendation

Start all advanced respiratory support or organ support with a clear plan of how it will address the diagnosis and lead to agreed treatment goals (outcomes).

Stop advanced respiratory support or organ support when it is considered that it will no longer result in the desired overall goals (outcomes). Record the decision and the discussion with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate).

Info Box

NICE is reviewing evidence on respiratory support and further recommendations will be added in a future version of this guideline.

6.2.3 - Delivering services in critical care and respiratory support units

Consensus recommendation

Trusts should review their management for people who are deteriorating strategy, and use of the track-and-trigger system (NEWS2 has been endorsed by NHS England and Improvement), to allow for telephone advice rather than face-to-face review from critical care or respiratory support units when clinically appropriate. See the NICE guideline on acutely ill adults in hospital for recommendations on identifying patients whose clinical condition is deteriorating or is at risk of deterioration.

See the Royal College of Physician's information on the place of NEWS2 in managing patients with COVID-19.

7 - Therapeutics for COVID-19

7.1 - Antibiotics

Consensus recommendation

Do not use antibiotics for preventing or treating COVID-19.

Only use antibiotics if there is strong clinical suspicion of additional bacterial infection.

7.2 - Corticosteroids

Strong recommendation

New

Offer dexamethasone, or either hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable, to people with COVID-19 who:

- need supplemental oxygen to meet their prescribed oxygen saturation levels or
- have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

Continue corticosteroids for up to 10 days unless there is a clear indication to stop early, which includes discharge from hospital or a hospital-supervised virtual COVID ward.

Being on a hospital-supervised virtual COVID ward is not classed as being discharged from hospital.

See Practical info for dosage information.

For full details of adverse events and contraindications, see the summaries of product characteristics.

For children with a greater than 44-week corrected gestational age, follow the risk criteria set out in Royal College of Paediatric and Child Health guidance for assessing children admitted to hospital with COVID-19. For preterm babies with a corrected gestational age of less than 44 weeks, seek specialist advice.

Practical Info

Adult dosage

Dexamethasone:

- 6 mg orally once a day for 10 days (three 2 mg tablets or 15 ml of 2 mg/5 ml oral solution) or
- 6 mg intravenously once a day for 10 days (1.8 ml of 3.3 mg/ml ampoules [5.94 mg])

For people able to swallow and in whom there are no significant concerns about enteral absorption, prescribe tablets. Only use intravenous administration when tablets or oral solutions are inappropriate or unavailable.

Suitable alternatives:

- **Prednisolone**: 40 mg orally once a day for 10 days
- **Hydrocortisone**: 50 mg intravenously every 8 hours for 10 days (0.5 ml of 100 mg/ml solution; powder for solution for injection or infusion is also available); this may be continued for up to 28 days for people with septic shock

Dosage in pregnancy
Follow Royal College of Obstetrics and Gynaecology guidance.

Dosage for children with a greater than 44-week corrected gestational age

- **Dexamethasone**: 150 micrograms/kg (as a base) orally, nasogastrically or intravenously once a day for 10 days (max 6 mg)
- **Prednisolone**: 1 microgram/kg orally, nasogastrically or intravenously once a day for 10 days (max 40 mg; doses can be rounded as per routine clinical practice)

For people able to swallow and in whom there are no significant concerns about enteral absorption, prescribe tablets. Only use intravenous administration when tablets or oral solutions are inappropriate or unavailable.

Dosage for preterm babies with a corrected gestational age of less than 44 weeks
Seek specialist advice.

Evidence To Decision

Benefits and harms Substantial net benefits of the recommended alternative

For adults with COVID-19 needing supplemental oxygen, corticosteroids compared with usual care or placebo lower all-cause mortality, improve discharge from hospital, and may decrease the need for invasive mechanical ventilation (IMV) and death within 28 days of starting treatment.

For adults with COVID-19 not needing supplemental oxygen, corticosteroids may increase the need for IMV and death within 28 days of starting treatment.

Based on indirect evidence from non-COVID-19 populations, hyperglycaemia is the only statistically significant adverse event associated with corticosteroids.

Discussion
The panel noted the evidence to support using corticosteroids for adults with COVID-19 on supplemental oxygen, or adults with a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. They noted that it is now established standard practice to offer dexamethasone. This is based on the most robust evidence on corticosteroids covering this treatment, and its widespread availability, ease of administration and acceptable safety profile. The panel indicated that, if dexamethasone cannot be used or is unavailable, suitable alternatives are hydrocortisone or prednisolone. Because of the risk of harm, the panel cautioned against using corticosteroids for other people with COVID-19.

The panel noted the need for clear and unambiguous terminology. Therefore, they agreed that reference to COVID-19 severity would not be used. Instead, they agreed that a person's oxygen saturation should be used to determine whether corticosteroid treatment was appropriate. The panel highlighted the need to allow for varying prescribed oxygen saturation levels in different population groups. Because of this, they agreed that the recommendation should not detail specific oxygen saturation levels.

The course duration recommended, for up to 10 days unless there is a clear indication to stop early (including discharge from hospital or a hospital-supervised virtual COVID ward), is based on that used in the RECOVERY trial. The panel recognised the importance of minimising risk of harm caused by continuing treatment for people whose condition is improving and who are discharged. They agreed that the long pharmacodynamic half-life of dexamethasone would reduce the risk of any rebound effect caused by stopping the course before 10 days in the event of discharge. The panel agreed that, where patients are transferred to a virtual ward environment, the course could be completed safely under clinical supervision.

The panel acknowledged the lack of evidence outside the hospital setting. They also acknowledged that the supply and use of corticosteroids in other settings is based on clinical experience and knowledge of service delivery. It was the panel's opinion that, when corticosteroids are first started in community settings, GPs are suitably qualified to assess oxygen levels

with pulse oximetry and the need for corticosteroids. They agreed that it is realistic that treatment with dexamethasone could be started in the community setting. They also agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

Use of corticosteroids in children was considered. The panel decided that the recommendation should not be limited to adults because the evidence included both adults and children. The panel therefore agreed to avoid age-specific wording in the recommendation. Instead, they agreed that the dosing for adults and children should be provided as supplementary advice. Paediatric experts highlighted that the risk of progression for a child with a stable minimal oxygen requirement is not as high as for adults. Therefore, they suggested cross reference to Royal College of Child and Paediatric Health risk criteria markers for assessing corticosteroid use. For preterm babies with a corrected gestational age of less than 44 weeks, specialist advice is considered necessary because evidence is lacking for corticosteroid use in this age group.

The panel noted the indirect evidence about the risk of hyperglycaemia in other non-COVID-19 populations. They agreed that whether to monitor for hyperglycaemia and other adverse effects should be determined by their healthcare professionals, without the need for specific advice in the guideline. They added that potential adverse effects and contraindications would need to be balanced against the risks of depriving a person of a potentially life-saving treatment.

The panel considered that clinical judgement should guide management for people who do not need supplemental oxygen and who are already having corticosteroids for pre-existing or new comorbid conditions, without the need for specific advice in the guideline.

Certainty of the Evidence Moderate

Certainty of the evidence is moderate for all-cause mortality within 28 days in both subgroups (adults needing oxygen, and adults not needing oxygen) because of serious imprecision (inconsistent direction of effects for studies of adults needing oxygen and only a single study for adults not needing oxygen). The panel noted that, despite serious imprecision, the pooled effect was statistically significantly in favour of corticosteroids for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of the evidence is moderate for invasive mechanical ventilation or death at 28 days in both subgroups because of serious imprecision (only a single study for both subgroups). The panel noted that, despite serious imprecision, the effect was statistically significantly in favour of dexamethasone for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of evidence is moderate for discharge from hospital in both subgroups because of serious imprecision (inconsistent confidence intervals for studies of adults needing oxygen and only a single study for adults not needing oxygen). However, the panel noted that, for adults with COVID-19 needing oxygen, there was a statistically significant effect in favour of corticosteroids for improving discharge from hospital at 28 days.

Certainty of evidence was moderate for serious adverse events of corticosteroids in adults with COVID-19 needing oxygen. The panel noted that corticosteroids probably have little effect on serious adverse events in this group of people, but were aware of indirect systematic review evidence showing a statistically significant risk of hyperglycaemia among people without COVID-19.

Certainty of evidence was low to moderate for other individual adverse effects, none of which showed statistically significant effects estimates.

Preference and values No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that,

in view of the probable mortality benefits for people with COVID-19 who need oxygen, most would choose corticosteroids after shared decision making with healthcare professionals. Dexamethasone was considered to be the preferred corticosteroid treatment because of the larger amount of data supporting its use. The panel agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

Resources

No important issues with the recommended alternative

Use of corticosteroids in adults with COVID-19 who are on supplemental oxygen is unlikely to affect the availability of these medicines for other indications.

The panel expressed concern over specifying oxygen therapy as a requirement for corticosteroid treatment in a recommendation. They agreed that this might result in inequalities in access to treatments because of certain groups of people not being able to have oxygen therapy, even though their oxygen saturations may indicate that they should. This may also result in supply issues in the event of oxygen shortages. The panel agreed that the emphasis should be on oxygen saturation targets for people who need oxygen supplementation.

The panel noted possible supply issues with corticosteroids in community pharmacies where people have treatment outside the hospital setting, such as in residential care. However, they agreed that GP assessment with pulse oximetry and treatment with dexamethasone is realistic in the community setting. The class effect of corticosteroids would allow for suitable alternatives. The panel acknowledged the lack of evidence outside the hospital setting. They also noted that the use and supply of corticosteroids in other settings is based on clinical experience and knowledge of service delivery.

Equity

Important issues, or potential issues not investigated

The panel noted limited evidence on the use of corticosteroids in children with COVID-19 but that children should not be excluded from the recommendations. The panel agreed that all age groups should be encompassed with appropriate age-specific advice on dosage.

The panel also noted the lack of evidence on the use of corticosteroids in community settings and the risk of inequitable treatment if limited to people in hospital. The panel were aware of people with COVID-19 needing supplemental oxygen who are having treatment outside the hospital setting and would benefit from corticosteroids. For this reason, the panel agreed that the recommendation should not specify any treatment setting.

See the Resources section for the panel's concern over potential inequality of access to corticosteroids if oxygen therapy is stated as a requirement for corticosteroid treatment, and the need for this to be reflected in the wording of the recommendation.

Acceptability

No important issues with the recommended alternative

The panel considered that acceptability of corticosteroids would be high given the widespread availability, ease of oral ingestion in any setting and established safety profile. They anticipated that, when considering the risks and benefits of treatment through shared decision making, most people with COVID-19 who:

- need supplemental oxygen would choose to have corticosteroids
- do not need supplemental oxygen would choose not to have corticosteroids.

Feasibility

No important issues with the recommended alternative

Although there is no systematically collected evidence about feasibility, the panel noted that the established distribution, supply and use of corticosteroids in clinical practice is an indicator of feasibility.

Rationale

There is evidence to support using corticosteroids for people with COVID-19 who need supplemental oxygen, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. It is now established standard practice to offer dexamethasone. The growing evidence base, combined with its widespread availability, ease of administration and acceptable safety profile, supports its continued use. Hydrocortisone and prednisolone are suitable alternatives if dexamethasone cannot be used or is unavailable. The course duration recommended, for up to 10 days unless there is a clear indication to stop early (including discharge from hospital or a hospital-supervised virtual COVID ward), is based on that used in clinical trials.

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Corticosteroids
Comparator: Control

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 *[1]* of seven randomised controlled trials (RCTs) of patients with critical COVID-19 *[2][12][3][9][8][2][7]*, one study of patients with moderate, severe and critical COVID-19 *[6]*, and one study of patients with severe COVID-19 *[5]*. Over 5,700 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 *[10]* and sepsis *[13]* – provided indirect evidence for serious adverse events.

Study characteristics
Three RCTs compared dexamethasone with standard care *[2][9][6]*, three compared hydrocortisone with standard care *[8][3][4]* and three compared methylprednisolone with standard care *[12][7][5]*.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, PaO_2/FiO_2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cm H_2O, 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 RCTs). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and discharge from hospital within 28 days.

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 showed no difference in the incidence of gastrointestinal bleeding, bacterial co-infections, 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 24 studies).

Our confidence in the results
In patients with COVID-19 requiring oxygen, 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 (due to only one study), and discharge from hospital (due to serious inconsistency).

In patients with COVID-19 who do not require oxygen, certainty is moderate for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to serious imprecision (reliance on a single study and wide confidence intervals).

For the adverse events (gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects), certainty is low due to serious indirectness (evidence from non-COVID-19 patients) and serious imprecision. For hyperglycaemia, certainty is moderate due to serious indirectness (evidence from non-COVID-19 patients).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Control	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 within 28 days 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. [3] (Randomized controlled)	140 per 1000	178 per 1000 Difference: **38 more** per 1000 (CI 95% 0 fewer - 85 more)	**Moderate** Only data from one study	Corticosteroids probably increase death in adults who do not require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [4]	Relative risk 0.88 (CI 95% 0.79 - 0.97) Based on data from 3,883 patients in 1 studies. [5] (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	Corticosteroids probably decrease invasive mechanical ventilation or death in adults who require oxygen

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Control	Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Within 28 days of commencing treatment 9 Critical					
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. [6] (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 [7]	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 after commencing treatment 9 Critical	Relative risk 0.96 (CI 95% 0.9 - 1.01) Based on data from 1,535 patients in 1 studies. [8] (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 [9]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 1.1 (CI 95% 1.06 - 1.15) Based on data from 4,952 patients in 2 studies. [10] (Randomized controlled)	582 per 1000	640 per 1000 Difference: **58 more** per 1000 (CI 95% 35 more - 87 more)	**Moderate** Due to serious inconsistency [11]	Corticosteroids probably increases discharge from hospital in adults who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment	Relative risk 0.8 (CI 95% 0.53 - 1.19) Based on data from 696 patients in 6 studies. [12] (Randomized controlled)	234 per 1000	187 per 1000 Difference: **47 fewer** per 1000 (CI 95% 110 fewer - 44 more)	**Moderate** Due to serious inconsistency [13]	Corticosteroids probably have little impact on serious adverse events in adults who require oxygen.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Control	 Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain text summary
6 Important					
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.82 - 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000	51 per 1000 Difference: **3 more** per 1000 (CI 95% 9 fewer - 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Bacterial co-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.	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.	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.	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.	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 [1] with included studies: REMAP-CAP 2020, COVID STEROID 2020, Edalatifard 2020, CAPE COVID 2020, RECOVERY, DEXA-COVID 19 2020, METCOVID 2020, CoDEX 2020, RECOVERY, Steroids-SARI 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 [1] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
4. Detailed description 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

5. Systematic review [1] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [1] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: Serious.** Only data from one study.
8. Systematic review [1] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Imprecision: Serious.** Only data from one study.
10. Systematic review [1] with included studies: Edalatifard 2020, RECOVERY, RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
11. **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..
12. Systematic review [1] with included studies: CAPE COVID 2020, CoDEX 2020, COVID STEROID 2020, REMAP-CAP 2020, Steroids-SARI 2020, DEXA-COVID 19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies.

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Weak recommendation against

New

Do not routinely use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen, unless there is another medical indication to do so.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

For adults with COVID-19 needing supplemental oxygen, at 28 days, corticosteroids compared with usual care or placebo lower mortality, improve discharge from hospital, and may decrease the risk of needing invasive mechanical ventilation (IMV) and death.

For adults with COVID-19 not needing oxygen, corticosteroids may increase the risk of needing IMV and death within 28 days of starting treatment.

Based on indirect evidence from non-COVID-19 populations, hyperglycaemia is the only statistically significant adverse event associated with corticosteroids.

Discussion

The panel noted the evidence that corticosteroids may be harmful for people with COVID-19 not needing supplemental oxygen. Because of the risk of harm, the panel cautioned against using corticosteroids for people with COVID-19 not on oxygen unless there is another medical indication to do so.

The panel noted the need for clear and unambiguous terminology. Therefore, they agreed that reference to COVID-19 severity would not be used. Instead, they agreed that a person's oxygen saturation should be used to determine whether corticosteroid treatment was appropriate. The panel highlighted the need to allow for varying prescribed oxygen saturation levels in different population groups. Because of this, they agreed that the recommendation should not detail specific oxygen saturation levels.

The panel noted the indirect evidence about the risk of hyperglycaemia in other non-COVID-19 populations. They agreed that whether to monitor for hyperglycaemia and other adverse effects in individuals should be determined by their healthcare professionals, without the need for specific advice in the guideline. They added that potential adverse effects and contraindications would need to be balanced against the risks of depriving a person of a potentially life-saving treatment.

The panel considered that clinical judgement should guide management for people who do not need supplemental oxygen and who are already having corticosteroids for pre-existing or new comorbid conditions, without the need for specific advice in the guideline.

Certainty of the Evidence Moderate

Certainty of the evidence is moderate for all-cause mortality within 28 days in both subgroups (adults needing oxygen, and adults not needing oxygen) because of serious imprecision (inconsistent direction of effects for studies of adults needing oxygen and only a single study for adults not needing oxygen). The panel noted that, despite serious imprecision, the pooled effect was statistically significantly in favour of corticosteroids for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of the evidence is moderate for invasive mechanical ventilation or death at 28 days in both subgroups because of serious imprecision (only a single study for both subgroups). The panel noted that, despite serious imprecision, the effect was statistically significantly in favour of dexamethasone for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of evidence is moderate for discharge from hospital in both subgroups because of serious imprecision (inconsistent confidence intervals for studies of adults needing oxygen and only a single study for adults not needing oxygen). However, the panel noted that, for adults with COVID-19 needing oxygen, there was a statistically significant effect in favour of corticosteroids for improving discharge from hospital at 28 days.

Certainty of evidence was moderate for serious adverse events of corticosteroids in adults with COVID-19 needing oxygen. The panel noted that corticosteroids probably have little effect on serious adverse events in this group of people, but were aware of indirect systematic review evidence showing a statistically significant risk of hyperglycaemia among people without COVID-19.

Certainty of evidence was low to moderate for other individual adverse effects, none of which showed statistically significant effects estimates.

Preference and values No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need oxygen, most would choose corticosteroids after shared decision making with healthcare professionals. Dexamethasone was considered to be the preferred corticosteroid treatment because of the larger amount of data supporting its use. The panel agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

The panel also inferred that, because of the risk of harm, most fully informed people with COVID-19 who do not need supplemental oxygen would not want to have systemic corticosteroids. However, some people may want to consider having this intervention through shared decision making with their healthcare professional.

Resources No important issues with the recommended alternative

The panel expressed concern over specifying oxygen therapy as a requirement for corticosteroid treatment in a recommendation. They agreed that this may result in inequalities in access to treatments because of certain groups of people not being able to have oxygen therapy, even though their oxygen saturations may indicate that they should. This may also result in supply issues in the event of oxygen shortages. The panel agreed that the emphasis should be on oxygen saturation targets for people who need oxygen supplementation.

The panel noted possible supply issues with corticosteroids in community pharmacies where people are having treatment outside the hospital setting, such as in residential care. However, they agreed that GP assessment with pulse oximetry and treatment with dexamethasone is realistic in the community setting. The class effect of corticosteroids would allow for suitable alternatives.

Equity Important issues, or potential issues not investigated

The panel noted limited evidence on the use of corticosteroids in children with COVID-19 but that children should not be excluded from the recommendations. The panel agreed that all age groups should be encompassed with appropriate age-specific advice on dosage.

The panel also noted the lack of evidence on the use of corticosteroids in community settings and the risk of inequitable treatment if limited to people in hospital. The panel were aware of people with COVID-19 needing supplemental oxygen who are having treatment outside the hospital setting and would benefit from corticosteroids. For this reason, the panel agreed that the recommendation should not specify any treatment setting.

See the Resources section for the panel's concern over potential inequality of access to corticosteroids if oxygen therapy is stated as a requirement for corticosteroid treatment, and the need for this to be reflected in the wording of the recommendation.

Acceptability No important issues with the recommended alternative

The panel considered that acceptability of corticosteroids would be high given the widespread availability, ease of oral ingestion in any setting and established safety profile. They anticipated that, when considering the risks and benefits of treatment through shared decision making, most people with COVID-19 who:

- need supplemental oxygen would choose to have corticosteroids
- do not need supplemental oxygen would choose not to have corticosteroids.

Feasibility No important issues with the recommended alternative

Although there is no systematically collected evidence about feasibility, the panel noted that the established distribution, supply and use of corticosteroids in clinical practice is an indicator of feasibility.

Rationale

Evidence suggests that, in people with COVID-19 who do not need supplemental oxygen, corticosteroids may increase the risk of needing invasive mechanical ventilation and death at 28 days. The recommendation therefore cautions against using corticosteroids for people not on supplemental oxygen, unless there is another medical indication to do so.

7.3 - Remdesivir

Info Box

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Remdesivir
Comparator: Placebo or standard care

Summary

Evidence indicates that remdesivir probably reduces the risk of death slightly in hospitalised adults not requiring invasive ventilation and increases the risk of death in hospitalised adults who require invasive 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 *[16][18][19][20]*. 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 *[18][16]*.

Study characteristics
Mean or median age ranged from 56 to 66 years and women comprised 32 to 44% of patients across the studies. Pregnant patients and children were ineligible, with the exception of one trial*[19]* which included children over 12 years weighing 40kg or more. There was variability in disease severity among patients included in the trials (see table).

Disease severity	Number of people	References
Moderate	584	*[19]*
Moderate to critical	6513	*[16][18]*
Severe to critical	236	*[20]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require invasive ventilation (19 fewer deaths per 1000 patients (RR 0.79, 95% CI 0.61 to 1.01; 6511 patients in 4 studies)). Remdesivir probably increases death at day 28 in patients who require invasive ventilation (60 more deaths per 1000 patients (RR 1.24 CI 95% 1.00 to 1.533; 811 patients in 3 studies)).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies. Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the eight-point WHO ordinal scale *[16]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[19]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[19]* or 6-point ordinal scale *[20]*.

Compared with standard care, remdesivir probably reduces serious adverse events (63 fewer SAEs per 1000 patients (RR 0.75, CI 95% 0.63 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, the need for invasive mechanical ventilation or ECMO, 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 invasive ventilation, and patients who require invasive 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 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). Certainty of the evidence is very low for septic shock (due to non-blinding of patients and personnel, inconsistency in direction of effect and wide confidence intervals).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality (day 28; hospital no invasive ventilation) Within 28 days of commencing treatment 9 Critical	Relative risk 0.79 (CI 95% 0.61 - 1.01) Based on data from 6,511 patients in 4 studies. [1] (Randomized controlled)	90 per 1000	71 per 1000 Difference: **19 fewer** per 1000 (CI 95% 35 fewer - 1 more)	**Moderate** Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients not on invasive ventilation at baseline.
All-cause mortality (day 28; invasive ventilation) Within 28 days of commencing treatment 9 Critical	Relative risk 1.24 (CI 95% 1 - 1.53) Based on data from 811 patients in 3 studies. [3] (Randomized controlled)	248 per 1000	308 per 1000 Difference: **60 more** per 1000 (CI 95% 0 fewer - 131 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients on invasive ventilation at baseline.
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 in hospitalised patients not on invasive ventilation at baseline.
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 imprecision and serious risk of bias [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO in hospitalised patients not on invasive ventilation at baseline.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Patients requiring ventilation [9] 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. [10] (Randomized controlled)	115 per 1000	118 per 1000 Difference: 3 more per 1000 (CI 95% 13 fewer - 23 more)	**Moderate** Due to serious imprecision [11]	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. [12] (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 [13]	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. [14] (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, serious inconsistency and serious imprecision [15]	We are uncertain whether remdesivir increases or decreases septic shock
Serious adverse events [16] 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. [17] (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 [18]	Remdesivir probably results in slightly fewer serious adverse 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. [19] (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 [20]	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. [21] (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, serious inconsistency and serious imprecision [22]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or standard care	 Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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. [23] (Randomized controlled)	720 per 1000	713 per 1000 Difference: **7 fewer** per 1000 (CI 95% 29 fewer - 22 more)	**Moderate** Due to serious imprecision [24]	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 [25]	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 [26]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [14] with included studies: Spinner 2020, SOLIDARITY 2020 low/hi flow, Beigel 2020 lo-flow, SOLIDARITY 2020 no O2, Wang 2020, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
3. Systematic review [14] with included studies: Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation, Beigel 2020 Inv vent, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. Systematic review [14] 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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. Systematic review [14] 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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
9. Listed as critical in PICO
10. Systematic review [14] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**

12. Systematic review [14] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **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 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.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
14. Systematic review [14] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
15. **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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
16. Listed as critical in PICO
17. Systematic review [14] with included studies: Spinner 2020, Spinner 2020, Wang 2020, Beigel 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: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
19. Systematic review [14] 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. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
21. Systematic review [14] with included studies: Spinner 2020, Beigel 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
23. Systematic review [14] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
24. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
25. **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: No serious. Publication bias: No serious.**
26. **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: No serious. Publication bias: No serious.**

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Weak recommendation

Consider remdesivir for 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, who are in hospital and on supplemental oxygen but not on invasive mechanical ventilation.

Complete the 5-day course of treatment if remdesivir has been started and there is subsequent progression to invasive mechanical ventilation.

It is unclear whether the 5-day or the 10-day regimen of remdesivir is the optimal treatment duration.

The criteria for accessing remdesivir in the UK are outlined in NHS England's Interim Clinical Commissioning Policy on remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older).

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel noted the opposing directions of effect between people receiving invasive mechanical ventilation (IMV), which showed a trend towards higher all-cause mortality, and people not receiving IMV, which showed a trend towards lower all-cause mortality. The duration and severity of disease was considered to be the explanation for this. The benefit of remdesivir as an antiviral agent would therefore be most apparent in people early in their disease course, when viral replication is a driver of disease, before the need for IMV.

Evidence from randomised controlled trials of remdesivir compared with standard care show that remdesivir has an acceptable safety profile and may reduce the incidence of serious adverse events.

Based on the results of 2 studies that compared 10-day with 5-day courses of remdesivir, it is unclear which of these regimens provide the optimal duration of treatment. The current evidence does not suggest any clear benefit for 10-day duration and shows that it may be more harmful than a 5-day course. For this reason, along with resource impact considerations (see also Resources), the panel agreed to recommend a 5-day regimen.

The panel noted the unclear additive benefit of remdesivir when used with dexamethasone, particularly since the 2 main trials, SOLIDARITY and ACTT-1, were done before the routine use of dexamethasone.

The panel also reviewed academic-in-confidence data from an observational study but did not consider this to have any effect on the recommendations.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for death in both subgroups (people who do not need invasive mechanical ventilation [IMV], and people who need IMV), all because of serious imprecision (wide confidence intervals). The panel noted difficulties in disaggregating data on different modalities of respiratory support to inform subgroup analysis, with some trials covering both invasive and non-invasive ventilation. However, the panel agreed that subgroup data should be distinguished between IMV and non-IMV modalities in the pooled meta-analysis of included studies. The panel noted that, despite serious imprecision, the direction of effect was consistently in favour of remdesivir across studies for people not receiving IMV. It was felt that a 'consider' recommendation for people on supplementary oxygen and not on IMV would allow clinical discretion in making individualised treatment decisions and would reflect the level of uncertainty in the evidence.

Certainty is also moderate for the outcomes of number of people needing ventilation and discharge from hospital (because of reliance on a single study), serious adverse events, time to recovery and time to improvement (because of non-blinding of people in the trial and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (because of inconsistency in direction of effect and wide confidence intervals), number of people needing invasive mechanical ventilation or extracorporeal membrane oxygenation (because of non-blinding of people in the trial and personnel, and reliance on a single study), clinical recovery and adverse events (because of non-blinding of people in the trial and personnel, and inconsistency in direction of effect) and stopping treatment because of adverse events (because of non-blinding of people in the trial and personnel, and wide confidence intervals). Certainty of the evidence is very low for septic shock (because of non-blinding of people in the trial and personnel, inconsistency in direction of effect and wide confidence intervals).

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who do not need invasive ventilation, most would choose remdesivir.

Resources

Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review.

The panel raised concerns about opportunity costs where remdesivir is being used in critical care, and the importance of not diverting resources away from best supportive care. The panel noted the value of targeting treatment to optimise use of resources. The panel also noted the lack of evidence indicating any benefit of a 10-day over a 5-day regimen, a direction of effect indicating potential harms of the 10-day duration and the resource impact for a longer duration of treatment. See also the benefits and harms section.

Equity

Important issues, or potential issues not investigated

The panel noted an absence of evidence on the use of remdesivir in children. However, it was considered unlikely that most children would benefit from this intervention because most children will recover without the need for it. It is also not licensed for use in children under 12 years. Children over 12 years, and weighing 40 kg or more with adult phenotype disease should have treatment based on the same indications as those used for adults, in particular if there is progressive respiratory deterioration. Children with comorbidities with significant lung disease may have benefit from treatment with remdesivir, but they should be discussed on a case-by-case basis with the paediatric infectious diseases team.
The panel also noted the absence of evidence on the use of remdesivir in community settings. However, it was considered unlikely to be used outside the hospital setting because the criteria for accessing remdesivir in the UK currently stipulate hospitalisation with COVID-19.
No other equity issues were identified.

Acceptability Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is only moderate. However, the panel noted the consistent direction of effect in favour of remdesivir.
It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and:

- do not need invasive mechanical ventilation would choose to have remdesivir
- need invasive mechanical ventilation would choose not to have remdesivir.

Feasibility Important issues, or potential issues not investigated

Although there is no systematically collected evidence about feasibility, the panel noted that current widespread use of remdesivir in clinical practice is an indicator of feasibility.

Rationale

We recommend considering remdesivir for 5 days for adults and young people 12 years and over in hospital with COVID-19 pneumonia who are not on invasive mechanical ventilation (IMV). This is because remdesivir probably reduces the risk of death for these people.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [WHO].*[21]*

There are several factors that contribute to differences in recommendations between NICE and WHO:

- NICE considers that delineation of subgroups based on disease severity is credible, and that the observed differences in direction of effect on mortality between subgroups is plausible. See the evidence to decision section on benefits and harms for the panel's explanation of differing effects on mortality depending on severity.
- NICE highlights the differential effect of remdesivir on mortality within these subgroups (that is, the absolute effect estimate of 19 fewer deaths per 1,000 in people in hospital who do not need IMV, and the absolute effect estimate of 60 more deaths per 1,000 in people in hospital who need IMV).
- NICE is more certain that the effect of remdesivir on mortality is closer to the true effect than WHO because certainty was not downgraded because of risk of bias (NICE has determined certainty for mortality outcomes as moderate, compared with the low certainty assessment by WHO).
- Because NICE develops recommendations specific to the UK healthcare context, there are fewer resource limitations and barriers to implementing these recommendations than in many low and middle income countries within the operational sphere of WHO.

Clinical Question/ PICO

Population:	People with COVID-19
Intervention:	Remdesivir
Comparator:	Placebo or standard care

Summary

Evidence indicates that remdesivir probably reduces the risk of death slightly in hospitalised adults not requiring invasive ventilation and increases the risk of death in hospitalised adults who require invasive 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 *[16][18][19][20]*. 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 *[18][16]*.

Study characteristics
Mean or median age ranged from 56 to 66 years and women comprised 32 to 44% of patients across the studies. Pregnant patients and children were ineligible, with the exception of one trial*[19]* which included children over 12 years weighing 40kg or more. There was variability in disease severity among patients included in the trials (see table).

Disease severity	Number of people	References
Moderate	584	*[19]*
Moderate to critical	6513	*[16][18]*
Severe to critical	236	*[20]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require invasive ventilation (19 fewer deaths per 1000 patients (RR 0.79, 95% CI 0.61 to 1.01; 6511 patients in 4 studies)). Remdesivir probably increases death at day 28 in patients who require invasive ventilation (60 more deaths per 1000 patients (RR 1.24 CI 95% 1.00 to 1.533; 811 patients in 3 studies)).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies. Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the eight-point WHO ordinal scale *[16]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[19]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[19]* or 6-point ordinal scale *[20]*.

Compared with standard care, remdesivir probably reduces serious adverse events (63 fewer SAEs per 1000 patients (RR 0.75, CI 95% 0.63 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, the need for invasive mechanical ventilation or ECMO, 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 invasive ventilation, and patients who require invasive 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 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). Certainty of the evidence is very low for septic shock (due to non-blinding of patients and personnel, inconsistency in direction of effect and wide confidence intervals).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality (day	Relative risk 0.79 (CI 95% 0.61 - 1.01)	90	71	**Moderate** Due to serious	Remdesivir probably decreases death slightly

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
28; hospital no invasive ventilation) Within 28 days of commencing treatment 9 Critical	Based on data from 6,511 patients in 4 studies. [1] (Randomized controlled)	per 1000	per 1000 Difference: **19 fewer** per 1000 (CI 95% 35 fewer - 1 more)	imprecision [2]	in hospitalised patients not on invasive ventilation at baseline.
All-cause mortality (day 28; invasive ventilation) Within 28 days of commencing treatment 9 Critical	Relative risk 1.24 (CI 95% 1 - 1.53) Based on data from 811 patients in 3 studies. [3] (Randomized controlled)	**248** per 1000	**308** per 1000 Difference: **60 more** per 1000 (CI 95% 0 fewer - 131 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients on invasive ventilation at baseline.
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 in hospitalised patients not on invasive ventilation at baseline.
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 imprecision and serious risk of bias [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO in hospitalised patients not on invasive ventilation at baseline.
Patients requiring ventilation [9] 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. [10] (Randomized controlled)	**115** per 1000	**118** per 1000 Difference: **3 more** per 1000 (CI 95% 13 fewer - 23 more)	**Moderate** Due to serious imprecision [11]	Remdesivir probably has no impact on number of patients requiring ventilation.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or 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. [12] (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 [13]	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. [14] (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, serious inconsistency and serious imprecision [15]	We are uncertain whether remdesivir increases or decreases septic shock
Serious adverse events [16] 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. [17] (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 [18]	Remdesivir probably results in slightly fewer serious adverse 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. [19] (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 [20]	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. [21] (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, serious inconsistency and serious imprecision [22]	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. [23] (Randomized controlled)	720 per 1000	713 per 1000 Difference: **7 fewer** per 1000 (CI 95% 29 fewer - 22 more)	**Moderate** Due to serious imprecision [24]	Remdesivir probably makes little or no difference to discharge from hospital.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Placebo or 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)			Moderate Due to serious risk of bias [25]	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 [26]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [14] with included studies: Spinner 2020, SOLIDARITY 2020 low/hi flow, Beigel 2020 lo-flow, SOLIDARITY 2020 no O2, Wang 2020, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
3. Systematic review [14] with included studies: Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation, Beigel 2020 Inv vent, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. Systematic review [14] 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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. Systematic review [14] 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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
9. Listed as critical in PICO
10. Systematic review [14] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
12. Systematic review [14] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **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 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.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
14. Systematic review [14] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
15. **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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

16. Listed as critical in PICO

17. Systematic review [14] with included studies: Spinner 2020, Spinner 2020, Wang 2020, Beigel 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: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

19. Systematic review [14] 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. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

21. Systematic review [14] with included studies: Spinner 2020, Beigel 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.

22. **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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

23. Systematic review [14] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.

24. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**

25. **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: No serious. Publication bias: No serious.**

26. **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: No serious. Publication bias: No serious.**

References

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18. Pan H., Peto R., Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V., Abdool Karim Q., et al. : Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med 2020; Journal

19. Spinner CD, Gottlieb RL, Criner GJ, Arribas L?pez JR, Cattelan AM, Soriano Viladomiu A., et al. : Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama 2020;324(11):1048-1057 Journal

20. Wang Y., Zhang D., Du G., Du R., Zhao J., Jin Y., et al. : Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569-1578 Journal

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Remdesivir 5 days
Comparator: Remdesivir 10 days

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 *[17][19]*.

Study characteristics
For a comprehensive description, see the study characteristics table from the National COVID-19 Clinical Evidence Taskforce, Australia.

What are the main results?
There may be 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 or discontinuation due to adverse event within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation *[17]*, 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). Certainty of the evidence is very low for septic shock due to lack of blinding and reliance on a single study with few patients and 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) *[17]*. The trial completed recruitment in July 2020 and we await the results from the full cohort of patients.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remdesivir 10 days	Remdesivir 5 days	**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 compared to 10-day treatment.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remdesivir 10 days	Remdesivir 5 days	**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 compared to 10-day treatment.
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 compared to 10-day treatment.
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)	25 per 1000	10 per 1000 Difference: **15 fewer** per 1000 (CI 95% 23 fewer - 25 more)	**Very Low** Due to very serious imprecision and serious risk of bias [8]	We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock compared to 10-day treatment.
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 serious imprecision [10]	Remdesivir 5-day treatment may improve clinical recovery slightly compared to 10-day treatment.
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 compared to 10-day treatment.
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 compared to 10-day treatment.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remdesivir 10 days	Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain text summary
Discontinued due to adverse event Within 14 days of commencing 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 serious imprecision [16]	Remdesivir 5-day treatment may make little or no difference to discontinuation due to adverse events compared to 10-day treatment.
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 compared to 10-day treatment.
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 compared to 10-day treatment.

1. Systematic review [15] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** due to few events.
3. Systematic review [15] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study, due to few events.
5. Systematic review [15] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **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 [15] with included studies: Goldman 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.** Low number of patients, Only data from one study. **Publication bias: No serious.**
9. Systematic review [15] 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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
11. Systematic review [15] 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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
13. Systematic review [15] with included studies: Spinner 2020, Goldman 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: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
15. Systematic review [15] 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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** due to few events. **Publication bias: No serious.**
17. Systematic review [15] with included studies: Spinner 2020, Goldman 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: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
19. Systematic review [15] with included studies: Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**

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15. Remdesivir dosage for COVID-19.

17. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R., Montejano R., et al. : Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020; Journal

19. Spinner CD, Gottlieb RL, Criner GJ, Arribas L?pez JR, Cattelan AM, Soriano Viladomiu A., et al. : Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama 2020;324(11):1048-1057 Journal

Only in research settings

Do not use remdesivir for COVID-19 pneumonia in adults, young people and children who are in hospital and on invasive mechanical ventilation, except within the context of a clinical trial setting.

Evidence To Decision

Benefits and harms

Important harms

The panel noted the opposing directions of effect between people receiving invasive mechanical ventilation (IMV), which showed a trend towards higher all-cause mortality, and people not receiving IMV, which showed a trend towards lower all-cause mortality. The duration and severity of disease was considered to be the explanation for this. The benefit of remdesivir as an antiviral agent would therefore be most apparent in people early in their disease course, when viral replication is a driver of disease, before the need for IMV.

Evidence from randomised controlled trials of remdesivir compared with standard care show that remdesivir has an acceptable safety profile and may reduce the incidence of serious adverse events. However, for people receiving IMV there is evidence to suggest that remdesivir may increase 28-day mortality.

Based on the results of 2 studies that compared 10-day with 5-day courses of remdesivir, it is unclear which of these regimens provide the optimal duration of treatment. The current evidence does not suggest any clear benefit for 10-day duration and shows that it may be more harmful than a 5-day course. For this reason, along with resource impact considerations (see also Resources), the panel agreed to recommend a 5-day regimen.

The panel noted the unclear additive benefit of remdesivir when used with dexamethasone, particularly since the 2 main trials, SOLIDARITY and ACTT-1, were done before the routine use of dexamethasone.

The panel also reviewed academic-in-confidence data from an observational study but did not consider this to have any effect on the recommendations.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for death in both subgroups (people who do not need invasive ventilation, and people who need invasive ventilation), all because of serious imprecision (wide confidence intervals). The panel noted difficulties in disaggregating data on different modalities of respiratory support to inform subgroup analysis, with some trials covering both invasive and non-invasive ventilation. However, the panel agreed that subgroup data should be distinguished between invasive mechanical ventilation (IMV) and non-invasive ventilation modalities in the pooled meta-analysis of included studies. The panel noted that, despite serious imprecision, the direction of effect was consistently in favour of control across subgroup data covering people on IMV, suggesting that remdesivir is associated with higher mortality.

Certainty is also moderate for the outcomes of number of people needing ventilation and discharge from hospital (because of reliance on a single study), serious adverse events, time to recovery and time to improvement (because of non-blinding of people in the trial and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (because of inconsistency in direction of effect and wide confidence intervals), number of people needing IMV or extracorporeal membrane oxygenation (because of non-blinding of people in the trial and personnel, and reliance on a single study), clinical recovery and adverse events (because of non-blinding of people in the trial and personnel, and inconsistency in direction of effect) and stopping treatment because of adverse events (because of non-blinding of people in the trial and personnel, and wide confidence intervals). Certainty of the evidence is very low for septic shock (because of non-blinding of people in the trial and personnel, inconsistency in direction of effect and wide confidence intervals).

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who do not need invasive ventilation, most would choose remdesivir.

Resources Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review.

The panel raised concerns about opportunity costs where remdesivir is being used in critical care, and the importance of not diverting resources away from best supportive care. The panel noted the value of targeting treatment to optimise use of resources. The panel also noted the lack of evidence indicating any benefit of a 10-day over a 5-day regimen, a direction of effect indicating potential harms of the 10-day duration and the resource impact for a longer duration of treatment. See also the benefits and harms section.

Equity Important issues, or potential issues not investigated

The panel noted an absence of evidence on the use of remdesivir in children. However, it was considered unlikely that most children would benefit from this intervention because most children will recover without the need for it. It is also not licensed for use in children under 12 years. Children over 12 years, and weighing 40 kg or more with adult phenotype disease should have treatment based on the same indications as those used for adults, in particular if there is progressive respiratory deterioration. Children with comorbidities with significant lung disease may have benefit from treatment with remdesivir, but they should be discussed on a case-by-case basis with the paediatric infectious diseases team.
The panel also noted the absence of evidence on the use of remdesivir in community settings. However, it was considered unlikely to be used outside the hospital setting because the criteria for accessing remdesivir in the UK currently stipulate hospitalisation with COVID-19.
No other equity issues were identified.

Acceptability Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is only moderate. However, the panel noted the consistent direction of effect in favour of remdesivir.
It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and:

- do not need invasive mechanical ventilation would choose to have remdesivir
- need invasive mechanical ventilation would choose not to have remdesivir.

Feasibility No important issues with the recommended alternative

Although there is no systematically collected evidence about feasibility, the panel noted that current widespread use of remdesivir in clinical practice is an indicator of feasibility.

Rationale

We recommend against using remdesivir for adults and children in hospital with COVID-19 pneumonia who are on invasive mechanical ventilation (IMV) because remdesivir probably increases the risk of death for these people.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization (WHO).[22]

There are several factors that contribute to differences in recommendations between NICE and WHO:

- NICE considers that delineation of subgroups based on disease severity is credible, and that the observed differences in direction of effect on mortality between subgroups is plausible. See the evidence to decision section on benefits and harms for the panel's explanation of differing effects on mortality depending on severity.
- NICE highlights the differential effect of remdesivir on mortality within these subgroups (that is, the absolute effect estimate of 19 fewer deaths per 1,000 in people in hospital who do not need IMV, and the absolute effect estimate of 60

more deaths per 1,000 in people in hospital who need IMV.

- NICE is more certain that the effect of remdesivir on mortality is closer to the true effect than WHO because certainty was not downgraded because of risk of bias (NICE has determined certainty for mortality outcomes as moderate, compared with the low certainty assessment by WHO).

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Remdesivir
Comparator: Placebo or standard care

Summary

Evidence indicates that remdesivir probably reduces the risk of death slightly in hospitalised adults not requiring invasive ventilation and increases the risk of death in hospitalised adults who require invasive 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 *[16][18][19][20]*. 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 *[18][16]*.

Study characteristics
Mean or median age ranged from 56 to 66 years and women comprised 32 to 44% of patients across the studies. Pregnant patients and children were ineligible, with the exception of one trial*[19]* which included children over 12 years weighing 40kg or more. There was variability in disease severity among patients included in the trials (see table).

Disease severity	Number of people	References
Moderate	584	*[19]*
Moderate to critical	6513	*[16][18]*
Severe to critical	236	*[20]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require invasive ventilation (19 fewer deaths per 1000 patients (RR 0.79, 95% CI 0.61 to 1.01; 6511 patients in 4 studies)). Remdesivir probably increases death at day 28 in patients who require invasive ventilation (60 more deaths per 1000 patients (RR 1.24 CI 95% 1.00 to 1.533; 811 patients in 3 studies)).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies. Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the eight-point WHO ordinal scale *[16]* or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale *[19]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale *[19]* or 6-point ordinal scale *[20]*.

Compared with standard care, remdesivir probably reduces serious adverse events (63 fewer SAEs per 1000 patients (RR 0.75, CI 95% 0.63 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, the need for invasive mechanical ventilation or ECMO, 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 invasive ventilation, and patients who require invasive 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 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). Certainty of the evidence is very low for septic shock (due to non-blinding of patients and personnel, inconsistency in direction of effect and wide confidence intervals).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality (day 28; hospital no invasive ventilation) Within 28 days of commencing treatment 9 Critical	Relative risk 0.79 (CI 95% 0.61 - 1.01) Based on data from 6,511 patients in 4 studies. [1] (Randomized controlled)	90 per 1000	71 per 1000 Difference: **19 fewer** per 1000 (CI 95% 35 fewer - 1 more)	**Moderate** Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients not on invasive ventilation at baseline.
All-cause mortality (day 28; invasive ventilation) Within 28 days of commencing treatment 9 Critical	Relative risk 1.24 (CI 95% 1 - 1.53) Based on data from 811 patients in 3 studies. [3] (Randomized controlled)	248 per 1000	308 per 1000 Difference: **60 more** per 1000 (CI 95% 0 fewer - 131 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients on invasive ventilation at baseline.
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 in hospitalised patients not on invasive ventilation at baseline.
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment	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 imprecision and serious risk of bias [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO in hospitalised patients not on invasive ventilation at baseline.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical					
Patients requiring ventilation [9] 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. [10] (Randomized controlled)	115 per 1000	118 per 1000 Difference: **3 more** per 1000 (CI 95% 13 fewer - 23 more)	**Moderate** Due to serious imprecision [11]	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. [12] (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 [13]	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. [14] (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, serious inconsistency and serious imprecision [15]	We are uncertain whether remdesivir increases or decreases septic shock
Serious adverse events [16] 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. [17] (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 [18]	Remdesivir probably results in slightly fewer serious adverse 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. [19] (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 [20]	We are uncertain whether remdesivir increases or decreases adverse events.
Discontinuation due to adverse events	Relative risk 1.73 (CI 95% 0.57 - 5.28) Based on data from 1,880 patients in 3	93 per 1000	161 per 1000	**Very Low** Due to serious risk of bias, serious	We are uncertain whether remdesivir increases or decreases adverse events leading

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or standard care	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
During treatment 6 Important	studies. [21] (Randomized controlled)	Difference: 68 more per 1000 (CI 95% 40 fewer - 398 more)		inconsistency and serious imprecision [22]	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. [23] (Randomized controlled)	720 per 1000	713 per 1000 Difference: 7 fewer per 1000 (CI 95% 29 fewer - 22 more)	**Moderate** Due to serious imprecision [24]	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 [25]	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 [26]	Remdesivir may decrease time to improvement slightly.

1. Systematic review [14] with included studies: Spinner 2020, SOLIDARITY 2020 low/hi flow, Beigel 2020 lo-flow, SOLIDARITY 2020 no O2, Wang 2020, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
3. Systematic review [14] with included studies: Beigel 2020 hi flow or NIV, SOLIDARITY 2020 ventilation, Beigel 2020 Inv vent, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. Systematic review [14] 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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. Systematic review [14] 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. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**

9. Listed as critical in PICO
10. Systematic review [14] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
12. Systematic review [14] with included studies: Spinner 2020, Beigel 2020, Spinner 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **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 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.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
14. Systematic review [14] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
15. **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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
16. Listed as critical in PICO
17. Systematic review [14] with included studies: Spinner 2020, Spinner 2020, Wang 2020, Beigel 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: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
19. Systematic review [14] 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. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
21. Systematic review [14] with included studies: Spinner 2020, Beigel 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
22. **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: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
23. Systematic review [14] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
24. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
25. **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: No serious. Publication bias: No serious.**
26. **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: No serious. Publication bias: No serious.**

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7.4 - Tocilizumab

Info Box

New

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'.

Strong recommendation

New

Offer tocilizumab to adults in hospital with COVID-19 if all of the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.

And they either:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

In April 2021, the marketing authorisations for tocilizumab do not cover use in COVID-19. See NICE's information on prescribing medicines for more about off-label and unlicensed use of medicines.

The recommended dosage for tocilizumab is a single dose of 8 mg/kg by intravenous infusion. The total dose should not exceed 800 mg.

For tocilizumab use in pregnancy, follow the Royal College of Obstetrics and Gynaecology guidance on coronavirus (COVID-19) infection and pregnancy.

For full details of adverse events and contraindications, see the summaries of product characteristics for tocilizumab.

See NHS England's Interim Clinical Commissioning Policy on tocilizumab for hospitalised patients with COVID-19 pneumonia (adults) for further information.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Available evidence suggests that tocilizumab is statistically significantly more effective than standard care alone at reducing death and the need for invasive mechanical ventilation in adults in hospital with COVID-19 who have evidence of hypoxia. The panel noted that standard care varied across trials. In particular, corticosteroids were not offered routinely in trials carried out before the results of the dexamethasone arm of the RECOVERY trial was published. The panel discussed that the evidence showed an additional benefit when tocilizumab is used with corticosteroids. The evidence also suggested that, compared with standard care, tocilizumab may increase the number of people who are discharged from hospital and may decrease the number of people admitted to intensive care. However, the results did not reach statistical significance.

The evidence suggests that tocilizumab probably has little effect on clinical progression (worsening of the condition measured on an ordinal scale), serious adverse events and adverse events. However, the panel noted that outcomes were limited to 28-day follow up, so the longer-term effects are unknown. Long-term use of tocilizumab is associated with the risk of opportunistic infections because of its effect on the immune system. The panel acknowledged that most people in the trials had a single dose of tocilizumab, with a second dose permitted when the condition worsened. Therefore, the risks associated with long-term use may not apply to people having tocilizumab for COVID-19. However, the panel did acknowledge the effect that tocilizumab can have on C-reactive protein levels, which is important for ongoing care after treatment. To identify serious adverse reactions to tocilizumab, there is a Yellow Card reporting system for the Medicines and Healthcare products Regulatory Agency in place. Details of special warnings and precautions for tocilizumab use are in the summaries of product characteristics. It would also be beneficial to ensure that ongoing care providers in the community are informed about people's treatments when they are transferred from a hospital setting, so that they are aware of any potential long-term treatment effects.

Certainty of the Evidence

Moderate

The certainty of the evidence for critical outcomes ranges from moderate to high. All-cause mortality has been downgraded to moderate certainty for serious inconsistency because of different directions of effect sizes. However, sensitivity analysis suggest that these differences may be explained, in part, by differences in the co-administration of corticosteroids across the trials. This supports current best practice because corticosteroids are now routinely offered for managing COVID-19. The need for invasive mechanical ventilation is rated as high certainty. The serious adverse events outcome has been downgraded to moderate certainty for serious imprecision because of a wide confidence interval.

For important outcomes, the evidence is rated between low and moderate certainty. Adverse events, septic shock, clinical progression, admission to intensive care and discharge from hospital have been downgraded to moderate certainty because of serious imprecision or serious inconsistency. There is less evidence on other outcomes including clinical recovery, clinical improvement, duration of ventilation, time to improvement or duration of hospital stay. These have all been downgraded to low certainty because of very serious imprecision caused by wide confidence intervals and evidence coming from single studies.

None of the outcomes have been downgraded for indirectness. This is because the largest randomised controlled trial contributing to the evidence base was carried out in the UK. Therefore, the panel considered that the population in the trial was generalisable to the UK context and representative of people admitted to hospital in the UK. Although eligibility criteria varied across the studies, there were few restrictions in the entry criteria for RECOVERY because it was a pragmatic trial. The restrictions included other active infection or hypersensitivity to tocilizumab which reflects the summaries of product characteristics for tocilizumab.

Preference and values

No substantial variability expected

The panel identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to patients. These outcomes were not as commonly reported in studies.

Resources

Important issues, or potential issues not investigated

The panel commented that a recommendation offering tocilizumab may be dependent on its availability across different hospitals. They also acknowledged that the eligibility criteria in the commissioning policy for tocilizumab use allows people to have treatment as early as possible. This may reduce the need to use more critical resources in the hospital setting.

Equity

Important issues, or potential issues not investigated

The trials identified do not provide data on tocilizumab use in pregnancy. While the evidence base is limited, there is currently no evidence that tocilizumab is teratogenic or fetotoxic. Therefore, the decision about whether someone who is pregnant meets the eligibility criteria should be considered by a multidisciplinary team that includes an obstetric specialist where possible. There are also additional considerations for people who are breastfeeding or of childbearing potential who have tocilizumab. This is outlined in the summaries of product characteristics.

The panel discussed that oxygen supplementation may not be suitable for all people. Although this may be more of an issue in the community, the panel wanted to ensure that tocilizumab use was not reliant on having oxygen supplementation, rather that the person would meet the requirements for oxygen supplementation.

No evidence has been identified that evaluated the efficacy of tocilizumab in groups of people with other protected

characteristics such as ethnicity.

Acceptability Important issues, or potential issues not investigated

No qualitative evidence was identified that could be used to assess the acceptability of tocilizumab use. However, in the context of the COVID-19 pandemic, patients, and their families and clinicians, would likely accept tocilizumab use because the benefits of reducing death and the need for invasive mechanical ventilation seem to outweigh the risk of adverse events.

Feasibility No important issues with the recommended alternative

The trials were all carried out in a hospital setting. The panel considered this to be appropriate, and agreed that it reflects current practice for use and availability of tocilizumab.

Rationale

There is evidence that tocilizumab reduces both all-cause mortality and the need for invasive mechanical ventilation. Corticosteroids are now part of standard care for people with COVID-19, and there is evidence of an additional benefit when tocilizumab is also used. The entry criteria for the RECOVERY and REMAP-CAP trials were representative of people admitted to hospital in the UK, so based the eligibility criteria for tocilizumab use on these trials.

The entry criteria for RECOVERY were:

- clinically suspected or microbiologically confirmed COVID-19
- low oxygen levels
- C-reactive protein levels of more than 75 mg/litre.

The entry criteria for REMAP-CAP were:

- clinically suspected or microbiologically confirmed COVID-19
- severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an intensive care unit.

Respiratory organ support was defined as invasive or non-invasive mechanical ventilation, including via high flow nasal cannula if flow rate was more than 30 litres/min and fraction of inspired oxygen was less than 0.4. The criteria for severe disease state were still met if non-invasive ventilation would normally have been provided but was being withheld because of infection control concerns associated with aerosol generating procedures.

Cardiovascular organ support was defined as the intravenous infusion of any vasopressor or inotrope.

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Tocilizumab
Comparator: Standard care or placebo

Summary

The evidence suggests that tocilizumab slightly decreases the risk of death and the need for invasive mechanical ventilation in people hospitalised with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from ten randomised trials that compared tocilizumab with standard care or placebo in 6570 adults hospitalised with COVID-19 *[23][24][25][26][27][28][29][30][31][33]*. There was variability in disease severity among patients included in the trials (see table). Standard care varied across studies. Some of the earlier trials were conducted or published before the results of the dexamethasone arm of the RECOVERY trial *[6]* were published which meant that corticosteroids were not routinely given across all studies.

Results from the tocilizumab arm of the REMAP-CAP trial—published as a preprint on 9 January 2021*[23]* —showed a strong mortality benefit in patients with critical illness who were receiving organ support. These data contrasted with the existing meta-analysis of randomised trials conducted by the National COVID-19 Clinical Evidence Taskforce (Australia), 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 (see table), with the exception of the COVACTA trial *[26]*, which included 108 patients with critical illness. In addition, results from the tocilizumab arm of the RECOVERY trial *[31]*– published as a pre-print on 11 February 2021- which included 4116 people, showed a mortality benefit in patients with moderate to critical illness and the COVINTOC trial *[33]* which included 180 people showed a reduction in mortality for those with moderate to severe COVID-19.

To determine whether differences in observed effect on mortality might be explained by differences in disease severity, the National COVID-19 Clinical Evidence 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.

Publication status
Three studies are only available as preprints (Rosas et al. (COVACTA) posted to medRxiv on 12 September 2020 *[26]*, Gordon et al. (REMAP-CAP) posted to medRxiv on 9 January 2021 *[23]*) and Horby et al 2021 posted to medRxiv on 11 February 2021 *[31]* and have therefore not been peer reviewed.

Study characteristics
Mean or median age ranged from 55 to 64 years and women comprised 14 to 50% of patients across the studies. Pregnant and breastfeeding women were ineligible except for the RECOVERY trial which included 3 pregnant women. Studies included patients with moderate, severe and critical COVID-19 (see table).

Disease severity	Number of patients	References
Moderate-Severe	4506	*[20] [25][29][28] [27][31][33]*
Moderate-Critical	567	*[26][24]*
Critical	1317	*[23][31]*

What are the main results?
Tocilizumab decreases the risk of death in hospitalised people (32 fewer per 1000 people; RR 0.89 CI 95% 0.80 - 0.99; 6481 patients in 9 studies) but probably has little impact on adverse or serious adverse events, septic shock or clinical progression. Tocilizumab decreases the number of patients who require invasive mechanical ventilation (30 fewer per 1000 patients; RR 0.81, CI 95% 0.70 to 0.93; 4248 patients in 4 studies) and may increase the number of people discharged from hospital (35 more per 1000 patients; RR 1.07 CI 95% 0.99 to 1.16). Tocilizumab may decrease the number of admissions to ICU (76 fewer per 1000 patients; RR 0.82 95% CI 0.54 to 1.23). The effect of tocilizumab on other outcomes is uncertain.

Our confidence in the results
Certainty of the evidence is moderate for mortality. This outcome was downgraded for inconsistency due to different directions of effect. Certainty of the evidence was also moderate for admission to ICU, adverse or serious adverse events, septic shock, discharge from hospital and clinical progression. These outcomes were downgraded for serious imprecision due to wide confidence intervals and inconsistency due to different directions of effect. Certainty in the evidence is high for reducing the requirement of invasive mechanical ventilation. Certainty for all remaining outcomes is low due to very serious imprecision (reliance on a single study).

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care or placebo	 Tocilizumab	Certainty of the Evidence (Quality of evidence)	Plain text summary
All-cause mortality [All patients] Day 21-28 after commencing treatment 9 Critical	Relative risk 0.89 (CI 95% 0.8 - 0.99) Based on data from 6,481 patients in 9 studies. [1] (Randomized controlled)	290 per 1000	258 per 1000 Difference: **32 fewer** per 1000 (CI 95% 58 fewer - 3 fewer)	**Moderate** Due to serious inconsistency [2]	Tocilizumab decreases death in hospitalised patients
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.81 (CI 95% 0.7 - 0.93) Based on data from 4,248 patients in 4 studies. [3] (Randomized controlled)	159 per 1000	129 per 1000 Difference: **30 fewer** per 1000 (CI 95% 48 fewer - 11 fewer)	**High**	Tocilizumab decreases the requirement for invasive mechanical ventilation.
Respiratory failure or ARDS Within 14 days of commencing treatment 6 Important	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
Serious adverse events End of follow-up 9 Critical	Relative risk 0.9 (CI 95% 0.76 - 1.06) Based on data from 2,309 patients in 8 studies. [6] (Randomized controlled)	162 per 1000	146 per 1000 Difference: **16 fewer** per 1000 (CI 95% 39 fewer - 10 more)	**Moderate** Due to serious imprecision [7]	We are uncertain whether tocilizumab increases or decreases serious adverse events
Adverse events End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.87 - 1.34) Based on data from 1,562 patients in 7 studies. [8] (Randomized controlled)	466 per 1000	503 per 1000 Difference: **37 more** per 1000 (CI 95% 61 fewer - 158 more)	**Moderate** Due to serious imprecision [9]	We are uncertain whether tocilizumab increases or decreases adverse events
Septic shock End of follow-up 6 Important	Relative risk 0.59 (CI 95% 0.26 - 1.35) Based on data from 815 patients in 2 studies. [10] (Randomized controlled)	37 per 1000	22 per 1000 Difference: **15 fewer** per 1000 (CI 95% 27 fewer - 13 more)	**Moderate** Due to serious imprecision [11]	We are uncertain whether tocilizumab increases or decreases septic shock

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care or placebo	Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Admission to ICU End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.54 - 1.23) Based on data from 699 patients in 4 studies. [12] (Randomized controlled)	423 per 1000	347 per 1000 Difference: **76 fewer** per 1000 (CI 95% 195 fewer - 97 more)	**Moderate** Due to serious imprecision [13]	Tocilizumab may decrease admission to ICU
Discharge from hospital End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.99 - 1.16) Based on data from 4,611 patients in 4 studies. (Randomized controlled)	506 per 1000	541 per 1000 Difference: **35 more** per 1000 (CI 95% 5 fewer - 81 more)	**Moderate** Due to serious inconsistency [14]	Tocilizumab may increase discharge from hospital
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.92 - 1.27) Based on data from 65 patients in 1 studies. [15] (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 [16]	We are uncertain whether tocilizumab increases or decreases clinical improvement.
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. [17] (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 [18]	We are uncertain whether tocilizumab increases or decreases clinical improvement.
Clinical progression Within 14 days of commencing treatment 6 Important	Relative risk 1 (CI 95% 0.69 - 1.44) Based on data from 544 patients in 3 studies. [19] (Randomized controlled)	181 per 1000	181 per 1000 Difference: **0 fewer** per 1000 (CI 95% 56 fewer - 80 more)	**Moderate** Due to serious imprecision [20]	Tocilizumab probably has little impact on clinical progression
Duration of mechanical ventilation Days 6 Important	Based on data from: 19 patients in 1 studies. [21] (Randomized controlled)	27.9 (Median)	15 (Median) Difference: **12.9 fewer** CI 95%	**Low** Due to very serious imprecision [22]	We are uncertain whether tocilizumab decreases duration of mechanical ventilation

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care or placebo	 Tocilizumab	Certainty of the Evidence (Quality of evidence)	Plain text summary
Time to improvement Days 6 Important	Based on data from: 219 patients in 1 studies. [23] (Randomized controlled)	5 (Median)	6 (Median) Difference: 1 more CI 95%	Low Due to very serious imprecision [24]	We are uncertain whether tocilizumab increases or decreases time to improvement.
Duration of hospital stay Days 6 Important	Based on data from: 129 patients in 1 studies. [25] (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 [26]	We are uncertain whether tocilizumab decreases duration of hospital stay.

1. Systematic review [32] with included studies: Veiga 2021, RECOVERY 2021, Salvarini 2020, Soin 2021, REMAP-CAP tocilizumab, Hermine 2020, Rosas 2020, Stone 2020, Salama 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: No serious. Imprecision: No serious.**
3. Systematic review [32] with included studies: Rosas 2020, Soin 2021, Stone 2020, RECOVERY 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [32] with included studies: Hermine 2020. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients.
6. Systematic review [32] with included studies: Soin 2021, REMAP-CAP tocilizumab, Rosas 2020, Salama 2020, Stone 2020, Wang 2020, Veiga 2021, Hermine 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
8. Systematic review [32] with included studies: Stone 2020, Hermine 2020, Veiga 2021, Wang 2020, Rosas 2020, Salama 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
10. Systematic review [32] with included studies: Salama 2020, Rosas 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** due to few events. **Publication bias: No serious.**
12. Systematic review [32] with included studies: Hermine 2020, Rosas 2020, Salvarini 2020. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
14. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 57%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
15. Systematic review [32] with included studies: Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **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.**

17. Systematic review [32] with included studies: Stone 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **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.**
19. Systematic review [32] with included studies: Salvarini 2020, Soin 2021, Stone 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
21. Systematic review [32] . **Baseline/comparator:** Control arm of reference used for intervention.
22. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
23. Systematic review [32] . **Baseline/comparator:** Control arm of reference used for intervention.
24. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only data from one study, Low number of patients. **Publication bias: No serious.**
25. Systematic review [32] . **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [22],
26. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**

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Only in research settings

New

Consider tocilizumab for children and young people who have severe COVID-19 or paediatric inflammatory multisystem syndrome only if they are 1 year and over, and only in the context of a clinical trial.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

No evidence on tocilizumab use in children was identified. However, the panel acknowledged that the RECOVERY trial is assessing tocilizumab use in children and young people 1 year and over with paediatric inflammatory multisystem syndrome, and that tocilizumab is licensed for children and young people over 2 years. Therefore, tocilizumab may be considered for children and young people in a research setting.

Certainty of the Evidence

Very Low

Because no evidence on tocilizumab in children was identified, the overall assessment of certainty is very low, and the recommendation includes a requirement for such use to be part of a clinical trial.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on patients' preferences and values. Despite the absence of evidence for tocilizumab in children, the serious consequences of paediatric inflammatory multisystem syndrome mean that tocilizumab is likely to be preferred over no treatment.

Resources

No important issues with the recommended alternative

No formal analysis of resource impact has been carried out. The panel commented that the availability of tocilizumab may differ across hospitals.

Equity

Important issues, or potential issues not investigated

The evidence identified does not include children and young people under 18 years. However, the RECOVERY trial is assessing tocilizumab use in children and young people 1 year and over with paediatric inflammatory multisystem syndrome, and tocilizumab is licensed for children and young people over 2 years. Therefore, tocilizumab may be considered for children and young people in a research setting.

Acceptability Important issues, or potential issues not investigated

No qualitative evidence was identified that could be used to assess the acceptability of tocilizumab use. However, in the context of the COVID-19 pandemic, parents, children and clinicians would likely accept tocilizumab use for paediatric inflammatory multisystem syndrome as part of a clinical trial rather than having no treatment.

Feasibility No important issues with the recommended alternative

The planned trial is expected to be carried out in a hospital setting. The panel considered this to be appropriate, and agreed that it reflects current practice for use and availability of tocilizumab.

Rationale

There is no evidence for tocilizumab use in children and young people with COVID-19. However, there is an ongoing UK trial (RECOVERY) including children and young people 1 year and over with severe COVID-19 or paediatric inflammatory multisystem syndrome. So, tocilizumab can be considered for children and young people in the context of a clinical trial.

7.5 - Sarilumab

Info Box New

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'.

Weak recommendation

New

Consider sarilumab for adults in hospital with COVID-19 only if tocilizumab cannot be used or is unavailable. Use the same eligibility criteria as those for tocilizumab. That is, if all of the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by sarilumab.

And they either:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

In April 2021, the marketing authorisations for sarilumab do not cover use in COVID-19. See NICE's information on prescribing medicines for more about off-label and unlicensed use of medicines.

The recommended dosage for sarilumab is a single dose of 400 mg by intravenous infusion.

For sarilumab use in pregnancy, follow the Royal College of Obstetrics and Gynaecology guidance on coronavirus (COVID-19) infection and pregnancy.

For full details of adverse events and contraindications, see the summaries of product characteristics.

See NHS England's Interim Clinical Commissioning Policy on sarilumab for critically ill patients with COVID-19 pneumonia (adults) for further information.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The evidence for sarilumab for both reduction in mortality and adverse events is uncertain. The panel discussed whether these findings were because the evidence suggests an absence of effect or because of an absence of statistical power to detect an effect.

Fewer than 900 people were in the studies of sarilumab. In comparison, nearly 6,500 people were in the studies of tocilizumab, which is a similar drug. Also, the evidence for tocilizumab shows a statistically significant reduction in mortality. The panel commented that the point estimates for the effects of both drugs are similar, which provides some support for a lack of statistical power in the sarilumab studies.

The panel believed that the drugs, both of which are interleukin-6 inhibitors, are likely to have similar benefits and harms. However, in the absence of evidence of effectiveness, the panel thought that a consider recommendation, that is, for using sarilumab when tocilizumab is unavailable or cannot be used, would be appropriate (see the recommendation on tocilizumab in adults for further details). Details of special warnings and precautions for sarilumab use are in the summaries of product characteristics. It would also be beneficial to ensure that ongoing care providers in the community are informed about peoples' treatments when they are transferred from a hospital setting, so that they are aware of any potential long-term treatment effects.

Certainty of the Evidence

Very Low

The certainty of the effects for both all-cause mortality and adverse events is very low because there have been very few events and the confidence intervals are wide.

Preference and values — No substantial variability expected

The panel were not aware of any systematically collected data on patients' preferences and values. They discussed patient preferences and concluded that many people would rather have a treatment than have no treatment. However, the panel agreed that, given the absence of evidence of effectiveness for sarilumab in the data reviewed, it should only be used when tocilizumab is unavailable.

Resources — Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. There are no data on reduction of disease progression for sarilumab. So, it is unknown whether sarilumab used early in COVID-19 disease might prevent later use of intensive care resources.

Equity — Important issues, or potential issues not investigated

Sarilumab has not been studied in people who are pregnant or breastfeeding, or in children. The decision about whether someone who is pregnant meets the eligibility criteria should be considered by a multidisciplinary team that includes an obstetric specialist where possible. There are additional considerations for people who are breastfeeding or of childbearing potential who have sarilumab. This is outlined in the summaries of product characteristics.

No evidence has been identified that evaluated the efficacy of sarilumab in groups of people with other protected characteristics such as ethnicity.

Acceptability — No important issues with the recommended alternative

No evidence accessing acceptability of sarilumab has been identified. However, in the context of the COVID-19 pandemic, it is likely that patients, their families and clinicians would accept sarilumab as an alternative if tocilizumab is unavailable or cannot be used despite the uncertainty around the effects of sarilumab.

Feasibility — No important issues with the recommended alternative

The trials were carried out in a hospital setting. The panel considered this to be appropriate and agreed that it reflects where sarilumab is used in current practice.

Rationale

Although evidence for the effectiveness of sarilumab is uncertain, it is an acceptable alternative if tocilizumab cannot be used or is unavailable. This is because, like tocilizumab, it is an interleukin-6 inhibitor and likely to have similar benefits and harms. Use the same eligibility criteria as those for tocilizumab (see the recommendation on tocilizumab in adults for further details).

Clinical Question/ PICO

Population: People 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 two randomised trials that compared sarilumab with control in 866 adults hospitalised with severe or critical COVID-19 *[23][35]*.

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

Publication status
Both studies are only available as a preprint (posted to medRxiv on 9 January 2021 *[23]* and 3 February 2021 *[35]*) and have therefore not been peer reviewed.

Study characteristics
One study *[23]* included people with suspected or confirmed COVID-19 who were admitted to an intensive care unit and were receiving respiratory or cardiovascular organ support. The other study *[35]* included people with confirmed COVID-19 who were admitted to hospital with 'severe' or 'critical' disease as defined in the study. This meant that the patient population ranged from people needing supplemental oxygen through non-invasive and invasive ventilation to treatment in intensive care.

Mean age of participants was between 59 and 63 years. The proportion of women was 19% and 30% in the sarilumab and standard care arms, respectively in one trial *[23]*. and 37% in the second trial *[35]* There was a higher proportion of patients with diabetes (37% vs 27%) and severe cardiovascular disease (12% vs 2%) in the standard care arm compared with the sarilumab arm in one trial *[23]* but baseline characteristics were more similar across the groups in the second trial *[35]*. The majority of patients in REMAP-CAP*[23]* (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.

One study *[23]* assessed sarilumab 200 mg and 400 mg doses and the other *[35]* assessed sarilumab 400 mg.

What are the main results?
There was a non-significant reduction in proportion of deaths in the sarilumab arm compared with standard care (RR 0.74 95% CI 0.47 to 1.18), and no difference in incidence of serious adverse events (RR 1.14 95% CI 0.75 to 1.73).

There did not appear to be any dose-dependent differences in effect on mortality or serious adverse events.

Our confidence in the results Certainty of the evidence is low for all-cause mortality and serious adverse events due to very serious imprecision (wide confidence intervals and few events).

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 Within 29 days of commencing treatment 9 Critical	Relative risk 0.74 (CI 95% 0.47 - 1.18) Based on data from 858 patients in 2 studies. [1] (Randomized controlled)	310 per 1000	229 per 1000 Difference: **81 fewer** per 1000 (CI 95% 164 fewer - 56 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether sarilumab reduces risk of death in critical patients

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Sarilumab	Certainty of the Evidence (Quality of evidence)	Plain text summary
Serious adverse events End of follow-up 6 Important	Relative risk 1.14 (CI 95% 0.75 - 1.73) Based on data from 866 patients in 2 studies. [3] (Randomized controlled)	64 per 1000	73 per 1000 Difference: 9 more per 1000 (CI 95% 16 fewer - 47 more)	Low Due to very serious imprecision [4]	We are uncertain whether sarilumab increases or decreases serious adverse events in patients

1. Systematic review [32] with included studies: Lescure 2021 Sarilumab 400mg, REMAP-CAP sarilumab, Lescure 2021 Sarilumab 200mg. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals, due to few events.
3. Systematic review [32] with included studies: Lescure 2021 Sarilumab 200mg, Lescure 2021 Sarilumab 400mg, REMAP-CAP sarilumab. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** due to few events, Wide confidence intervals. **Publication bias: No serious.**

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7.6 - Colchicine

Info Box

New

NICE is reviewing the evidence for colchicine.

7.7 - Low molecular weight heparins

Info Box

For recommendations on the therapeutic use of low molecular weight heparins, see the section on venous thromboembolism (VTE) prophylaxis.

7.8 - Vitamin D supplementation

Info Box

For recommendations on vitamin D, see the NICE COVID-19 rapid guideline on vitamin D.

8 - Preventing and managing acute complications

8.1 - Acute kidney injury (AKI)

Info Box

In people with COVID-19, AKI:

- may be common, but prevalence is uncertain and depends on clinical setting (the Intensive Care National Audit and Research Centre's report on COVID-19 in critical care provides information on people in critical care who need renal replacement therapy for AKI)
- is associated with an increased risk of dying
- can develop at any time (before, during or after hospital admission)
- may be caused by volume depletion (hypovolaemia), haemodynamic changes, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology or rhabdomyolysis
- may be associated with haematuria, proteinuria and abnormal serum electrolyte levels (both increased and decreased serum sodium and potassium).

Info Box

In people with COVID-19:

- maintaining optimal fluid status (euvolaemia) is difficult but critical to reducing the incidence of AKI
- treatments for COVID-19 may increase the risk of AKI
- treatments for pre-existing conditions may increase the risk of AKI
- fever and increased respiratory rate increase insensible fluid loss.

8.1.1 - Assessing and managing acute kidney injury (AKI)

Info Box

The potassium binders patiromer and sodium zirconium cyclosilicate can be used as options alongside standard care for the emergency management of acute life-threatening hyperkalaemia (see NICE's technology appraisal guidance on patiromer and sodium zirconium cyclosilicate for treating hyperkalaemia).

Info Box

For information on assessing and managing AKI, see the NICE guideline on acute kidney injury: prevention, detection and management.

For information on using intravenous fluids, see the NICE guideline on intravenous fluid therapy in adults in hospital and NICE guideline on intravenous fluid therapy in children and young people in hospital.

8.1.2 - Follow up

Consensus recommendation

Monitor people with chronic kidney disease for at least 2 years after AKI, in line with the NICE guideline on chronic kidney disease in adults: assessment and management.

See guidance on care after hospital discharge in the Royal College of General Practitioners AKI toolkit.

8.2 - Acute myocardial injury

8.2.1 - Diagnosing acute myocardial injury

Consensus recommendation

For people in hospital with COVID-19 with signs or symptoms that suggest acute myocardial injury, measure high sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro B-type natriuretic peptide, and do an ECG.

Use the following test results to help inform a diagnosis:

- evolving ECG changes suggesting myocardial ischaemia
- an NT-proBNP level above 400 ng/litre
- high levels of hs-cTnI or hs-cTnT, particularly levels increasing over time.

Info Box

Elevated troponin levels may reflect cardiac inflammatory response to severe COVID-19 rather than acute coronary syndrome.

8.2.2 - Managing myocardial injury

Consensus recommendation

For all people with COVID-19 and suspected or confirmed acute myocardial injury:

- monitor in a setting where cardiac or respiratory deterioration can be rapidly identified
- do continuous ECG monitoring
- monitor blood pressure, heart rate and fluid balance.

Consensus recommendation

For people with a clear diagnosis of myocardial injury:

- seek specialist cardiology advice on treatment, further tests and imaging
- follow local treatment protocols.

Consensus recommendation

For people with a high clinical suspicion of myocardial injury, but without a clear diagnosis:

- repeat high sensitivity troponin (hs-cTnI or hs-cTnT) measurements and ECG monitoring daily, because dynamic change may help to monitor the course of the illness and establish a clear diagnosis
- seek specialist cardiology advice on further investigations such as transthoracic echocardiography and their frequency.

See also the management section for recommendations on care planning and recommendations on escalating and de-escalating treatment.

Info Box

See the Medicines and Healthcare products Regulatory Agency's Drug Safety Update on erythromycin: caution required due to cardiac risks (QT interval prolongation); drug interaction with rivaroxaban.

8.3 - Venous thromboembolism (VTE) prophylaxis

Info Box

Definitions

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'

Hospital-led acute care in the community is defined as a setting in which people who would otherwise be admitted to hospital have acute medical care provided by members of the hospital team, often working with the person's GP team. They include hospital at home services and COVID-19 virtual wards.

Intermediate dose VTE prophylaxis is defined as the standard prophylactic dose of anticoagulant for people who are acutely ill and having medical care, given twice daily instead of once daily (and doubling of the usual daily dose).

Treatment dose is defined as the licensed dose of anticoagulation used to treat confirmed VTE.

8.3.1 - In hospital

Consensus recommendation

For young people and adults with COVID-19 that is being managed in hospital, assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review. Use a risk assessment tool published by a national UK body, professional network or peer-reviewed journal.

Practical Info

A tool commonly used to develop a treatment plan for patients is the Department of Health VTE risk assessment tool.

Evidence To Decision

Benefits and harms

The panel were presented with academic-in-confidence data from a multiplatform trial that evaluated whether empiric use of treatment-dose anticoagulation improves clinical outcomes in people in hospital with confirmed COVID-19.

The evidence shows that treatment-dose anticoagulation is associated with an increased risk of bleeding. The panel agreed that risk of bleeding should therefore be assessed as soon as possible using a risk assessment tool to uncover any potential harm to people with a high risk.

Rationale

The panel acknowledged that there was a lack of good-quality evidence specific to people with COVID-19. They used their clinical knowledge and experience to build on the limited evidence base to develop the recommendations.

The panel agreed that all people with COVID-19 have an increased risk of VTE. Initial risk assessment for these people (as soon as possible after admission or by the time of their first consultant review) should focus on identifying those whose bleeding risk contraindicates pharmacological VTE prophylaxis.

The panel agreed that a risk assessment tool published by a national UK body, professional body or peer reviewed journal should be prioritised for use.

Consensus recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH), unless contraindicated, for young people and adults with COVID-19 who:

- are likely to be in hospital for the next 3 days
- need supplemental oxygen and who are not yet receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Treatment should be for a minimum of 14 days or until discharge. Dose reduction may be needed to respond to any changes in a person's clinical circumstances. See the recommendation on people with COVID-19 who need high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation or palliative care.

For people with COVID-19 who do not need supplemental oxygen, follow the recommendations in the NICE guideline on venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism.

In March 2021, the use of a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See NICE's information on prescribing medicines.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

The panel were presented with academic-in-confidence data from a multiplatform trial (mpRCT) that evaluated whether empiric use of treatment-dose anticoagulation improves clinical outcomes in people in hospital with confirmed COVID-19. Three multicenter, randomised, open-label trials (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia [REMAP-CAP] and Accelerating COVID-19 Therapeutic Interventions and Vaccines [ACTIV-4a]) were started and harmonised for protocol and outcomes measured.

The panel agreed, based on the analysis presented to them that, for people defined as having moderate COVID-19 in the mpRCT (adults in hospital not initially needing intensive care therapies or levels of care), treatment-dose anticoagulation for VTE prophylaxis was effective in reducing mortality and keeping people from needing admission to the intensive care unit (ICU). This is an important outcome for both minimising progression of COVID-19 pneumonia and avoiding other adverse outcomes.

The panel agreed that the evidence showed that treatment-dose prophylactic anticoagulation was not beneficial for people defined in the mpRCT as having severe or critical COVID-19 (people admitted to ICU and receiving organ support [such as needing a vasopressor or inotrope]). The panel noted that this population could be described as people needing high flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation. Therefore, the panel noted that treatment-dose anticoagulation for VTE prophylaxis should be stepped down when people progress to needing these modalities of respiratory support. For people receiving these modalities of support, treatment-dose VTE prophylaxis should not be used unless as part of a clinical trial. Recommendations were made to reflect these conclusions.

The panel discussed that the 2 findings appeared to be contradictory – benefits seen with treatment-dose anticoagulation in people in with moderate disease, but harms seen in people with severe disease. However, they noted that similar findings had been seen for other drug treatments for COVID-19. Therefore, although questions remain about the mechanism of this effect, the panel thought that it was a true effect.

The occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. The panel noted that the rate of major bleeding events was relatively low for people in hospital with moderate COVID-19. Thus

the benefits of treatment-dose prophylactic anticoagulation outweighed the potential harms in this population.

The panel recommended not to base prophylactic dosing of heparin on levels of D-dimer because the trial evidence presented from the mpRCT showed that a person's D-dimer measurements did not influence the effects of VTE prophylaxis.

The panel noted that the duration of treatment recommended should match the duration of studies in the trials, which was 14 days.

The panel discussed what to do if someone is already on treatment-dose anticoagulation at admission. The panel noted that people would normally remain on their prescribed anticoagulation if they can take oral medicines. However, they would switch to a low molecular weight heparin when they could no longer take oral medicines such as when admitted to the intensive care unit. This is consistent with an existing recommendation for this population.

Certainty of the Evidence Moderate

The panel were presented with academic-in-confidence data from a multiplatform trial that evaluated whether empiric use of treatment-dose anticoagulation improves clinical outcomes in people in hospital with confirmed COVID-19. Three multicenter, randomised, open-label trials (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia [RECAP], and Accelerating COVID-19 Therapeutic Interventions and Vaccines [ACTIV-4a]) were started and harmonised for protocol and outcomes measured.

The panel noted that the interim results from these 3 trials have not been peer-reviewed or adjudicated and were therefore interpreted with the appropriate caution. However, the panel considered that the evidence was certain enough to make recommendations to consider treatment-dose VTE prophylaxis in young people and adults with COVID-19 who are likely to be in hospital for the next 3 days, need supplemental oxygen, have moderate COVID-19 and are not yet receiving high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and to step down this dose when someone needs advanced respiratory support.

Preference and values No substantial variability expected

We have no systematically collected information about people's preferences and values.

The panel noted that restricting the recommendation to people in hospital could affect people who preferred treatment in the community through 'hospital at home' services or COVID-19 'virtual wards'. However, the new evidence did not cover this population so no changes to the existing recommendation that was developed for the original NICE rapid guideline on reducing the risk of venous thromboembolism in people over 16 years with COVID-19 (published November 2020) were proposed for this population.

Resources No important issues with the recommended alternative

We have no systematically collected evidence about cost-benefit.

The recommendations to offer treatment-dose VTE prophylaxis were not considered to have an important effect on resources because using a higher dose and longer duration of an established treatment constitutes a relatively small change in clinical practice.

Additionally, cost savings from reducing length of stay in hospital and preventing admissions to the intensive care unit

are expected to be substantially higher than the increased cost of the prescribed drugs.

Equity No important issues with the recommended alternative

The panel noted an absence of evidence for anticoagulation in children. It was recognised that younger children have different haematological physiology, meaning that VTE is less likely. However, their clinical experience suggested that, after puberty, people under 18 years were also at risk of VTE if admitted to hospital with COVID-19 pneumonia. For that reason, the panel included young people in the recommendations as well as adults. Additionally, a research recommendation was made for this population.

No other equity issues were identified.

Acceptability No important issues with the recommended alternative

It is anticipated that, after considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia:

- who do not need invasive mechanical ventilation would choose to have treatment-dose anticoagulation
- who need invasive mechanical ventilation would choose not to have treatment-dose anticoagulation.

However, we have no systematically collected evidence about acceptability.

Feasibility No important issues with the recommended alternative

Implementing the use of treatment-dose VTE prophylaxis in people in hospital who are not receiving advanced respiratory support is expected to be feasible because it represents an increase in the dose and duration of an established treatment. Using standard prophylaxis doses in people receiving advanced respiratory support is a minor treatment adjustment that should be feasible to implement.

Rationale

We recommend treatment-dose low molecular weight heparins (LMWHs) for VTE prophylaxis in this population (adults and young people) because of fewer deaths and less likelihood of needing intensive care with this dose than with a standard prophylaxis dose, without a notable increase in major bleeding.

Treatment-dose LMWH for VTE prophylaxis is not recommended for people with COVID-19 receiving advanced respiratory support because it is likely to cause harm in this group. This recommendation lists the types of advanced respiratory support to clarify what this involves, and to reflect what was included in the evidence considered (high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation).

We recommend that people are likely to be in hospital for at least 3 days to monitor any changes in the severity of their COVID-19 symptoms. If symptoms become more severe, or the person needs invasive mechanical ventilation, the dose of LMWH for VTE prophylaxis should be reduced because of potential harms.

This recommendation has been classified as weak because the panel were presented with academic-in-confidence data from a multiplatform trial and noted that the interim results from the evidence base have not been peer-reviewed or adjudicated. Results were therefore interpreted with the appropriate caution.

Consensus recommendation

For young people and adults with COVID-19 who are having supplemental oxygen and a treatment dose of a low molecular weight heparin (LMWH), and now need high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation or palliative care:

- reduce the dose of the LMWH to a locally agreed intermediate or standard dose
- reassess VTE and bleeding risks daily.

In March 2021, the use of intermediate or treatment doses of a LMWH for VTE prophylaxis were off-label uses of parenteral anticoagulants. See NICE's information on prescribing medicines.

Evidence To Decision

Benefits and harms

See the evidence to decision section at the recommendation on treatment-dose VTE prophylaxis.

Rationale

We recommend against using a treatment-dose low molecular weight heparin for VTE prophylaxis in people needing advanced respiratory support because it did not prevent deaths or reduce duration of intensive care, but risk of bleeding was increased.

Consensus recommendation

For young people and adults who are already receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation and are on a standard prophylactic dose of a low molecular weight heparin (LMWH) for VTE prophylaxis:

- consider increasing anticoagulation to an intermediate dose
- reassess VTE and bleeding risks daily.

In March 2021, the use of an intermediate dose of a LMWH for VTE prophylaxis was an off-label use of parenteral anticoagulants. See NICE's information on prescribing medicines.

Evidence To Decision

Benefits and harms

See the evidence to decision section at the recommendation on treatment-dose VTE prophylaxis.

Rationale

This recommendation was adapted from the original NICE rapid guideline on reducing the risk of venous thromboembolism in people over 16 years with COVID-19 (NG186, published November 2020 but now withdrawn). That guideline considered intermediate doses in this population and, during its development, the panel noted the high incidence of VTE in people with COVID-19 who need advanced respiratory support. The panel, based on their experience, agreed that consideration should be given to increasing the standard prophylactic dose of parenteral anticoagulation (such as a low molecular weight heparin) to an intermediate dose to mitigate the increased risk of VTE while minimising the risk of bleeding associated with higher

doses. The panel therefore recommended increasing anticoagulation to an intermediate dose in this group.

Consensus recommendation

Do not base prophylactic dosing of heparin on levels of D-dimer.

Evidence To Decision

Benefits and harms

See the evidence to decision section at the recommendation on treatment-dose VTE prophylaxis.

Rationale

The panel were presented with academic-in-confidence data from 3 multicentre, randomised, open-label trials (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia [REMAP-CAP], and Accelerating COVID-19 Therapeutic Interventions and Vaccines [ACTIV-4a]) that evaluated whether empiric use of treatment-dose anticoagulation improves clinical outcomes in people in hospital with confirmed COVID-19. Based on the data presented, the panel recommended not to base prophylactic dosing of heparin on levels of D-dimer because the evidence showed that D-dimer levels do not influence peoples' response to treatment-dose anticoagulation.

Consensus recommendation

For young people and adults with COVID-19 who need supplemental oxygen and who progress onto high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, only offer continuing a treatment dose of a low molecular weight heparin as part of a nationally approved clinical trial.

Evidence To Decision

Benefits and harms

See the evidence to decision section at the recommendation on treatment-dose VTE prophylaxis.

Rationale

The evidence suggests that starting a treatment-dose low molecular weight heparin for VTE prophylaxis in people already receiving advanced respiratory support is not beneficial and may increase the risk of bleeding. However, we remain uncertain about whether continuing this dose in people who subsequently need advanced respiratory support is beneficial or harmful.

Consensus recommendation

For people at extremes of body weight or with impaired renal function, consider adjusting the dose of low molecular weight heparins in line with the summary of product characteristics and locally agreed protocols.

Rationale

This recommendation was adapted from the original NICE rapid guideline on reducing the risk of venous thromboembolism in over 16s with COVID-19 (NG186, published November 2020 and now withdrawn) that considered intermediate doses in this population. In its development, the panel indicated that dose adjustments may be needed for people at extremes of body weight and those with renal impairment. To ensure that everyone gets an appropriate dose, the panel included dose adjustment in their recommendation. They added that summary of product characteristics and local protocols should be used to guide decisions on dose adjustment.

Consensus recommendation

For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).

In March 2021, LMWHs, fondaparinux sodium and UFH were off label for people under 18 years. See NICE's information on prescribing medicines.

Consensus recommendation

Start VTE prophylaxis as soon as possible and within 14 hours of admission.

Consensus recommendation

For people who are already having anticoagulation treatment for another condition when admitted to hospital:

- continue their current treatment dose of anticoagulant unless contraindicated by a change in clinical circumstances
- consider switching to a low molecular weight heparin (LMWH) if their current anticoagulant is not an LMWH and their clinical condition is deteriorating.

Consensus recommendation

If a person's clinical condition changes, assess the risk of VTE, reassess bleeding risk and review VTE prophylaxis.

Consensus recommendation

Organisations should collect and regularly review information on bleeding and other adverse events in people with COVID-19 having treatment or intermediate doses of pharmacological VTE prophylaxis.

Consensus recommendation

Ensure that people who will be completing pharmacological VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.

8.3.2 - In hospital-led acute care in the community

Consensus recommendation

For people with COVID-19 managed in hospital-led acute care in the community settings:

- assess the risks of VTE and bleeding
- consider pharmacological prophylaxis if the risk of VTE outweighs the risk of bleeding.

Rationale

There was no evidence to inform recommendations on reducing the risk of VTE in people with COVID-19 pneumonia managed in hospital-led acute care in the community settings with input from hospital clinicians, such as 'hospital at home' services or COVID-19 'virtual wards'. People whose condition is managed in these settings have an increased risk of VTE that is similar to that of people having management in hospital. The panel therefore included a recommendation to consider pharmacological VTE prophylaxis for these people to ensure that they have the same care as those admitted to hospital.

The panel also made a recommendation for research on extending pharmacological VTE prophylaxis after discharge in people who have had treatment for COVID-19 pneumonia.

8.3.3 - People with COVID-19 and additional risk factors

Consensus recommendation

For women with COVID-19 who are pregnant or have given birth within the past 6 weeks, follow the advice on VTE prevention in the Royal College of Obstetricians and Gynaecologists guidance on coronavirus (COVID-19) in pregnancy.

Rationale

The panel noted the lack of evidence on pharmacological VTE prophylaxis for people with COVID-19 and additional risk factors. They agreed that VTE risk in women with COVID-19 who are pregnant or have given birth in the past 6 weeks should be managed in line with advice on COVID-19 in pregnancy published by the Royal College of Obstetricians and Gynaecologists.

There was no evidence on pharmacological VTE prophylaxis for specific groups with additional risk factors for VTE, including people who are having treatment with sex hormones, have or have previously had cancer, are having renal replacement therapy or extracorporeal membrane oxygenation, have a clotting condition or history of VTE, or have obesity (body mass index 30 kg/m^2 or higher). The panel made a recommendation for research on standard-dose compared with intermediate-dose pharmacological VTE prophylaxis in people with COVID-19 who have additional risk factors for VTE.

Consensus recommendation

For children with COVID-19 admitted into hospital, follow the advice on COVID-19 guidance for management of children admitted to hospital in the Royal College of Paediatrics and Child Health guidance.

8.3.4 - Information and support

Consensus recommendation

Give people with COVID-19, and their families or carers if appropriate, information about the benefits and risks of VTE prophylaxis.

See the recommendations on giving information and planning for discharge in the NICE guideline on venous thromboembolism in over 16s, including information on alternatives to heparin for people who have concerns about using animal products.

Consensus recommendation

Offer people the opportunity to take part in ongoing clinical trials on COVID-19.

8.4 - Suspected or confirmed co-infection

Consensus recommendation

Do not offer an antibiotic for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.

Antibiotics do not work on viruses, and inappropriate antibiotic use may reduce availability. Also, inappropriate use may lead to Clostridioides difficile infection and antimicrobial resistance, particularly with broad-spectrum antibiotics.

Info Box

Evidence as of March 2021 suggests that bacterial co-infection occurs in less than about 8% of people with COVID-19, and could be as low as 0.1% in people in hospital with COVID-19. Viral and fungal co-infections occur at lower rates than bacterial co-infections.

Secondary infection or co-infection (bacterial, viral or fungal) is more likely the longer a person is in hospital and the more they are immunosuppressed (for example, because of certain types of treatment).

The type and number of secondary infections or co-infections will vary depending on the season and any restrictions in place (for example, lockdowns).

8.4.1 - Identifying secondary bacterial pneumonia

Consensus recommendation

In hospitals or other acute delivery settings (for example, virtual wards), to help identify non-SARS-CoV-2 viral, fungal or bacterial pneumonia, and to inform decision making about using antibiotics, consider the following tests:

- a full blood count
- chest imaging (X-ray, CT or ultrasound)
- respiratory and blood samples (for example, sputum or a tracheal aspirate sample, blood culture; see Public Health England's COVID-19: guidance for sampling and for diagnostic laboratories)
- urine samples for legionella and pneumococcal antigen testing
- throat samples for respiratory viral (and atypical pathogen) polymerase chain reaction testing.

Info Box

High C-reactive protein levels do not necessarily indicate whether pneumonia is due to bacteria or SARS-COV-2.

Low C-reactive protein level indicates that a secondary bacterial infection is less likely.

Consensus recommendation

Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.

Info Box

There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about antibiotics. Centres already using procalcitonin tests are encouraged to participate in research and data collection.

Procalcitonin tests could be useful in identifying whether there is a bacterial infection. However, it is not clear whether they add benefit beyond what is suggested in the recommendation on tests to help differentiate between viral and bacterial pneumonia to guide decisions about antibiotics. The most appropriate threshold for procalcitonin is also uncertain.

8.4.2 - Antibiotic treatment in the community

Consensus recommendation

Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.

Consensus recommendation

If a person has suspected or confirmed secondary bacterial pneumonia, start antibiotic treatment as soon as possible. Take into account any different methods needed to deliver medicines during the COVID-19 pandemic (see the recommendation on minimising face-to-face contact in communication and shared decision making).

Info Box

For antibiotic choices to treat community-acquired pneumonia caused by a secondary bacterial infection, see the recommendations on choice of antibiotic in the NICE antimicrobial prescribing guideline on community-acquired pneumonia.

Consensus recommendation

Advise people to seek medical help without delay if their symptoms do not improve as expected, or worsen rapidly or significantly, whether they are taking an antibiotic or not.

Consensus recommendation

On reassessment, reconsider whether the person has signs and symptoms of more severe illness (see the recommendation on signs and symptoms to help identify people with COVID-19 with the most severe illness) and whether to refer them to hospital, other acute community support services or palliative care services.

8.4.3 - Starting antibiotics in hospital

Consensus recommendation

Start empirical antibiotics if there is clinical suspicion of a secondary bacterial infection in people with COVID-19. When a decision to start antibiotics has been made:

- start empirical antibiotic treatment as soon as possible after establishing a diagnosis of secondary bacterial pneumonia, and certainly within 4 hours
- start treatment within 1 hour if the person has suspected sepsis and meets any of the high-risk criteria for this outlined in the NICE guideline on sepsis.

8.4.4 - Choice of antibiotics in hospital

Info Box

To guide decision making about antibiotics for secondary bacterial pneumonia in people with COVID-19, see the NICE guideline on pneumonia (hospital acquired): antimicrobial prescribing.

Consensus recommendation

When choosing antibiotics, take account of:

- local antimicrobial resistance data and
- other factors such as their availability.

Consensus recommendation

Give oral antibiotics if the person can take oral medicines and their condition is not severe enough to need intravenous antibiotics.

Consensus recommendation

Consider seeking specialist advice on antibiotic treatment for people who:

- are immunocompromised
- have a history of infection with resistant organisms
- have a history of repeated infective exacerbations of lung disease
- are pregnant
- are receiving advanced respiratory support or organ support.

Consensus recommendation

Seek specialist advice if:

- there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic or
- there is clinical or microbiological evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.

8.4.5 - Reviewing antibiotic treatment in hospital

Consensus recommendation

Review all antibiotics at 24 to 48 hours, or as soon as test results are available. If appropriate, switch to a narrower spectrum antibiotic, based on microbiological results.

For intravenous antibiotics, review within 48 hours and think about switching to oral antibiotics (in line with the NICE guideline on pneumonia (hospital-acquired): antimicrobial prescribing)

Give antibiotics for 5 days, and then stop them unless there is a clear indication to continue (see the recommendation on when to seek specialist advice).

Consensus recommendation

Reassess people if their symptoms do not improve as expected, or worsen rapidly or significantly.

9 - Discharge, follow up and rehabilitation

Info Box

NICE is reviewing evidence on follow up, discharge and rehabilitation. More recommendations will be added in a future version of the guideline.

Info Box

For follow up and rehabilitation for people who have either ongoing symptomatic COVID-19 or post-COVID-19 syndrome, see the NICE guideline on the long-term effects of COVID-19.

10 - Palliative care

10.1 - Principles of care

Info Box

For people who are nearing the end of their life, see:

- The NICE guideline on care of dying adults in the last days of life: this includes recommendations on recognising when a person may be in the last days of life, communication and shared decision making.
- The NICE guideline on end of life care for adults: service delivery: this includes recommendations for service providers on systems to help identify adults who may be at the end of their life, providing information and advanced care planning.
- The NICE guideline on care and support of people growing older with learning disabilities: this includes recommendations on accessing end-of-life care services, person-centred care, and involving families and support networks in end-of-life care planning.

10.2 - Medicines for end-of-life care

Consensus recommendation

Consider an opioid and benzodiazepine combination. See the table in practical info for managing breathlessness in the last days and hours of life for people 18 years and over with COVID-19 who:

- are at the end of life and
- have moderate to severe breathlessness and
- are distressed.

Consider concomitant use of an antiemetic and a regular stimulant laxative. Seek specialist advice for children and young people under 18 years.

Practical Info

Treatments in the last days and hours of life for managing breathlessness for people 18 years and over

Treatment	**Dosage** Higher doses may be needed for symptom relief in people with COVID-19. Lower doses may be needed because of the person's size or frailty The doses are based on the BNF and the Palliative care formulary
Opioid	Morphine sulfate 10 mg over 24 hours via a syringe driver, increasing stepwise to morphine sulfate 30 mg over 24 hours as required
Benzodiazepine if required in addition to opioid	Midazolam 10 mg over 24 hours via the syringe driver, increasing stepwise to midazolam 60 mg over 24 hours as required
Add parenteral morphine or midazolam if required	Morphine sulfate 2.5 mg to 5 mg subcutaneously as required Midazolam 2.5 mg subcutaneously as required (See the BNF for more details on dosages)
Special considerations	

	Consider concomitant use of an antiemetic and a regular stimulant laxative Continue with non-pharmacological strategies for managing breathlessness when starting an opioid Sedation and opioid use should not be withheld because of a fear of causing respiratory depression

Info Box

For more recommendations on pharmacological interventions and anticipatory prescribing, see the NICE guideline on care of dying adults in the last days of life and prescribing information in the BNF's prescribing in palliative care.

Consensus recommendation

For people with COVID-19 who are out of hospital, when prescribing and supplying anticipatory medicines at the end of life:

- Take into account potential waste, medicines shortages and lack of administration equipment by prescribing smaller quantities or by prescribing a different medicine, formulation or route of administration when appropriate.
- If there are fewer health and care staff, you may need to prescribe subcutaneous, rectal or long-acting formulations. Family members could be considered as an alternative option to administer medications if they so wish and have been provided with appropriate training.

Consensus recommendation

For people with COVID-19 who are out of hospital, consider different routes for administering medicines if the person is unable to take or tolerate oral medicines, such as sublingual or rectal routes, subcutaneous injections or continual subcutaneous infusions.

11 - Research recommendations

What is the effectiveness and safety of standard-dose compared with intermediate-dose pharmacological venous thromboembolism (VTE) prophylaxis for people with COVID-19, with or without additional risk factors for VTE?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over being treated for COVID-19 pneumonia in hospital or the community who have:
- *no additional risk factors for VTE*
- *additional risk factors for VTE*

I: intermediate dose:
- *low molecular weight heparins (LMWH)*
- *unfractionated heparin (UFH)*
- *fondaparinux sodium*
- *direct-acting anticoagulant*
- *vitamin K antagonists*

C: Standard-dose:
- *LMWH*
- *UFH*
- *fondaparinux sodium*
- *direct-acting anticoagulants*
- *vitamin K antagonists*
- *antiplatelets*

O:
- *incidence of VTE*
- *mortality (all-cause, inpatient, COVID-19 related)*
- *admission to critical care (including use of advanced organ support)*
- *serious adverse events such as major bleeding or admission to hospital*

What is the effectiveness and safety of extended pharmacological venous thromboembolism (VTE) prophylaxis for people who have been discharged after treatment for COVID-19?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over who have been discharged after treatment for COVID-19 pneumonia

I: extended (2 to 6 weeks) pharmacological VTE prophylaxis with standard-dose:
- *low molecular weight heparins*
- *unfractionated heparins*
- *fondaparinux sodium*
- *direct-acting anticoagulant*
- *vitamin K antagonists*

C: No extended pharmacological VTE prophylaxis

O:
- *incidence of VTE*
- *mortality (all-cause, inpatient, COVID-19 related)*
- *serious adverse events such as major bleeding or admission to hospital*

What is the effectiveness and safety of a treatment dose with a low molecular weight heparin (LMWHs) compared with a standard prophylactic dose for venous thromboembolism (VTE) prophylaxis in young people under 18 years with COVID-19?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 18 years and under who have COVID-19 pneumonia

I: treatment-dose LMWH

C: standard prophylaxis with LMWH

O:
- *incidence of VTE*
- *mortality (all-cause, inpatient, COVID-19 related)*
- *admission to critical care (including use of advanced organ support)*
- *serious adverse events such as major bleeding or admission to hospital*

Does early review and referral to specialist palliative care services improve outcomes for adults with COVID-19 thought to be approaching the end of their life?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients with a confirmed diagnosis of COVID-19 in hospital or community approaching the last days of life

I: early referral to specialist palliative care services (for example, in the last days of life)

C: late referral (for example, within the final day of life) or no referral

O:
- *quality of life*
- *changes to clinical care*
- *patient or carer satisfaction (feeling supported)*
- *identification and/or achievement of patient wishes such as preferred place of death*

12 - Equality considerations

12.1 - Equalities impact assessment during scoping - draft scope

Is the proposed primary focus of the guideline a population with a specific communication or engagement need, related to disability, age or other equality consideration?

No

Have any potential equality issues been identified during the check for an update or during development of the draft scope and, if so, what are they?

Exacerbating inequalities
There is potential for recommendations to exacerbate inequalities, if individual circumstances are not acknowledged. Protected characteristics and assumptions about individual circumstances need to be considered:

Sex
Public Health England's report on disparities in the risk and outcomes of COVID-19 indicated that diagnosis rates of COVID-19 are higher in women under 40 years and men over 60 years. There are higher death rates from COVID-19 in men (nearly 60%) than women, and men make up a higher proportion of intensive care unit admissions (70% of admissions). This could mean that people in these groups may be at higher risk of poorer outcomes.

Age
Public Health England's report on disparities in the risk and outcomes of COVID-19 highlighted that both diagnosis of COVID-19 and mortality are more likely as age increases (people 80 years or over are 70 times more likely to die than those under 40 years). Older people are more likely to be frail, and have comorbidities and underlying health conditions. These factors mean that people in these groups are at higher risk of poorer outcomes.

Older people may find it more difficult to access many services, including using digital technology to access remote consultations. This may increase the risk of them not being able to access appropriate services and care. Older people may need support from carers (both paid and unpaid) for both remote and face-to-face consultations, again this may increase the risk of them not being able to access the appropriate care. For some medications, different doses may be needed for older people. Whenever medication dosing is referred to, this should be used with information in the BNF.

Ethnicity
Public Health England's report on disparities in the risk and outcomes of COVID-19 identified that people from black, Asian and minority ethnic groups are at higher risk of getting COVID-19, more likely to have severe symptoms because of the infection and at higher risk of poorer outcomes. The highest age-standardised diagnosis rates of COVID-19 per 100,000 population are in people from black ethnic groups.

Survival analysis in people with confirmed COVID-19 (after accounting for sex, age, deprivation and region) indicated that people with a Bangladeshi family background have twice the risk of death compared with white British people. It also found that people with a Chinese, Indian, Pakistani, other Asian, Caribbean or other black family background had 10% to 50% higher risk of death compared with white British people. Emerging evidence suggests that excess mortality from COVID-19 is higher in black, Asian and minority ethnic groups. Individuals from black African or black Caribbean family backgrounds may have the highest risk.

Poorer outcomes in black, Asian and minority ethnic groups have been linked to several potential factors. These include higher rates of comorbidities that have been associated with COVID-19 mortality (such as cardiovascular disease, obesity and diabetes) in some black, Asian and minority ethnic populations. They also include a person's occupation (for example, over-representation in key worker roles in health and social care), and pre-existing socioeconomic factors such as housing conditions that could affect a person's ability to maintain infection control and prevention measures.

People from black, Asian and minority ethnic groups may feel marginalised, have experienced racism or have had previous experiences with a culturally insensitive health service that could create barriers to engagement with those services. This could mean that people in these groups may be at higher risk of poorer outcomes.

Disability
The scope of the guideline includes consideration of communication and shared decision making. For effective communication and shared decision making, specific consideration may need to be given to:

- people with a learning disability (including autism)
- people with a physical impairment (for example, a visual impairment or disability affecting communication)
- people with cognitive impairment (for example, mild or fluctuating dementia)
- people with a mental health issue.

The section on how to use this guideline states that it should be used alongside usual professional guidelines, standards and laws (including equalities, safeguarding, communication and mental capacity).

Socioeconomic factors
People who live in more socially deprived areas may be more likely to live in overcrowded housing and have occupations that might make them more at risk of being exposed to COVID-19.

Some people may not have access to the equipment needed to take part in digital consultations. Depending on where a person lives, they may not have access to home delivery services (for example, if they live in a rural area).

Gender reassignment
None identified.

Pregnancy and maternity
Not all medications are appropriate for people who are pregnant or breastfeeding. Whenever medication dosing is referred to, this should be used with information in the BNF.

Religion or belief
Not all medications are acceptable to people of certain religions because of the products being animal derived. Whenever medication dosing is referred to, this should be used with information in the BNF.

Sexual orientation
None identified.

Other definable characteristics
Examples are:

- refugees
- asylum seekers
- migrant workers
- people who are homeless.

For people whose first language is not English, there may be communication difficulties, especially for effective shared decision making and minimising risk of infection.

It is recognised that people who are homeless, refugees, asylum seekers and migrant workers may be living in deprived areas (including overcrowded accommodation), which may mean they are more likely to be exposed to COVID-19.

People from these groups may also be less likely to be able to access services.

What is the preliminary view on the extent to which these potential equality issues need addressing by the panel?
The guideline will need to address the potential equality issues by looking at data from studies either focused on the groups identified or looking at subgroup data. No groups will be excluded from the population.

The scope of this guideline does not include specific review of situations in which people lack mental capacity to make their own decisions about healthcare at that point in time. NICE has produced guidance on decision making and mental capacity to help health

and social care practitioners:

- support people to make their own decisions as far as possible
- assess people's capacity to make specific health and social care decisions
- make specific best-interest decisions when people lack capacity, and maximise the person's involvement in those decisions.

12.2 - Equalities impact assessment during scoping - final scope

Have any potential equality issues been identified during review of the draft scope, and, if so, what are they?

Yes. In addition to those outlined in section 12.1 on the equalities impact assessment on the draft scope, the following issues were identified. No changes were made to the scope on the basis of these issues.

Age
Some older people or people who are very frail may receive 'over-treatment' and this could remove them from familiar carers and surroundings.

Disability
A person's mental health can influence their health-seeking behaviours and how they manage their physical health conditions.

Gender reassignment
There may be an interplay between sex hormones in trans people. It is unknown whether sex differences in COVID-19 outcomes are due to genetics, hormonal issues or social factors.

Pregnancy and maternity
There has been an increased rate of maternal death since the start of the COVID-19 pandemic. It has also been reported that COVID-19 infection during pregnancy increases the risk of preterm birth, which is in turn linked to increased elective delivery and ventilation.

Race
There have been reports of vaccine hesitancy in people from black, Asian and minority ethnic groups. Given people in these groups are at risk of worse outcomes with COVID-19, vaccine hesitancy may further increase inequalities in outcomes.

Religion or belief
No further issues identified.

Sex
During the COVID-19 pandemic, women have had barriers to accessing in vitro fertilisation services, contraception and abortion care. Also, there have been increasing inequalities because of the lack of information being provided about alternative options.

Sexual orientation
Some people may feel marginalised because of their sexual orientation, so may have barriers to care because of their differing family or community structures.

Socio-economic factors
No further issues identified.

Were any changes to the scope made as a result of consultation to highlight potential equality issues?

No.

Have any of the changes made led to a change in the primary focus of the guideline which would require consideration of a specific communication or engagement need, related to disability, age, or other equality consideration?
If so, what is it and what action might be taken by NICE or the developer to meet this need? (For example, adjustments to panel processes, additional forms of consultation)

No. The equalities issues identified have not led to a change in the primary focus of the guideline.

12.3 - Equalities impact assessment during guideline development

Have the potential equality issues identified during the scoping process been addressed by the panel, and, if so, how?

In the scoping process, a range of potential equality issues were identified. These have been addressed as follows:

Age
At scoping it was highlighted that older people with COVID-19 are at higher risk of poorer outcomes.

It was also noted that older people may have difficulties in accessing services, including using digital technology to access remote consultations, and that they may need carer support to access remote and face-to-face consultations. It is recommended in the communication and shared decision making section that, in the community, the risks and benefits of face-to-face and remote care should be considered for each person. This should allow issues such as an individual's ability to access remote care to be taken into account.

The panel also noted that some older people or people who are very frail could potentially receive 'over-treatment', which could remove them from familiar carers and surroundings. In the section on care planning in the community , it is recommended to discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (such as virtual wards, hospital at home teams). This should allow individualised decisions to be made that can take account of personal preferences to be cared for with familiar people in their usual surroundings.

It is noted that NEWS2 should not be used in children. This has been noted in the section on identifying severe COVID-19 in the community. The panel recommended the use of locally approved paediatric early warning scores in children.

Sex
It has been reported that there are higher death rates from COVID-19 in men than women and that men comprise a higher proportion of intensive care unit admissions. While this guideline does not make specific recommendations based on sex, the guideline allows for consideration of individual characteristics and risk factors in planning care. For example, in the section on assessment in hospital the guideline recommends that, on admission to hospital, a holistic assessment should be completed.

It was also noted that, during the COVID-19 pandemic, women have experienced barriers to accessing in vitro fertilisation services, contraception and abortion care. The provision of these services are outside the scope of this guideline.

Gender reassignment
It was noted during scoping that there may be an interplay between sex hormones in trans people and it is not known if sex differences in COVID-19 outcomes are due to genetic, hormonal or social factors. The panel did not make specific recommendations based on gender reassignment.

Sexual orientation
Some people may feel marginalised due to their sexual orientation and therefore may have barriers to care due to their differing family or community structures. No recommendations were made specific to sexual orientation.

Ethnicity
Emerging evidence suggests that excess mortality due to COVID-19 is higher in black, Asian and minority ethnic groups. The guideline does not make specific recommendations according to ethnicity. However, alongside the recommendation relating to the use of pulse oximetry it is noted that overestimation has been reported in people with dark skin.

There have been reports of vaccine hesitancy in people of from black, Asian and minority ethnic groups. Given that these groups are at risk of worse outcomes with COVID-19, vaccine hesitancy may further increase inequalities in outcomes. Vaccine uptake is outside the scope of this guideline.

Disability
Regarding communication and shared decision making, specific consideration may need to be given to people with a learning disability, people with physical impairments, people with cognitive impairment, and people with mental health issues. The section on communication and shared decision making recommends communicating with people with COVID-19, their families and carers to alleviate any fear or anxiety. This recommendation also advises to provide people with information in a way that they can use and understand, and to follow national guidance on communication, providing information (including in different formats and languages) and shared decision making. The guideline also recommends involving families and carers where appropriate to support discussions relating to care and shared decision making.

We state that this guideline should be used alongside usual professional guidelines, standards and laws (including equalities, safeguarding, communication and mental capacity).

It has also been noted that a person's mental health can influence their health-seeking behaviours and how they manage their physical health conditions. As above, the guideline recommends involving families and carers in discussions relating to care where appropriate.

Socioeconomic factors
People who live in more socially deprived areas may be more likely to live in conditions and have occupations that may increase the risk of being exposed to COVID-19. No recommendations were made based on levels of social deprivation, living conditions or occupation.

Some people may not have access to equipment needed for remote consultations. It is recommended in the section on communication and shared decision making that, in the community, the risks and benefits of face-to-face and remote care should be considered for each person. This should allow issues such as an individual's ability to access remote care to be considered.

Depending on where a person lives (for example in rural areas), they may have difficulty accessing home delivery services. The guideline recommends optimising remote care where appropriate, such as pharmacy deliveries, postal services, NHS volunteers and introducing drive-through pick up points for medicines. Providing a range of potential options may support access in different geographical areas. The guideline also covers use of anticipatory medicines at end of life. It is noted that, if there are fewer health and care staff, differing formulations may be prescribed and family members may be able to support administration of medications if they wish and have been provided with appropriate training.

Pregnancy and maternity
At scoping, increased rates of maternal death and an increased risk of preterm birth during the COVID-19 pandemic were highlighted. No recommendations were made specifically on pregnancy.

It is noted that NEWS2 should not be used when pregnant. This has been noted in the relevant recommendation under identifying severe COVID-19.

As not all medications are appropriate for people who are pregnant or breastfeeding, whenever medication dosing is referred to, this should be used with information in the BNF.

Religion or belief
Not all medications are acceptable to people of certain religions due to the products being animal derived.

Other definable characteristics
For people whose first language is not English, there may be communication difficulties, especially relating to shared decision making and minimising risk of infection. The section on communication and shared decision making recommends communicating with people with COVID-19, their families and carers to alleviate any fear or anxiety. This recommendation also advises to provide people with information in a way that they can use and understand, and to follow national guidance on communication, providing information (including in different formats and languages) and shared decision making.

People who are homeless, refugees, asylum seekers and migrant workers may be living in deprived areas (including overcrowded accommodation) and so may be more likely to be exposed to COVID-19 and may also experience difficulties in accessing services. No recommendations were made specific to people who are homeless, refugees, asylum seekers and migrant workers.

Have any other potential equality issues (in addition to those identified during the scoping process) been identified, and, if so, how has the panel addressed them?

Disability
The panel identified that children and young people under 18 years, or people with learning disabilities, may need additional consideration around capacity and decision making because of the isolated nature of treatment. The panel agreed that a recommendation should be added stating that, when making decisions about care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, the NICE guideline on decision making and mental capacity should be referred to. It was also recommended to ensure that discussions on significant care interventions involve family and carers, as appropriate, and local experts or advocates. The panel noted that infection prevention and control, including self-isolation, may be more challenging for some groups of people, including those with dementia or learning disabilities. A recommendation has been added to advise that, for carers of people with COVID-19 who should isolate but are unable to, relevant support and resources should be signposted to (for example, Alzheimer's society has information on staying safe from coronavirus and reducing the risk of infection).

Ethnicity
It was noted that pulse oximeters can be less accurate in people with dark skin, especially at the borderline range of 90% to 92%. Information about this has been added to the recommendation to alert healthcare practitioners to this.

Religion or belief
The panel identified that, for people who do not use animal products, honey would not be appropriate for cough. No change was made to this recommendation.

Do the preliminary recommendations make it more difficult in practice for a specific group to access services compared with other groups? If so, what are the barriers to, or difficulties with, access for the specific group?
No. None identified.

Is there potential for the preliminary recommendations to have an adverse impact on people with disabilities because of something that is a consequence of the disability?
No.

Are there any recommendations or explanations that the panel could make to remove or alleviate barriers to, or difficulties with, access to services identified, or otherwise fulfil NICE's obligation to advance equality?
Not applicable.

13 - Methods and processes

Development
This guideline was developed using the methods and process in our interim process and methods for guidelines developed in response to health and social care emergencies.

Structure
The guideline structure follows the main themes and overarching questions set out in the scope. Existing NICE COVID-19 rapid guidelines and international guidelines were reviewed to inform further subsections. The structure was designed to allow flexibility to refine, remove or add sections in future iterations within a living approach. The guideline includes disease severity definitions that are in line with WHO definitions and approved by the NICE expert advisory panel. These are used to inform severity-specific recommendations where applicable.

Mapping of existing content
We compiled a list of all recommendations in the COVID-19 rapid guidelines that were relevant to the scope of this guideline. These recommendations were added to the appropriate section in the draft structure of the new guideline. After NICE technical and clinical quality assurance of this mapping work, the recommendations were transferred to the relevant part of the structure on the publishing platform MAGICapp.

After the initial mapping, the structure was refined. The NICE expert advisory panel identified gaps in coverage and any recommendations that should be changed. The panel were also asked whether any of the recommendations from the rapid guidelines could be removed, if no longer relevant, due to new emergent evidence or due to recommendations being context specific and therefore bound to a particular time in the pandemic. Any changes to recommendation content were based on the consensus view of the expert advisory panel.

Therapeutics for COVID-19

Reviewing the evidence
As there is a need for prompt guidance on therapeutics for managing COVID-19, NICE is collaborating with other guideline development teams to produce evidence reviews. NICE has reused data from the National Australian COVID-19 clinical evidence taskforce for some recommendations. As the time of publication (March 2021), no specific literature searches were carried out for the therapeutics section of the guideline.

The use of evidence provided by the National Australian COVID-19 clinical evidence taskforce is achieved through the sharing of RevMan files, which the NICE team use to populate the evidence summary section and GRADE profiles for a review.

Because therapeutics for managing COVID-19 is an emerging area, data provided by other guideline developers may be supplemented with additional trial results that the NICE COVID-19 team have access to. Relevant trials are identified through NICE's Rapid C-19 initiative. On occasion, NICE may be given access to trial data before publication in a peer review journal (academic in confidence data). Data extraction and risk of bias will be carried out in line with the interim process and methods for guidelines developed in response to health and social care emergencies. Where academic-in-confidence data is used, this will be described in the evidence to decisions summary for that section of the guideline. As this is a living guideline, trial results from academic in confidence data will be revisited when published and reconsidered by the expert advisory panel.

All evidence reviews are quality assured before they are presented to the expert advisory panel. For reviews generated by the National Australian COVID-19 clinical evidence taskforce, the expert advisory panel will assess the relevance and applicability to the UK context, which will feed into the considerations for developing the recommendations.

Expert advisory panel members and declarations of interest
Declarations of interest (DOI) were recorded according to the 2019 NICE conflicts of interest policy. For a list of panel members and corresponding DOI registry for this guideline see the NICE guideline page on managing COVID-19.

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