1.1.4 Before deciding to refer, consider repeating visual field assessment and IOP measurement on another occasion to confirm a visual field defect or IOP of 24 mmHg or more, unless clinical circumstances indicate urgent or emergency referral is needed. [2017]

1.1.5 Refer for further investigation and diagnosis of COAG and related conditions, after considering repeat measures as in recommendation 1.1.4, if:

- there is optic nerve head damage on stereoscopic slit lamp biomicroscopy or
- there is a visual field defect consistent with glaucoma or
- IOP is 24 mmHg or more using Goldmann-type applanation tonometry. [2017]

1.1.6 Provide results of all examinations and tests with the referral. [2017]

1.1.7 Advise people with IOP below 24 mmHg to continue regular visits to their primary eye care professional. [2017]

The following recommendations are for people planning and providing eye care services before referral.

1.1.8 People planning and providing eye care services should use a service model that includes Goldmann-type applanation tonometry before referral for diagnosis of COAG and related conditions. [2017]

1.1.9 People planning eye care services should consider commissioning referral filtering services (for example, repeat measures, enhanced case-finding, or referral refinement) for COAG and related conditions. [2017]

1.2 Diagnosis

1.2.1 To diagnose COAG and related conditions, offer all of the following tests:

- visual field assessment using standard automated perimetry (central thresholding test), repeated if necessary to establish severity at diagnosis
- optic nerve assessment and fundus examination using stereoscopic slit lamp biomicroscopy, with pupil dilatation

- IOP measurement using Goldmann applanation tonometry (slit lamp mounted)
- peripheral anterior chamber configuration and depth assessments using gonioscopy
- central corneal thickness (CCT) measurement. [2017]

1.2.2 Adopt professional or Department of Health and Social Care guidance to reduce the risk of transmitting infective agents via contact tonometry or gonioscopy.

See the Royal College of Ophthalmologists' ophthalmic services guidance and the Department of Health and Social Care's guidance on minimising transmission risk of CJD and vCJD in healthcare settings. [2009]

1.2.3 Use the van Herick peripheral anterior chamber depth assessment if clinical circumstances rule out gonioscopy (for example, when people with physical or learning disabilities are unable to participate in the examination). [2009]

1.2.4 Obtain an optic nerve head image at diagnosis for baseline documentation (for example, a stereoscopic optic nerve head image or OCT). [2009, amended 2017]

1.2.5 After referral, consider an early assessment appointment if there is clinical concern based on the information provided. [2017]

1.2.6 At the time of diagnosis of ocular hypertension (OHT), assess the risk of future visual impairment, taking into account risk factors such as:

- level of IOP
- CCT
- family history
- life expectancy. [2017]

1.3 Standard practice for all assessments

1.3.1 Ensure that all of the following are available at each clinical episode to all healthcare professionals involved in a person's care:

- records of all previous tests and images relevant to COAG and OHT assessment

- records of past medical history that could affect medicine choice
- current systemic and topical medication
- glaucoma medication record
- drug allergies and intolerances. [2009]

1.3.2 Use alternative methods of assessment if clinical circumstances rule out standard methods (for example, when people with physical or learning disabilities are unable to participate in the examination). [2009]

1.3.3 Ensure that all machines and measurement instruments are calibrated regularly according to the manufacturers' instructions. [2009]

1.4 Treatment

1.4.1 Take into account any cognitive and physical impairments when making decisions about management and treatment. [2017]

1.4.2 Check that there are no relevant comorbidities or potential drug interactions before offering pharmacological treatment. [2009]

Treatment for people with OHT

1.4.3 Do not offer treatment to people with OHT who are not at risk of visual impairment within their lifetime. Advise people to continue regular visits to their primary eye care professional, at clinically appropriate intervals. [2017]

Initial treatment for people with OHT

1.4.4 Offer 360° selective laser trabeculoplasty (SLT) to people with newly diagnosed OHT with IOP of 24 mmHg or more (excluding cases associated with pigment dispersion syndrome) if they are at risk of visual impairment within their lifetime (see the recommendation on taking account of risk factors in the section on diagnosis). To help inform their decision, tell people:

- that having 360° SLT can delay the need for eye drops and can reduce but does not remove the chance they will be needed at all

- how long it may take for their IOP to improve after the procedure
- about 360° SLT-specific side effects and complications and how long they are likely to last
- that a second 360° SLT procedure may be needed at a later date. [2022]

1.4.5 Consider a second 360° SLT for people with OHT if the effect of an initial successful SLT has subsequently reduced over time. [2022]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on selective laser trabeculoplasty for people with ocular hypertension or chronic open angle glaucoma.

Full details of the evidence and the committee's discussion are in evidence review A: selective laser trabeculoplasty in ocular hypertension or chronic open-angle glaucoma adult patients.

1.4.6 Offer a generic prostaglandin analogue (PGA) to people with OHT with IOP of 24 mmHg or more if they are at risk of visual impairment within their lifetime (see the recommendation on taking account of risk factors in the section on diagnosis) and:

- they choose not to have 360° SLT or
- 360° SLT is not suitable (for example, because they have pigment dispersion syndrome) or
- they are waiting for 360° SLT and need an interim treatment or
- they have had 360° SLT but need additional treatment to reduce their IOP sufficiently to prevent the risk of visual impairment.

  Demonstrate correct eye drop installation technique and observe the person using the correct technique when eye drops are first prescribed. [2022]

See the recommendations on when to reassess for advice on when the next appointment should take place to assess the impact of any new treatments started.

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on generic PGAs for people with OHT or COAG.

Full details of the evidence and the committee's discussion are in evidence review A: selective laser trabeculoplasty in ocular hypertension or chronic open-angle glaucoma adult patients.

Ongoing treatment for people with OHT

1.4.7 Offer another pharmacological treatment to people with an IOP of 24 mmHg or more who cannot tolerate their current treatment. The first choice should be an alternative generic PGA, and if this is not tolerated, offer a beta-blocker. If neither of these options is tolerated, offer a non-generic PGA, carbonic anhydrase inhibitor, sympathomimetic, miotic or a combination of treatments. [2017, amended 2022]

1.4.8 Offer a medicine from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to people with an IOP of 24 mmHg or more whose current treatment is not reducing IOP sufficiently to prevent the risk of progression to sight loss. Topical medicines from different therapeutic classes may be needed at the same time to control IOP. [2009, amended 2017]

1.4.9 Refer people to a consultant ophthalmologist to discuss other options if their IOP cannot be reduced sufficiently with 360° SLT or pharmacological treatment or both to prevent the risk of progression to sight loss. [2009, amended 2022]

1.4.10 Offer preservative-free eye drops to people who have an allergy to preservatives or people with clinically significant and symptomatic ocular surface disease, but only if they are at high risk of conversion to COAG. [2009, amended 2017]

Treatment for people with suspected COAG

1.4.11 Do not offer treatment to people with suspected COAG and IOP less than 24 mmHg unless they are at risk of visual impairment within their lifetime. Advise people to continue regular visits to their primary eye care professional, at clinically appropriate intervals. [2017, amended 2022]

Stopping treatment for people with OHT or suspected COAG

1.4.12 Discuss the benefits and risks of stopping treatment with people with OHT or suspected COAG who have both:

- a low risk of developing visual impairment within their lifetime and
- an acceptable IOP.

If a person decides to stop treatment after this discussion, offer to assess their IOP in 1 month to 4 months with further reassessment if clinically indicated. [2009]

Treatment for people with COAG

In November 2021 the use of mitomycin-C (MMC) in recommendations 1.4.13 and 1.4.20 to 1.4.22 was off label. See NICE's information on prescribing medicines.

Treatment for people with advanced COAG

1.4.13 Offer people with advanced COAG, glaucoma surgery with pharmacological augmentation (MMC) as indicated. Give them information on the risks and benefits of surgery. [2009, amended 2022]

1.4.14 Offer people who present with advanced COAG and who are listed for glaucoma surgery, interim treatment with a generic PGA. [2009, amended 2022]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on selective laser trabeculoplasty for people with ocular hypertension or chronic open angle glaucoma.

Full details of the evidence and the committee's discussion are in evidence review A: selective laser trabeculoplasty in ocular hypertension or chronic open-angle glaucoma adult patients.

Initial treatment for people with COAG

1.4.15 Offer 360° SLT to people with newly diagnosed COAG (excluding cases associated with pigment dispersion syndrome). For people with advanced COAG see the section on treatment for people with advanced COAG and

recommendation 1.4.24. To help inform their decision, tell people:

- that having 360° SLT can delay the need for eye drops and can reduce but does not remove the chance they will be needed at all
- how long it may take for their IOP to improve after the procedure
- about 360° SLT-specific side effects and complications and how long they are likely to last
- that a second 360° SLT procedure may be needed at a later date. [2022]

1.4.16 Consider a second 360° SLT for people with COAG if the effect of an initial successful SLT has subsequently reduced over time. [2022]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on selective laser trabeculoplasty for people with ocular hypertension or chronic open angle glaucoma.

Full details of the evidence and the committee's discussion are in evidence review A: selective laser trabeculoplasty in ocular hypertension or chronic open-angle glaucoma adult patients.

1.4.17 Offer a generic PGA to people with COAG if:

- they choose not to have 360° SLT or
- 360° SLT is not suitable (for example because they have pigment dispersion syndrome) or
- they are waiting for an 360° SLT and need an interim treatment or
- they have previously had 360° SLT but need additional treatment to reduce their IOP sufficiently to prevent the risk of visual impairment.

  Demonstrate correct eye drop installation technique and observe the patient using the technique when eye drops are first prescribed. [2022]

See recommendations on when to reassess for advice on when the next appointment should take place to assess the impact of any new treatments started.

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on generic PGAs for people with OHT or COAG.

Full details of the evidence and the committee's discussion are in evidence review A: selective laser trabeculoplasty in ocular hypertension or chronic open-angle glaucoma adult patients.

Ongoing treatment for people with COAG

1.4.18 Encourage people to continue with the same pharmacological treatment unless:

- their IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss
- there is progression of optic nerve head damage
- there is progression of visual field defect
- they cannot tolerate the medicine. [2009]

1.4.19 Ask about adherence to treatment and check the eye drop instillation technique in people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss, despite pharmacological treatment with a generic PGA. [2009, amended 2022]

1.4.20 Offer 1 of the following to people with satisfactory adherence to treatment and eye drop instillation technique whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss:

- a medicine from another therapeutic class (a beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); topical medicines from different therapeutic classes may be needed at the same time to control IOP or
- 360° SLT or
- glaucoma surgery with pharmacological augmentation (MMC) as indicated. [2009, amended 2022]

1.4.21 Consider 360° SLT or glaucoma surgery with pharmacological augmentation (MMC) as indicated for people with COAG who are at risk of progressing to sight loss despite treatment with medicines from 2 therapeutic classes. Give

them information on the risks and benefits of surgery. [2009, amended 2022]

1.4.22 Consider 1 of the following for people with COAG who cannot tolerate a pharmacological treatment:

- a medicine from another therapeutic class (a beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or
- preservative-free eye drops if there is evidence that the person is allergic to the preservative or has clinically significant and symptomatic ocular surface disease.

  After treatment with medicines from 2 therapeutic classes, consider 360° SLT or glaucoma surgery with pharmacological augmentation (MMC) as indicated. [2009, amended 2022]

1.4.23 Offer 1 of the following to people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss after glaucoma surgery:

- pharmacological treatment; topical medicines from different therapeutic classes may be needed at the same time to control IOP or
- further glaucoma surgery or
- 360° SLT or
- cyclodiode laser treatment. [2009, amended 2022]

1.4.24 Offer 1 of the following to people with COAG (including advanced COAG) who prefer not to have glaucoma surgery or for whom glaucoma surgery is not suitable:

- pharmacological treatment; topical medicines from different therapeutic classes may be needed at the same time to control IOP or
- 360° SLT (for example in people with systemic comorbidities) or
- cyclodiode laser treatment. [2009, amended 2022]

1.5 Reassessment

Reassessment tests

1.5.1 At each assessment, offer the following tests to people with COAG, people with suspected COAG and people with OHT:

- Goldmann applanation tonometry (slit lamp mounted)
- anterior segment slit lamp examination with van Herick peripheral anterior chamber depth assessment when clinically indicated. [2017]

1.5.2 When clinically indicated, repeat gonioscopy, for example, if a previous examination has been inconclusive or there is suspicion of a change in clinical status of the anterior chamber angle. [2017]

1.5.3 When clinically indicated, repeat visual field testing using standard automated perimetry (central thresholding test) for people with COAG and those with suspected visual field defects who are being investigated for possible COAG (see table 2 and table 3 for recommended reassessment intervals). [2009, amended 2017]

1.5.4 When clinically indicated, repeat visual field testing using either a central thresholding test or a supra-threshold test for people with OHT and those with suspected COAG whose visual fields have previously been documented by standard threshold automated perimetry (central thresholding test) as being normal (see table 1 and table 2 for recommended reassessment intervals). [2009, amended 2017]

1.5.5 When a visual field defect has previously been detected, use the same measurement strategy for each visual field assessment. [2009]

1.5.6 When clinically indicated, repeat assessment of the optic nerve head (for example, stereoscopic slit lamp biomicroscopy or imaging). [2017]

1.5.7 When a change in optic nerve head status is detected by stereoscopic slit lamp biomicroscopy, obtain a new optic nerve head image for the person's records to provide a fresh benchmark for future assessments. [2009]

1.5.8 When an adequate view of the optic nerve head and surrounding area is unavailable at reassessment, people should have their pupils dilated before stereoscopic slit lamp biomicroscopy or optic nerve head imaging is repeated. [2009]

When to reassess

People with COAG, suspected COAG and OHT

1.5.9 At each assessment, re-evaluate the risk of conversion to COAG and the risk of sight loss to set time to next assessment. [2017]

1.5.10 At each assessment, ask about general health and, if appropriate, factors affecting adherence to treatment, including cognitive impairment and any treatment side effects. [2017]

People with treated OHT (baseline IOP 24 mmHg or more) and a normal optic nerve head and visual field at most recent assessment

1.5.11 For people with treated OHT (baseline IOP of 24 mmHg or more) and a normal optic head and visual field at the most recent assessment:

- use clinical judgement to assess control of IOP and the risk of conversion to COAG, and
- reassess according to table 1. [2017]

Table 1 Time to next assessment for people being treated for OHT

Conversion from ocular hypertension to chronic open angle glaucoma	Control of intraocular pressure	Time to next assessment
Not detected or uncertain conversion	No	Review management plan and reassess between 1 month and 4 months
Uncertain conversion	Yes	Reassess between 6 months and 12 months
No conversion detected	Yes	Reassess between 18 months and 24 months

Conversion from ocular hypertension to chronic open angle glaucoma	Control of intraocular pressure	Time to next assessment
Conversion	No or yes	See recommendations on diagnosis and reassessment of chronic open angle glaucoma

Use clinical judgement to decide when the next appointment should take place within the recommended interval, including the need to assess the impact of any new treatments started.

Uncertain conversion includes having insufficient accurate information (perhaps because the person was unable to participate in the assessment).

People with suspected COAG

1.5.12 For people with suspected COAG:

- use clinical judgement to assess control of IOP and risk of conversion to COAG (optic nerve head damage and visual field defect), and
- reassess according to table 2. [2017]

Table 2 Time to next assessment for people with suspected COAG

Conversion to chronic open angle glaucoma	Control of intraocular pressure	Time to next assessment
Not detected or uncertain conversion	No	Review management plan and reassess between 1 month and 4 months
Uncertain conversion	Yes	Reassess between 6 months and 12 months
No conversion detected	Yes	Reassess between 12 months and 18 months
Conversion	No or yes	See recommendations on diagnosis and reassessment of chronic open angle glaucoma

Use clinical judgement to decide when the next appointment should take place within the recommended interval, including the need to assess the impact of any new treatments started.

Uncertain conversion includes having insufficient accurate information (perhaps because the person was unable to participate in the assessment).

People with COAG

1.5.13 For people with COAG:

- use clinical judgement to assess risk of COAG progression to sight loss, and
- reassess according to table 3. [2017]

Table 3 Time to next assessment for people with COAG

Progression of chronic open angle glaucoma	Control of intraocular pressure	Time to next assessment
Not detected	No	Review treatment plan and reassess between 1 month and 4 months
Uncertain progression or progression	No	Review treatment plan and reassess between 1 month and 2 months
No progression detected and low clinical risk	Yes	Reassess between 12 months and 18 months
No progression detected and high clinical risk	Yes	Reassess between 6 months and 12 months
Uncertain progression or progression	Yes	Review treatment plan and reassess between 2 months and 6 months

Use clinical judgement to decide when the next appointment should take place within the recommended interval, including the need to assess the impact of any new treatments started.

Uncertain conversion includes having insufficient accurate information (perhaps because the person was unable to participate in the assessment).

Discharge back to primary care

1.5.14 Discharge people back to primary eye care services if:

- they were referred for OHT but do not need treatment
- they were referred for suspected COAG but this is no longer suspected.

  Advise people that they should continue with regular visits to their primary eye care professional, at clinically appropriate intervals. [2017]

1.5.15 Give a discharge summary to people who have been assessed and discharged to primary care. Send a copy to their GP and, with patient consent, copy the relevant information to the primary eye care professional nominated by the patient. Advise people to take their discharge summary with them when attending future sight tests. [2017]

1.6 Organisation of care

1.6.1 Refer people to a consultant ophthalmologist for consideration of a definitive diagnosis and formulation of a management plan if:

- they have suspected optic nerve damage or repeatable visual field defect, or both, or
- SLT treatment is suitable (see recommendation 1.4.4 and recommendation 1.4.15 for people with newly diagnosed OHT and COAG). [2009, amended 2022]

1.6.2 Diagnosis of OHT and suspected COAG and formulation of a management plan should be made by a suitably trained healthcare professional with:

- a specialist qualification and
- relevant experience. [2009, amended 2017]

1.6.3 Be aware that holding an independent or non-medical prescribing qualification alone (without a specialist qualification relevant to the case complexity of glaucoma being managed) is insufficient for managing glaucoma and related conditions. [2017]

1.6.4 Healthcare professionals involved in the diagnosis of OHT and COAG suspect status, and preliminary identification of COAG, should be trained in case detection and referral refinement and be able to identify abnormalities based on relevant clinical tests and assessments. They should understand the principles of diagnosis of OHT and COAG and be able to perform and interpret all of the

following:

- medical and ocular history
- differential diagnosis
- Goldmann applanation tonometry (slit lamp mounted)
- standard automated perimetry (central thresholding test)
- central supra-threshold perimetry
- stereoscopic slit lamp biomicroscopic examination of anterior segment
- examination of the posterior segment using slit lamp binocular indirect ophthalmoscopy
- gonioscopy
- van Herick peripheral anterior chamber depth assessment
- CCT measurement. [2009]

1.6.5 People with OHT, suspected COAG or COAG should have monitoring and treatment from a trained healthcare professional who has all of the following:

- a specialist qualification
- relevant experience
- ability to detect a change in clinical status. [2009, amended 2017]

1.6.6 Healthcare professionals involved in monitoring and treating OHT, suspected COAG and established COAG should be trained to make management decisions on:

- risk factors for conversion to COAG
- coexisting pathology
- risk of sight loss

- monitoring and detecting a change in clinical status (for example, visual field changes and stereoscopic slit lamp biomicroscopic examination of anterior segment and posterior segment)
- pharmacology of IOP-lowering medicines
- eligibility for 360° SLT
- treatment changes for COAG, suspected COAG and OHT (with consideration given to relevant contraindications and interactions). [2009, amended 2022]

1.6.7 Healthcare professionals should discuss with the responsible consultant ophthalmologist the decision to offer 360° SLT and how it will be performed. Healthcare professionals undertaking 360° SLT should be given support by the responsible consultant ophthalmologist. Training should include:

- the suitability of the procedure
- laser safety and procedures
- benefits and risks of 360° SLT, and how to discuss these with patients and their family members or carers (as appropriate)
- patient consent. [2022]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on organisation of care.

Full details of the evidence and the committee's discussion are in evidence review A: selective laser trabeculoplasty in ocular hypertension or chronic open-angle glaucoma adult patients.

1.6.8 People with a confirmed diagnosis of OHT or suspected COAG and who have an established management plan may have monitoring (but not treatment) from a suitably trained healthcare professional with knowledge of OHT and COAG, relevant experience and the ability to detect a change in clinical status. The healthcare professional should be able to perform and interpret all of the following:

- Goldmann applanation tonometry (slit lamp mounted)

- standard automated perimetry (central thresholding test)
- central supra-threshold perimetry (this visual field strategy may be used for monitoring OHT or suspected COAG when the visual field is normal)
- stereoscopic slit lamp biomicroscopic examination of the anterior segment
- van Herick peripheral anterior chamber depth assessment
- examination of the posterior segment using slit lamp binocular indirect ophthalmoscopy. [2009]

1.6.9 Healthcare professionals who diagnose, treat or monitor independently of consultant ophthalmologist supervision should take full responsibility for the care they provide. [2009]

1.7 Providing information

1.7.1 Ensure that people are offered the opportunity to discuss their diagnosis, referral, prognosis, treatment and discharge so they can take an active part in decision making (see NICE's guideline on shared decision making). Provide them with relevant information in an accessible format at initial and subsequent visits. This should include telling them:

- about their specific condition (OHT, suspected COAG and COAG), its life-long implications and their prognosis for retention of sight
- that COAG in the early stages and OHT and suspected COAG are symptomless
- that most people having treatment for COAG will have good quality of life and not go blind
- that once lost, sight cannot be recovered
- the different types of treatment options, including mode of action, frequency and severity of side effects, and risks and benefits of treatment
- that glaucoma can run in families and that family members may wish to be tested for the condition
- the importance of their role in their own treatment – for example, the ongoing regular application of eye drops to preserve sight. [2009, amended 2017]

1.7.2 Ensure that people are given practical information and advice on:

- how to apply eye drops, including technique (punctal occlusion and devices) and hygiene (storage)
- the need for regular monitoring as specified by the healthcare professional
- methods of investigation during assessment
- how long each appointment is likely to take and whether the person will need any help to attend (for example, driving soon after pupil dilatation would be inadvisable)
- how to contact the eye clinic liaison officer (ECLO) and what information and assistance they can provide
- support organisations and support groups
- compliance aids (such as dispensers) available from their GP or community pharmacist
- Letter of Vision Impairment (LVI), Referral of Vision Impairment (RVI) and Certificate of Vision Impairment (CVI), registration
- Driver and Vehicle Licensing Agency (DVLA) regulations. [2009, amended 2017]

Terms used in this guideline

COAG and related conditions

These include COAG, OHT and suspected COAG.

Enhanced case-finding

Enhanced community case-finding services use slit lamp mounted Goldmann-type applanation tonometry, dilated slit lamp indirect biomicroscopy and other tests deemed necessary by the healthcare professional.

MMC

Mitomycin-C is an antimetabolite used during the initial stages of trabeculectomy to prevent excessive postoperative scarring and therefore reduce the risk of failure.

Primary eye care professionals

These include optometrists, GPs with a special interest in ophthalmology and community orthoptists.

Referral filtering

A general term for any type of accuracy checking before referral to hospital eye services. Referral filtering may take the form of 'repeat measures', 'enhanced case-finding', 'referral refinement', 'hospital-based triage' or 'administrative paper-based triage'.

Referral refinement

A 2-tier assessment in which initial evidence of abnormality found during case-finding or screening is validated by an enhanced assessment, which adds value beyond that achieved through a simple 'repeat measures' scheme. A referral refinement service performs tests to diagnose OHT and suspected COAG and interprets the results in the light of clinical findings. Specialist practitioners who deliver this service independently have the qualifications and experience set out in the recommendations on organisation of care. Practitioners providing a referral refinement service should be qualified to make a diagnosis of OHT and suspected glaucoma, and to carry out gonioscopy to exclude angle-closure glaucoma.

Repeat measures

The repeated measurement of parameters related to the diagnosis of glaucoma. A simple repeat measures scheme may involve repeat measurement of IOP only. Other repeat measures schemes may also include repeated measurement of visual fields and other relevant ocular parameters when clinically necessary.

Sight loss

Sight loss in glaucoma is visual damage that manifests as blind spots in the field of vision. Early on these are mostly asymptomatic with many people being unaware of a problem. Sight loss may progress to visual impairment and eventually become symptomatic.

Sight test

A sight test determines whether or not a person has a sight defect, and if so, what is needed to correct, remedy or relieve it. An optometrist performing a sight test must conduct the examinations

specified in the Sight Testing (Examination and Prescription) (No 2) Regulations 1989. These include an internal and external examination of the eyes and any other examinations needed to detect signs of injury, disease or abnormality in the eye or elsewhere.

Visual impairment

A severe reduction in vision that cannot be corrected with standard glasses or contact lenses and reduces a person's ability to function in a visual environment.

Recommendations for research

The guideline committee has made the following recommendations for research.

Key recommendations for research

1 Risk tools to identify risk of developing chronic open angle glaucoma and risk of sight loss

What is the predictive value of risk tools for identifying people in the community who are at increased risk of developing chronic open angle glaucoma (COAG) and identifying people with COAG who are at increased risk of sight loss?

2 Long-term effectiveness of selective laser trabeculoplasty

What is the long-term effectiveness and cost effectiveness of selective laser trabeculoplasty as a first-line treatment compared with intraocular pressure-lowering eye drops in ocular hypertension or COAG in adults?

3 An instrument to measure quality of life in people with glaucoma

What instrument should be used to measure health-related quality of life in people with glaucoma?

4 Optical coherence tomography for glaucoma

What is the effectiveness and cost effectiveness of optical coherence tomography for diagnosing and monitoring glaucoma?

5 Referral filtering

What is the effectiveness and cost effectiveness of the different models for glaucoma filtering (pathways from case-finding to assessment in secondary ophthalmic care) for detecting glaucoma and glaucoma-related conditions (ocular hypertension and suspected glaucoma)?

Other recommendations for research

Treatment for people with an intraocular pressure of 22 mmHg or 23 mmHg

What is the clinical and cost effectiveness of treating an intraocular pressure of 22 mmHg or 23 mmHg in people with normal optic discs and visual fields?

For a short explanation of why the committee made the recommendation for research, see the rationale section on selective laser trabeculoplasty for people with ocular hypertension and chronic open angle glaucoma.

Full details of the evidence and the committee's discussion are in evidence review A: selective laser trabeculoplasty in ocular hypertension or chronic open-angle glaucoma adult patients.

Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice.

Selective laser trabeculoplasty for people with ocular hypertension or chronic open angle glaucoma

Recommendations 1.4.4 and 1.4.5 and recommendations 1.4.15 and 1.4.16

Why the committee made the recommendations

The committee agreed that the key outcome for adults with ocular hypertension (OHT) or chronic open angle glaucoma (COAG) was visual field progression that, in the long-term, could affect people's vision. Intraocular pressure (IOP) was considered to be a relevant surrogate outcome because lowering IOP can prevent the risk of optic nerve damage and sight loss. High-quality evidence showed that there is no meaningful difference between 360° selective laser trabeculoplasty (SLT) and eye drops in achieving a target IOP, health-related quality of life, risk of total adverse events, and treatment adherence. The evidence did show that that there were transient adverse events associated with SLT such as transient discomfort, blurred vision, photophobia and hyperaemia. It was also highlighted that there are rare complications associated with SLT. While rare events were not highlighted in the evidence, corneal failure is possible after SLT procedures. In people who have first-line treatment with eye drops compared with first-line 360° SLT, more people used eye drops and more people have more than 1 eye drop medication at 12 months.

The cost-effectiveness evidence showed that first-line treatment with 360° SLT was more effective and less costly compared with eye drops, with at least 90% probability of being the more cost-effective option. For costs, this result was driven by treatment involving 360° SLT costing less overall compared with eye drops alone. This is because the additional upfront costs of 360° SLT were outweighed by the accumulating costs of eye drops over time. For quality of life, 360° SLT resulted in a longer period without eye drops, or with fewer eye drops, and slightly slower estimated progression rates for glaucoma. Although no statistically significant direct benefit on quality of life was found in the trial, additional data on the natural history of glaucoma, which was incorporated into the cost-effectiveness analysis, suggests that quality of life was likely to be improved. The cost-effectiveness analysis included the costs and benefits of a second 360° SLT if

the clinicians deemed it necessary. Even if 360° SLT was assumed to have the same clinical effectiveness as eye drops, it would still be a highly cost-effective treatment, because of the estimated reduction in overall costs.

Based on this evidence and their clinical experience, the committee recommended 360° SLT as first-line treatment for people with newly diagnosed OHT or newly diagnosed COAG. The recommendation excludes cases associated with pigment dispersion syndrome. This was because there was no evidence on the use of 360° SLT in people with pigment dispersion syndrome and the committee agreed that eye drop treatment is more suitable for those people. The recommendation lists information to give to people to help them make a decision on having SLT as first-line treatment, including telling them about 360° SLT-specific side effects and complications and how long they are likely to last.

The committee noted that SLT may need to be repeated. This was included in the cost-effectiveness analyses (with approximately 15% of people in the SLT arm having a second procedure within the first year), which gave the committee more confidence in the result, as it reflected their expectations of how the treatment would be used in practice. The committee recommended that a second 360° SLT could be needed if the effect of an initial successful 360° SLT has subsequently reduced over time. This means that the IOP level has gone up and clinicians need to decide if there is risk of progression of COAG or conversion of OHT to COAG. The second 360° SLT should be given at the discretion of the responsible consultant ophthalmologist. This follows the procedure used in the main UK randomised trial (the LiGHT trial).

The committee further highlighted that in general, treatment to reduce IOP has to work for at least 6 months to be considered successful. However, this can also be based on clinician discretion.

The committee highlighted that there was a lack of long-term evidence on progression of glaucomatous visual field defect and progression of optic nerve head damage. The committee also highlighted that patients care more about vision outcomes than other outcomes such as IOP. A research recommendation was developed to cover this gap in the evidence on the long-term effectiveness of 360° SLT (with follow-up times of 3 years or more, 5 years and 10 years).

Impact on other recommendations

The committee considered the impact of recommending 360° SLT on other recommendations in the guideline. Recommendations were amended as necessary, taking into account the original evidence for each recommendation and the committee's knowledge and experience.

How the recommendations might affect practice

The recommendations are likely to result in a significant change in practice, because more people with newly diagnosed OHT or COAG could be offered 360° SLT as their first treatment. The committee also noted that larger centres may see more referrals, resulting in an increase in the number of clinics per week. The committee highlighted that, although the increase should not be significant, any increase means there will be a change to the organisation of care. Overall, this is not likely to have a substantial cost impact because evidence shows that first-line 360° SLT (including the purchase and maintenance of the SLT machine) was less costly than first-line use of eye drops. However, there will be changes in the types of costs incurred, with significant reductions in the cost of eye drop prescriptions but increases in costs for SLT devices and staffing.

Return to recommendations 1.4.4 and 1.4.5

Return to recommendations 1.4.15 and 1.4.16

Generic PGAs for people with OHT or COAG

Recommendation 1.4.6 and recommendation 1.4.17

Why the committee made the recommendations

The 2017 guideline recommended prostaglandin analogue (PGA) eye drops for OHT or COAG. The committee amended this to reflect the new 2022 recommendations on using 360° SLT. They agreed that people who prefer not to have 360° SLT or for whom it is not suitable should be offered generic PGA eye drops. This was because PGA eye drops were used for first-line treatment in the 2017 guideline and in the LiGHT trial.

The recommendations were also amended to highlight that eye drop installation technique should be demonstrated and that healthcare professionals should observe the person to confirm that their installation technique is correct. It is recommended that this be done when eye drops are first prescribed.

Return to recommendation 1.4.6

Return to recommendation 1.4.17

Organisation of care

Recommendations 1.6.6 and 1.6.7

Why the committee made the recommendations

The committee noted that the first-line use of 360° SLT to treat OHT or COAG might lead to a significant change in practice that requires different organisation of care and the establishment of a multidisciplinary team. The committee wanted to make clear that if 360° SLT is suitable for a person, that person should be referred to a consultant ophthalmologist. They also discussed the safety of the 360° SLT procedure and agreed that healthcare professionals should discuss with the responsible consultant ophthalmologist the decision to offer it and how it will be performed. This means that with support from a consultant ophthalmologist, healthcare professionals such as specialty doctors, associate specialists, specialist nurses, optometrists and allied health professionals can perform 360° SLT.

The committee also noted that healthcare professionals who provide 360° SLT should be given support and have relevant training on the suitability and safety of the procedure, including its benefits and risks. They should also be trained in discussing these points and patient consent with patients and their family members or carers. A similar approach was taken in the LiGHT trial, in which training was given to all treating surgeons before recruitment, and the chief investigator, who was a consultant ophthalmic surgeon, observed each surgeon perform at least 1 laser treatment. Based on these discussions, new recommendations were added to provide further clarification on organisation of care.

How the recommendations might affect practice

The recommendations are likely to result in a significant change in practice because training and support will be needed for healthcare professionals performing the 360° SLT procedure.

Return to recommendations 1.6.6 and 1.6.7

Context

The scope of this NICE guideline on diagnosis and management of glaucoma was extended to cover referral in 2017. This included the most effective service models for referral filtering schemes (repeat measures, enhanced case-finding and referral refinement), the tests to be used for finding people with chronic open angle glaucoma (COAG), suspected COAG and ocular hypertension (OHT), and thresholds for onward referral. In 2017, the guidance was also updated on tests for diagnosis and reassessment, pharmacological treatments for lowering intraocular pressure (IOP) and preserving visual field, and reassessment intervals, which depend on prognosis.

The 2017 update provided an opportunity to re-evaluate the clinical effectiveness, cost effectiveness and indications for treating OHT. Knowledge of corneal thickness is no longer needed to decide whether to treat OHT and a single threshold of 24 mmHg is now recommended for both onward referral and treatment. Changes in the costs of pharmacological treatments, acknowledgement of short- and long-term variations in IOP and the uneven relationship between rising pressure and increased risk have allowed a simplification of the indications for OHT treatment.

Control of IOP remains critical to the therapeutic approach. Intensity of treatment and ongoing management are guided by disease severity and progression as shown by visual field change, morphological change in the optic disc, and the likelihood of progressive sight loss. Reassessment at each visit is emphasised, encouraging flexible clinical judgement about the frequency of visits and options for treatment, including stopping treatment when the perceived lifetime risk of developing visual impairment is low.

Since the update in 2017, there has been new evidence on the use of 360° selective laser trabeculoplasty as a first-line treatment for OHT and COAG. Therefore, recommendations on treatment for people with OHT or COAG were updated.

Sections of the guideline on accuracy of visual field tests, surgical interventions, and information, education and support needed for adherence to treatment have not been updated because no new evidence was found.

Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE webpage on eye conditions.

For full details of the evidence and the guideline committee's discussions, see the evidence review. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.

Update information

January 2022: We have reviewed the evidence and made new recommendations on treatment and organisation of care for people with ocular hypertension and chronic open angle glaucoma (COAG). These recommendations are marked [2022].

We have also made the following changes to recommendations without an evidence review:

- Wording was added throughout to clarify that surgery refers to glaucoma surgery and to reflect the new recommendations on 360° selective laser trabeculoplasty.
- Wording was added to recommendation 1.4.11 to clarify that people with suspected COAG should be offered treatment if they are at risk of visual impairment within their lifetime.

These recommendations are marked [2009, amended 2022] and [2017, amended 2022]. In some cases, minor changes have been made to the wording of other recommendations to bring the language and style up to date, without changing the meaning.

Recommendations marked [2009] last had an evidence review in 2009.

November 2017: This guideline updated and replaced NICE guideline CG85 (published April 2009). New recommendations were added for case-finding, diagnosis, reassessment and treatment. These are marked as [2017]. Changes made without a new evidence review are marked [2009, amended 2017]

ISBN: 978-1-4731-2713-5

Accreditation

NICE National Institute for Health and Care Excellence

Putting NICE guidance into practice

Baseline assessment: Glaucoma: diagnosis and management NG81

Published: November 2017
Updated: January 2022

NICE

From the Chief Medical Officer
Prof Sir Michael McBride

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

HSS(MD)2/2022

FOR ACTION
Chief Executives, Public Health Agency/Health and Social Care Board/HSC Trusts/ NIAS
GP Medical Advisers, Health & Social Care Board
All General Practitioners and GP Locums *(for onward distribution to practice staff)*
OOHs Medical Managers (for onward distribution to staff)
RQIA *(for onward circulation to all independent sector health and social care providers)*

PLEASE SEE ATTACHED FULL CIRCULATION LIST

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Dear Colleague

MANAGEMENT OF HEALTH AND SOCIAL CARE STAFF WHO ARE CONFIRMED CASES OF COVID-19 - UPDATED GUIDANCE

The purpose of this letter is to provide updated operational guidance in the light of further changes to the general population isolation guidance for those who are cases. This letter updates guidance provided in HSS(MD)91/2021 https://www.health-ni.gov.uk/sites/default/files/publications/health/doh-hss-md-91-2021.pdf and HSS(MD)01/2022 https://www.health-ni.gov.uk/sites/default/files/publications/health/doh-hss-md-01-2022.pdf .

In line with the announcement of changes to the self-isolation guidance for those who have received a positive COVID-19 test result, health and social care staff who test positive will be able to leave self-isolation and return to work, if they test negative on days 5 and 6 after the date that symptoms started or the date of their initial positive test, whichever is the sooner.

This means if a staff member tests negative on the morning of day 6 and was also negative 24 hours earlier, they can return to work on day 6 provided they meet the following requirements:

- The do not have a temperature and are medically fit.
- The staff member should continue to undertake daily LFTs until day 10.

- If any of these LFD test results are positive the staff member should isolate and should wait 24 hours before taking the next LFD test.

- On days the staff member is working, the LFD test should be taken prior to beginning their shift, as close as possible to the start time.

- The staff member must continue to comply with all relevant infection control precautions throughout the day.

- If the staff member works with the most clinically vulnerable patients or clients (as determined by the organisation), a risk assessment should be undertaken, and consideration given to redeployment of the returning staff member for the remainder of the original 10 day isolation period.

- If the staff member following return to work has a positive LFT result between day 6 and 10 they must isolate and should not attend work.

- The likelihood of a positive LFT in the absence of symptoms after 10 days is low.

- Staff members who test positive at day 10 should take a daily lateral flow test on days 11 – 14 until they get a single negative result. After day 10 they can return to work immediately following a single negative result.

- The likelihood of a person who is well, being infectious after 14 days is considerably lower. If the staff member's LFT test result is still positive on the 14th day, they can stop testing and return to work on day 15. If the staff member works with patients or residents who are especially vulnerable to COVID-19 (as determined by the organisation), a risk assessment should be undertaken.

Guidance for staff working in low risk areas

It is recognised that many staff, whose attendance at the workplace is critical to the delivery of services, work in areas where the risk of nosocomial infections is extremely low. In these situations, and during the current phase of the pandemic, the organisation may risk assess and choose to apply the general population isolation guidance for cases with the added safeguard that the individual is asymptomatic and complies carefully with the required IPC practices for their area of work.

The general population guidance can be accessed at the following link:
Coronavirus (COVID-19): self-isolating and close contacts | nidirect

There is no change to isolation or testing of staff who are close contacts of someone confirmed COVID-19 positive.

I am very aware that there have been multiple changes to COVID guidance in recent weeks. While these are necessary to take account of the current phase of the pandemic, I appreciate that keeping up with these changes adds an additional pressure to those working in health and social care. I want to acknowledge the work

undertaken by staff across the service to ensure we continue to provide our services to our patient and clients while keeping them safe.

While the number of cases seen during this Omicron wave has been unprecedented, the large number of cases has not translated into the level of pressures on health services seen in previous waves. This is due in no small part to the efforts of colleagues across the service, in particular efforts made to accelerate the booster programme. However, we expect to see sustained pressure across services for the next 4-6 weeks. To support colleagues and to protect our patients and services, Trust are asked to continue to ensure that:

- Vaccination is promoted throughout the organisation alongside opportunities to avail of the vaccine.

- 1:1 conversations continue with any member of staff or student who has not been vaccinated, to understand and address their questions and concerns.

- As previously communicated robust local monitoring processes continue to be in place for regular testing of staff and students using LFD or where available LAMP testing, with Board level monitoring, reporting and assurance of uptake of regular testing. Staff (even if vaccinated) continue to carry out this regular asymptomatic (twice weekly) LFD or where available, LAMP testing, and report results so that COVID-19 cases can be identified and isolated early to help keep staff and patients safe.

- Staff report the LFD results of their twice weekly asymptomatic tests whether positive or negative at https://www.gov.uk/report-covid19-result

In addition to vaccination and regular systematic patient and staff testing, the consistent application of infection prevention and control (IPC) measures and the hierarchy of controls remains the most effective defence against the entry and spread of COVID-19 in healthcare settings. Trusts should ensure that staff are offered ongoing training and support to help them apply the required IPC and Public Health measures appropriately in all relevant settings. The most update to date guidance on IPC measures can be found at:

Infection prevention and control for seasonal respiratory infections in health and care settings (including SARS-CoV-2) for winter 2021 to 2022 - GOV.UK (www.gov.uk)

Thank you very much for your continued support in managing and mitigating the COVID-19 pandemic.

Yours sincerely

Personal information redacted by USI

PROF SIR MICHAEL McBRIDE
Chief Medical Officer

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Clinical Advisory Team
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This letter is available on the Department of Health website at https://www.health-ni.gov.uk/topics/professional-medical-and-environmental-health-advice/hssmd-letters-and-urgent-communications

Public Health Agency

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BY EMAIL
To All Care Home Managers

25 January 2022

Dear Care Home Manager

UPDATED OPERATIONAL GUIDANCE FOR CARE HOMES

The purpose of this letter is to provide updated operational guidance for care homes in Northern Ireland to support implementation of the guidance set out in the letters of 22 and 31 December 2021 issued jointly by the Public Health Agency (PHA) and the Regulation & Quality Improvement Authority (RQIA).

Annex 1 of this letter provides updated guidance on the following areas:

1. Isolation requirement for staff who are confirmed cases of COVID-19 (updated guidance from 31 December)
2. Management of care home staff who are confirmed cases who have a positive LFD test result at and beyond day 10.
3. Management of care home staff identified as close contacts of confirmed COVID-19 cases who are eligible for the COVID-19 booster dose but have either not received it or who were within 14 days of receipt when they were identified as close contacts.
4. Temporary removal of the guidance to confirm a positive Lateral Flow Device (LFD) test result with a Polymerase Chain Reaction (PCR) test for staff.
5. Recommencing regular PCR and LFD testing following a confirmed diagnosis of COVID-19 (90 day rule).
6. Update on logistics for LFD testing across the care home sector including resources to support implementation.

In addition, annex 2 contains an overview of COVID-19 testing arrangements in care homes and annex 3, answers a list of frequently asked questions (FAQs) gathered from meetings and communications over the past few weeks.

The PHA Health Protection Team has updated the outbreak definitions and risk assessments used to support care homes when positive or symptomatic cases of COVID-19 are notified from the care home sector. Dr Gillian Armstrong will write separately to care homes with further information in due course.

Given the rapidly changing situation it is likely that there will be further updates and those will be communicated either by the Department of Health or by the PHA. We would encourage all Responsible Individuals and Registered Managers to refer to the most up-to-date information on the PHA website and also on NI Direct.

If you have any queries in relation to the contents of this communication please contact the Health Protection Duty Room on: 0300 555 0119 (Monday to Friday 9am – 5pm) or Email: PHADutyRoom@hscni.net. Out of hours contact the on call Public Health Director via ambulance control on 028 9040 4045.

With our continued thanks to you and all your staff for your ongoing hard work and support.

Yours sincerely

Aidan Dawson
Chief Executive

cc RQIA Chief Executive
HSCB Chief Executive
HSC Trust Chief Executives

Enc

Annex 1

1 Isolation requirement for staff who are confirmed cases of COVID-19 (updated guidance from 31 December)

On the 31 December, the PHA issued guidance to care homes on isolation requirements for staff who are confirmed cases of COVID-19.

Following a further relaxation of isolation guidance for confirmed cases in the wider population, this letter (24 January 2021) updates guidance of 31 December 2021.

Care home staff who test positive will be able to leave self-isolation and return to work, if they test negative on days 5 and 6 after the date that symptoms started or the date of their initial positive test, whichever is the sooner.

The second LFT should be taken at least 24 hours after the first. If both LFT results are negative, they may end their self-isolation after the second negative LFT result. Staff should not take an LFT before the 5th day of their isolation period and should only end their self-isolation following 2 consecutive negative LFT tests (which should be taken at least 24 hours apart).

This means if a staff member tests negative on the morning of day 6 and was also negative 24 hours earlier, they can return to work on day 6 provided they meet the following requirements:

- They do not have a temperature and are medically fit.
- The staff member should continue to undertake daily LFTs until day 14.
- If any of these LFD test results are positive the staff member should isolate and should wait 24 hours before taking the next LFD test.
- On days the staff member is working, the LFD test should be taken prior to beginning their shift, as close as possible to the start time.
- The staff member must continue to comply with all relevant infection control precautions throughout the day.
- If the staff member works with the most clinically vulnerable patients or clients (as determined by the care home), a risk assessment should be undertaken, and consideration given to redeployment of the returning staff member for the remainder of the original 10 day isolation period.
- If the staff member following return to work has a positive LFT result between day 6 and 10 they must isolate and should not attend work. Staff should only end their self-isolation following 2 consecutive negative LFT tests (which should be taken at least 24 hours apart).

There is no change to the guidance for isolation or testing of staff who are close contacts of someone confirmed COVID-19 positive (see point 3).

2 Management of staff who are confirmed cases who have a positive lateral flow result at and beyond day 10

While this guidance has further shortened isolation periods for many and permitted staff to return to work, a small proportion of individuals (thought to be around 5%) will still test positive with a LFD test up to and including day 10.

For the general population, testing can be stopped at day 10 and the individual can leave isolation. However, additional safeguards are required for before care home staff can return to the workplace.

The likelihood of a positive LFT in the absence of symptoms after 10 days is low.

Care home staff members who test positive at day 10 should take a daily lateral flow test on days 11 – 14 until they get a single negative result. After day 10 they can return to work immediately following a single negative result.

The likelihood of a person who is well, being infectious after 14 days is considerably lower. If the staff member's LFT test result is still positive on the 14th day, they can stop testing and return to work on day 15. If the staff member works with patients or residents who are especially vulnerable to COVID-19 (as determined by the organisation), a risk assessment should be undertaken.

3 Management of staff identified as close contacts of confirmed COVID-19 cases who are eligible for the COVID-19 booster dose but have not received it.

On 31 December 2021, the PHA issued guidance to care homes setting out the actions required to support the return to work of staff identified as close contacts of confirmed cases of COVID-19. The guidance applied to staff who have had two doses of an approved vaccine and a booster dose at least 14 days prior to the date of their exposure to the confirmed case. It also applied to staff who were not yet eligible for their booster vaccine because it is less than three months since their second dose of vaccine.

The letter also outlined arrangements for a temporary exemption until 14th January 2022 which allowed staff who, were eligible for the booster but had either not yet received it or were within 14 days of their booster at the time of the exposure to COVID-19, to return to work following a risk assessment if there was a serious risk to service continuity as a result of workforce shortages. Care homes were asked to take steps to ensure eligible staff received a booster vaccine by 31 December 2021 to avoid negative impacts on staffing once the time limited exemption expired on 14 January 2022.

This letter confirms an extension to the exemption from 14 January 2022 onwards, with the caveat that staff in this situation cannot be considered for return to work unless all the following conditions are met:

- The safe delivery of services is threatened because of staffing;
- A full risk assessment has been carried out and appropriately documented;
- Each case is individually considered and authorised in writing by the Registered Manager; and
- Records are maintained for instances where staff return to work in this context.

This limited exemption will be kept under regular review and may be removed in the future. Responsible Individuals and Registered Managers in care homes are asked to immediately redouble all efforts to promote vaccine uptake among their staff.

4 Temporary removal of guidance to take a PCR test to confirm a positive Lateral Flow Device (LFD) test result.

When COVID-19 prevalence is as high as it is currently in Northern Ireland, a positive LFD test result is extremely likely to indicate that the individual has COVID-19 and that they are infectious. The risk of a false positive LFD result is small. There are fewer than 3 false positive results for every 10,000 LFD tests taken.

The risk of receiving a false positive LFD test result applies to health and social care workers (including care home staff) as well as the general population.

A health and social care worker (including care home staff) who tests positive on a LFD test should assume they have COVID-19 and isolate in line with current guidance. They should report the result on Report a COVID-19 rapid lateral flow test result - GOV.UK (www.gov.uk)

The current position is that there is no public health need for care home staff to book a confirmatory PCR test following a positive LFD test result, unless they are in one of the clinical groups who may be eligible for one of the new COVID-19 treatments. Information on these new COVID-19 treatments is available on NI Direct at: https://www.nidirect.gov.uk/articles/treatments-coronavirus-covid-19

The public health guidance on confirmatory PCR will be kept under review. It is important to note that confirmatory PCR is likely to be re-introduced when local prevalence of infection falls later in this wave of the pandemic.

5 Recommencing regular asymptomatic PCR and LFD testing following a confirmed diagnosis of COVID-19

- *Regular asymptomatic Polymerase Chain Reaction PCR testing following a positive test result*

Health and social care workers (including care home staff) who have had COVID-19 confirmed either by PCR, LAMP or LFD **should not re-commence regular asymptomatic PCR testing for 90 days after the initial positive test. Nor should they have a PCR test if they are later should they be identified as a close**

contact, unless they have developed new symptoms of COVID-19. PCR testing is very sensitive and can detect viral fragments long after the infection has been cleared and the individual is no longer infectious.

- *Regular asymptomatic Lateral Flow Device (LFD) testing following a positive test result*

Regular asymptomatic testing using LFD tests should recommence after **21 days (three weeks)** from the date of the initial positive test.

Those with a positive LFD test 21 days after the date of their last positive test should be considered a new infection and follow the isolation requirements for confirmed cases of COVID-19.

6 Implementing LFD testing for care home staff, care partners and residents

LFD testing for asymptomatic visitors (that is those with no symptoms) to care homes has been in place since June 2021. Care homes are strongly encouraged to continue to promote the availability of LFD testing to all visitors.

PHA and RQIA jointly wrote to care homes on 22 December 2021 advising that all care home staff should commence regular testing using LFDs three times per week in addition to their regular weekly PCR test. In a further communication on 31 December 2021, the guidance was updated to ask staff to undertake daily LFD tests. It is recommended that care home staff take a LFD test each day prior to commencing their shift in a care home.

Care partners should arrange to take a LFD test in their own home, before attending the care home.

Annex 3 of this letter contains frequently asked questions (FAQs), providing information and clarification on testing requirements and other matters outlined in our letter of 31 December 2021. This FAQ document will also be available on the PHA website here and will be updated as guidance continues to evolve.

Arrangements have now been put in place to facilitate care homes to order supplies of LFDs to provide to staff. Please note that care homes in Northern Ireland will be provided with **SureScreen** SARS-COV-2 Antigen Rapid Tests (nasal) packs of 25 – not Innova 25s as previously indicated.

A series of on-line resources are also available to care homes to support the implementation process for the **SureScreen** tests, including a video and written instructions for use here.

Over the coming months, an increasing range of licensed LFD test kits may become available to Health and Social Care services. It is important that care homes ensure

that they are familiar with the instructions for use and any training requirements appropriate to the testing kits being used in their home, in line with local policy.

- *Overview of testing in care homes*

A poster which provides an overview of the current care home testing policy is provided in Annex 2 of this letter (care home testing poster). This resource is also available to download from the PHA website here

Annex 2: Overview of Testing in Care homes – January 2022

COVID-19 testing for care homes

Updated January 2022

	Residents	Staff /Care Partners	Visitors
Without symptoms (asymptomatic)	Regular monthly PCR test - Pillar 2 Lateral flow device (LFD)* tests should also be used after any trip out of the home (daily for 10 days)	Regular weekly PCR test for staff and care partners (CP) – Pillar 2 AND an LFD test (done at the individual's home before shift/visit starts)	LFD test minimum twice weekly and before each visit (done in visitors' own home).
With symptoms (symptomatic)	Immediate PCR test Pillar 1 (do not use an LFD test)	Immediate PCR test Trust / local testing facility	Immediate PCR test local testing facility

*all LFD tests results (negative and positive) must be registered via https://www.gov.uk/report-covid19-result

Scenario	COVID-19 Testing
Single COVID-19 positive case **staff or care partner** regardless of symptoms AND no positive cases in the 14 days before test date	• Risk assessment by Health Protection Duty Room (HPDR) • Unless advised by HPDR, whole home testing (WHT) is NOT required – monitor closely • Continue with regular asymptomatic testing as above
One or more positive COVID-19 **resident** regardless of symptoms, without evidence of transmission in care home AND no positive cases in the last 14 days before test date **Situation of interest**	• Whole home testing (WHT) required immediately on **day 0 and again between days 4-7 in Pillar 1** • Recommence regular testing for residents in Pillar 2 after day 4-7 tests
Two or more positive cases in **staff or CPs** without obvious transmission links to the care home **Situation of interest**	• Whole home testing (WHT) required immediately on **day 0 and again between days 4-7 in Pillar 1** • Recommence regular testing for residents in Pillar 2 after day 4-7 tests

Testing guidance for an outbreak

Scenario	COVID-19 Testing
Two or more probable or confirmed COVID-19 cases in residents, staff or CPs (regardless of symptoms) with onset within 14 day period, where transmission within care home is considered likely	• Whole home testing (WHT) required immediately on **day 0 and again between days 4-7 in Pillar 1** • Recommence regular asymptomatic testing for residents, staff and CPs in Pillar 2 after day 4-7 tests. Staff should also continue with LFD testing before each shift.

Contact the Health Protection Duty Room on Tel: 0300 555 0119 (Mon-Fri 9am-5pm). For non-urgent communication only, email: PHA.DutyRoom@hscni.net

During evenings, weekends and bank/public holidays, you should contact the first on call Public Health Doctor via ambulance control on 028 9040 4045.

- Any individual who tests positive for COVID-19 and remains asymptomatic, should not be tested for 90 days with a PCR test. Testing using LFDs can commence after 3 weeks. Contact HPDR if advice is required.
- If a test is void/unclear or missing results within regular testing programme (Pillar 2) – unless the individual is symptomatic, retest on next care home regular testing day. In the interim, staff should continue with LFD tests before each shift.
- Staff may continue to test during periods of leave but it is not required. A LFD test should be taken at home before first shift on return to work.

- Please keep using the 119 service for help with regular testing: ordering, couriers, registration and test results.
- Please keep sharing your comments and queries – email carehometesting@hscni.net
- For more information go to: www.pha.site/CareHomeTesting

HSC Health and Social Care

Produced by Public Health Agency, 12-22 Linenhall Street, Belfast BT2 8BS.
Tel: 0300 555 0114 (local rate) www.publichealth.hscni.net

01/22

Annex 3: Also available here

Testing in care homes – FAQs

What are the different COVID-19 tests available for use in care homes?

There are two main types of tests for use in care homes.

- The lateral flow device test (LFD) test
  This is sometimes referred to as LFT. It provides a result within 30 minutes of testing
- The polymerase chain reaction (PCR) test, which requires a sample to be sent to the laboratory.

When should different test be used?

The use of the different tests depends on who is being tested and why they require a test.

Residents and PCR Testing

PCR testing remains the first line testing for care home residents. This includes:

- Regular asymptomatic testing every 28 days with PCR (pillar 2)
- Symptomatic residents should be referred for a PCR test

Residents and LFD Testing

LFD tests are only to be used in the following circumstances. LFDs should not be used in symptomatic residents.

All LFD tests must be registered here – regardless of result

Returning from time spent outside of the care home

Residents should be enabled to continue to enjoy going out of the home as they would wish to. Enhanced testing is advised to facilitate this happening during times of increased community prevalence of COVID-19 infection. Click here for letter to care homes issued on 22nd December.

1. Fully vaccinated (2 doses + booster) resident who is ASYMPTOMATIC
   - Daily LFD tests for 10 days after returning from a trip out from the date of their return

2. Unvaccinated resident who is ASYMPTOMATIC

- Daily LFD tests for 10 days after returning from a trip out from the date of their return **and**
- Isolation for 14 days from the date of their return.

Staff and LFD testing

All LFD tests must be registered here – regardless of result

1. Routine testing before every shift

- Letter of 31st Dec here care homes advised to ensure that staff take a LFD test every day just before the start of every shift in the care home.
- Whilst staff may wish to test every day, it is not essential during days off or periods of leave. However, from an operational point of view – care homes will want to ensure that they have as much notice as possible of any positive test result to organise staff cover. In this case care home managers may wish to ask staff to do a LFD test on the day before returning to work in addition to the test just before commencing their shift.

2. Close contact monitoring

- If a staff member is a close contact of a positive case, they must take a PCR test and if this is negative, and the staff member is fully vaccinated, they can return to work (with caveats as described in the letter of 31December).
- Please note if a staff member has had a positive PCR test for COVID-19 within the previous 90 days, they should not have a PCR test unless they develop new symptoms. Instead they should take an LFD test as soon as possible and if the LFD test is negative they can return to work.
- All staff members returning to work must also monitor their COVID-19 status by taking LFDs daily for 10 days from the date of the close contact
- Please read guidance fully for additional requirements before return to work. **This only applies to fully vaccinated staff.**
- Unvaccinated staff who are a close contact of a positive case should isolate for 10 days – PCR testing is not required unless the close contact develops symptoms.

3. Shortening isolation period

- Following a positive test, staff can potentially return to work from day 6 of isolation if they are asymptomatic and have 2 negative LFD tests 24 hours apart. Testing to end isolation can commence on or after day 5 of the isolation period if symptoms have resolved and 48 hours fever free. Refer to updated guidance in letter of 24 January here for full criteria to end isolation early

Staff returning to work after meeting the criteria for a shorter isolation period should take daily LFDs until day 14.

Staff and PCR testing

1. Regular weekly asymptomatic testing of all staff (Pillar 2)

- All staff should participate in weekly PCR testing unless they have had a PCR positive test in previous 90 days.
- Regular asymptomatic testing using LFD tests should recommence 21 days (three weeks) after the date of the positive test.

2. Symptomatic Testing (Pillar 1)

- If any staff member develops COVID-19 symptoms at any stage other than during a period of isolation after a positive LFD test, they should do a PCR test.
- As of 5 January 2021, if individual has a positive LFD, a confirmatory PCR is not required even if they develop symptoms during the period of isolation. See NI direct website for further information here. This is being kept under review.

3. Close contact testing

- Following being identified as a close contact of a positive case (own household or community), the staff member should self-isolate immediately and get a PCR test (or LFD test if PCR positive test in previous 90 days) .
- At times of exceptional staffing pressures, pending a detailed risk assessment, the staff member may work while awaiting the PCR results. Please refer to full guidance in letter of 31December here.

  If the initial PCR test is negative and the staff member develops symptoms at any stage during the 10 day period after their initial contact with the positive case – they should take an additional PCR test.

  Staff who are caring for COVID-19 +ve resident and who adhere to all required IPC measures including wearing of PPE will not be identified as a close contact.

- Unvaccinated staff who are asymptomatic who are identified as close contacts of a positive COVID-19 case should self-isolate immediately for 10 days from the date of contact. A PCR test is not required.
- Vaccinated staff with booster – exemption

Frequency of testing

Do staff have to test using LFD tests every day?

Letter of 31st December here advised that staff should take a LFD test every day and that preferably staff should take their daily LFD test just before commencing their work shift in the care home.

The expert testing group has agreed that, whilst staff may wish to test every day, it is not required during days off or periods of leave as long as they test before each shift

From an operational point of view – care homes will want to ensure that they have as much notice as possible of any positive test result to organise staff cover. In this case care home managers may wish to ask staff to do a LFD test on the day before returning to work in addition to just before commencing their shift.

How long before each shift should the test be completed?

Staff should take an LFD test at home just before commencing their work shift in the care home and every day that they are working in the care home. This also applies to agency staff who should also ensure that they take a test before they start work in any setting.

Care homes will wish to ensure that they have as much notice as possible of any positive test result to organise staff cover. In this case care home managers may also wish to ask staff to do a LFD test on the day before returning to work in addition to just before commencing their shift.

Is testing mandatory?

Testing is not mandatory but care homes managers may wish to remind all staff of their professional responsibility to act in the best interests of the people in their care.

Written consent should always be sought to ensure individuals are content to participate in testing. Care home managers should ensure that robust processes are in place to fulfil consent requirements for both staff and residents. Please see PHA website for the current care home testing protocol.

How should care homes monitor their staff doing LFD tests?

When staff register rapid lateral flow self-tests, managers will not automatically receive a copy of staff results by email or text. Managers must request this information from their staff directly. Make sure you have set up a system for staff to share their test results with you. Once you have set up a system for results to be shared, make sure all staff are aware of the expectations for sharing their results.

Individuals who have a positive PCR should not be tested again with PCR for 90 days unless they develop symptoms.

Regular asymptomatic PCR testing following a positive test result

Individuals who have had COVID-19 confirmed by either PCR, or LFD test should not re-commence regular asymptomatic PCR testing for 90 days after the positive test. Nor should they have a PCR test should they be identified as a close contact unless they have new symptoms of COVID-19. PCR testing is very sensitive and can detect viral fragments long after the infection has been cleared and the individual is no longer infectious.

Regular asymptomatic lateral flow testing following a positive test result

Regular asymptomatic testing using lateral flow tests should recommence three weeks after the date of the positive test.

Those with a positive LFD test 21 days after the date of their last positive test should be considered a new infection and follow the isolation requirements for confirmed cases of COVID-19.

Testing in individuals who are positive for SARS-COV-2 on a Lateral Flow test

Is a confirmatory PCR needed?

No.

If you get a positive lateral flow test result, you do not need to confirm the result with a PCR test unless one of the following apply:

- you are asked to book a PCR test by contact tracing, public health or your doctor or clinical team
- you're asked to do so as part of research
- you are a fully vaccinated traveller and have a positive lateral flow test on or before day two of arriving in NI from outside the UK
- you are eligible for new COVID-19 treatments because you have one of the conditions that put you at the very highest risk of serious illness should you catch COVID

These conditions include Down's Syndrome, blood cancer, severe liver and kidney disease, severe immunodeficiency, HIV or you are receiving certain cancer treatments.

More information is available at:

- Treatments for coronavirus (COVID-19) | nidirect

If you are in doubt, or think you are eligible, you should book a PCR test as soon as possible.

For most people a PCR test is no longer needed to confirm that the results of a positive LFD test is accurate. This guidance issued on 5th January and supersedes advice on confirmatory PCRs in the letter on 31 December to care homes.

Note: this only related to individuals who have tested positive with LFD. Separate advice is provided for those who are close contacts of a case.

If a staff member has a positive LFD test result (and starts isolation) and then develop symptoms a few days into isolation period – do they need a confirmatory PCR?

Not unless one of the reasons for booking a confirmatory PCR set out above apply. It is assumed that if you have a positive LFD test, you have COVID-19. This does not need confirmed by a PCR test. If symptoms are severe or you are worried contact your GP for further advice and assessment.

If an individual has been isolating after a positive COVID-19 test, but their LFD tests are still positive at day 6 or 7 - what should they do?

Guidance for Care homes issued on 24 January 2022 from the PHA and RQIA should be followed.

Individuals, including health and social care workers, who have tested positive can take an LFD from the 5th day of their isolation period, and another LFD test on the following day. The second LFD test should be taken at least 24 hours after the first. If both LFD results are negative, they may end their self-isolation after the second negative LFD result provided they do not have any symptoms.

The staff member should continue to undertake daily LFTs for the remaining days of the isolation period. For example, if the first LFT was taken on the fifth day, and the second LFT was taken on the sixth day, they should continue to take LFTs on day 7, 8, 9 and 10. If the first LFT was taken on the seventh day and the second LFT was taken on the eighth day, they should continue to take LFTs on day 9 and 10.

Staff should not take an LFD before the 5th day of their isolation period and should only end their self-isolation following 2 consecutive negative LFD tests (which should be taken at least 24 hours apart).

What if the LFDs are still positive at day 10?

The likelihood of a positive LFD in the absence of symptoms after 10 days is very low. If the staff member's LFD result is still positive on the 10th day, they should continue to take daily LFDs, and should not return to work until a single negative LFD result is received.

The likelihood of a person who is well, being infectious after 14 days is considerably lower. If the staff member's LFT test result is still positive on the 14th day, they can stop testing and return to work on day 15. If the staff member works with patients or residents who are especially vulnerable to COVID-19 (as determined by the care home), a risk assessment should be undertaken.

When can a staff member return to work after a positive result?

Health and social care workers who have tested positive may return to work after completing a minimum of 5 days isolation provided they have two negative LFD results at least 24 hours apart as described in guidance (24 January 2022) AND have no COVID-19 symptoms.

What if an agency staff member becomes positive? Who do they need to tell?

The agency staff member should isolate immediately, register their positive result if it was a LFD test and inform their agency.

The Agency should inform any care homes that the individual may have worked in during the previous 2 days to inform local risk assessment. The agency should also inform relevant care homes to make arrangements for other staff to fill gaps in imminent planned shifts where possible.

If the agency staff member cannot contact their agency (or if it is at a weekend/out of hours) – they should proactively contact any homes they have worked in during last 2 days.

How do I work out isolation periods?

The date that you first experienced COVID-19 symptoms OR the date your test (PCR or LFD) for COVID-19 was taken if you have no symptoms is day zero
Day 1 of the isolation period begins the next day and continues up to and including day 5 or 10 – whichever is applicable

Testing for staff who are close contacts of a case of COVID-19

If a staff member is a close contact of a positive COVID-19 case – can they return to work?

Any staff member who is fully vaccinated (refer to annex a in letter of 31 December 2021 for those who don't have their booster) and a close contact of a positive case should isolate and get a PCR ASAP (ref annex a for risk assessment re isolation if workforce challenges staffing).

If a fully vaccinated staff member has had a positive PCR test for COVID-19 within the previous 90 days, they should not have a PCR test unless they develop new symptoms. Instead they should take an LFD test as soon as possible.

If the PCR is negative they can return to work as long as they remain asymptomatic and take daily LFD tests until 10 days following the date of their last contact. If they develop symptoms or positive PCR they should isolate for minimum of 5 days and complete LFD testing to exit isolation in line with guidance.

Note – if the close contact is in the same household and has ongoing contact with the case, a risk assessment as per annex a should take place.

If the staff member is not vaccinated and is a close contact, they should isolate for 10 days.

If an unvaccinated member of staff is isolating after being a close contact (household or otherwise) and during their 10 day's isolation another family member becomes positive. Does the staff member restart their isolation period?

Situations such as this need individual risk assessment to ascertain the nature of the individual's exposure – both prior to commencing isolation and any potential exposure to the positive household member during the isolation period.

Contact the PHA health protection duty room for advice
Health Protection Duty Room on Tel: 0300 555 0119 (Mon-Fri 9am-5pm).
For non-urgent communication only, email: PHA.DutyRoom@hscni.net
During evenings, weekends and bank/public holidays, you should contact the first on call Public Health Doctor via ambulance control on 028 9040 4045.

Symptomatic testing

To date LFD test have only been used for asymptomatic testing. If there are any potential delays in PCR results, can care homes use LFDs to test symptomatic residents?

No, but this will be kept under review. If a resident is symptomatic – they should be supported to isolate and a PCR performed and processed in pillar 1. Follow PHA duty room advice to complete whole home testing.

Inconsistent test results

What do I do if a staff member LFD test results have flipped from positive to negative and positive again.

All positive tests must be acted on. If an individual has returned a positive LFD test at any stage– this is an indication of a high viral load in the nose and throat which carries the risk of infecting others. This should not be ignored even if a subsequent test is negative. The individual should isolate and complete testing as outlined in CMO Circular HSS (MD) 91/2021 (guidance for HCWs) issued on 31st December 2021.

If there are inconsistencies in test result, firstly ensure that the testing technique is correct. Ensure that the individual has read the test instructions and direct to online video resources. A supervised test may also be offered.

Check if there are any similar issues with other individuals in the home – if there is a pattern or cluster of unusual test results there may be a problem with the batch of test kits. Please contact 119 to report any issues with the tests in the first instance.

Note that no test or process is 100% fool proof – there is always a small risk of a false positive or a false negative result.

If an individual staff member has a positive LFD test and is isolating and subsequently returns a negative PCR result as part of their weekly testing routine (in the event that they have used a postal return kit and tested at home) – can they return to work? Similarly for residents who are completing LFD tests after a visit out of the home and have a positive LFD result but a negative PCR in their monthly test – what are the implications for their isolation?

High levels of community transmission make the risk of false positive LFD tests low. Therefore anyone with a positive LFD should isolate for the required period.

What should I do if I get a void or unclear LFD test?

Firstly repeat the test, ensuring that testing technique is correct. Refer to test instructions and on-line resources as required. A supervised test may also be offered. See here for instructions on using SureScreen tests

If the individual is confident that testing technique is correct and a second void result is returned there may be a problem with the batch of test kits. Please contact 119 to report any issues with the tests in the first instance.

Check if there are any similar issues with other individuals in the home – if there is a pattern or cluster of void test results there may be a problem with the batch of test kits. Please contact 119 to report any issues with the tests.

Regular asymptomatic and outbreak testing

Should regular PCR testing continue during an outbreak?

Yes, regular PCR testing should continue in care homes. This should be done once per week for staff, care partners and any agency staff on a block booking and every 28 days for residents

Can we use LFD tests in outbreak or Whole Home Testing (WHT)?

No, WHT and outbreak testing should be undertaken with PCR tests as per existing arrangements.

Others visiting the care home

What is the testing protocol for HSC Trust staff or GPs/other primary care professionals visiting care homes?

Visiting professionals to care homes should undertake a lateral flow test before visiting a care home (1 LFD test per day). All tests results should be registered add link.

What about visitors?

Visitors should be provided with packs of 7 LFD tests and should be encouraged to test at least twice weekly in addition to prior to visiting the care home. Visitors should be encouraged to register their result using the care home unique identification number (UON). As testing is done in the visitor's own home, ensure that they have a record of the care home UON to enable them to link their test to the care home when registering the result.

Care partners

Similar to care home staff, care partners should continue to participate in the care home asymptomatic testing programme and take a weekly PCR. In addition care partners should also take a LFD test before each visit to the care home. Care partners are asked to use the packs of 7 LFD tests.

Testing before discharge

What tests do residents need before being discharged from hospital?

In advance (48 hours) of hospital discharge to a care home the patient must be tested for COVID-19 using PCR (or equivalent such as Nucleic Acid Amplification Test (NAAT) test). Cepheid tests should not be used for this purpose.

If available, a LumiraDx test should also be performed on day of discharge to a care home.

Whilst every effort should be made to ensure that a PCR test is done 48 hours in advance, discharge should not be delayed while awaiting a PCR result - the result of a LumiraDX test may be used instead. LumiraDx is a 'rule out' test and any positive result from a LumiraDX test should always be confirmed by PCR prior to hospital discharge.

Discharge planning should take account of the results of the pre-discharge test.

Technical and practical questions about LFD tests

How effective are LFDs at picking up people with COVID-19?

Lateral Flow Devices are able to detect the Omicron Variant of Concern

- LFD tests have shown themselves to be a very effective and reliable public health tool in stopping spread of the virus
- The LFDs used in the national testing programme are routinely evaluated to detect early signals of changes in performance with emerging variants.
- The latest data published by the UK Health Security Agency shows the most widely used LFDs are effective at detecting the Omicron variant– now the most widely transmitted strain of COVID-19.
- Initial data from lab studies indicates a comparable sensitivity of LFDs to that observed for previous strains of SARS-CoV-2 including Delta.
- Adverse incidents such as suspected false negative LFD results can be reported to the MHRA Yellow Card scheme where this information will be collated and can be used to identify previously unknown safety issues.

Are the packs of 25 LFD tests more accurate than 7s?

No, the only difference is the number of swabs, extraction tubes, extraction buffer volumes and test cartridges. The method of swabbing may also vary depending on the type of test used, for example, some tests use a nasal swab only method.

Do staff need to be 'trained' to use the packs of 25 tests?

It depends on the type of tests being used. Care homes should ensure that they are familiar with any training requirements associated with the tests being used in their care home. Please contact Wendy Thornton in the PHA if you have any questions about LFD training needs Wendy.thornton@hscni.net

From 12th January, care homes are able to order supplies of larger packs of LFD tests for staff. In the first instance, packs of 25 SureScreen LFD tests will be issued, however, please note that suppliers may change in the future. Care homes should ensure that staff are familiar with the instructions for use associated with the tests being used in their care home.

SureScreen tests should be only be used by staff at this time (visitors, and care partners should use packs of Innova 7's).

All staff (registered nurses, care assistants and support staff) will be offered ECHO training sessions but it is not a requirement for the SureScreen tests. On line resources will also be available on the PHA website to support implementation.

- Instruction for use leaflet
- Video on how to take a SureScreen Test https://m.youtube.com/watch?v=uoAGBHFXxqk
- Personal Information redacted by the USI Tel: Personal Information redacted by the USI
- Free phone 119 / Personal Information redacted by the USI

7s or 25s - Who should use what type of LFD test?

The most important thing is to ensure that everyone is testing using LFDs kits in line with care home testing policy and registering every result. The available types of test may change over the next few months but as of January 2022:

- All staff should use packs of SureScreen tests (25 per pack) – this includes registered staff, care assistants and all other support staff. Staff should also continue to participate in weekly PCR testing.

- Staff may also support residents to test using LFDs after any trips out of the care home. Residents should use packs of 7s Innova LFD tests.

- Care partners and visitors should continue using packs of 7s. Care partners should also continue to participate in weekly PCR testing.

- Agency staff should normally use packs of 7's but if attached to a care home for an extended period of time, the home may wish to issue them with a pack of 25 tests

Supported living

Can supported living facilities order LFD tests for their staff?

Not yet but the logistics are being planned to facilitate this. Further information will be shared to the sector in the coming weeks. In the meantime staff can obtain LFDs from the online ordering site or from local pharmacies.

Testing and HCAIs

No outbreak

Patients

Patient has point of care test (Lumira/LIAT) in ED

Patient has PCR on arrival in the ward or within 24 hours if still in ED.

Patient tested every 5 days

Healthcare Workers

Regular testing twice a week of asymptomatic workers using LFTs or LAMP

HCAI Outbreak

Assumes outbreak control team (OCT) convened

The need for enhanced testing is a standing agenda item and outcome of discussion recorded*.

Outbreak confirmed :

All staff and patients in ward are PCR tested and then proceed to

Daily testing of close contacts using LAMP (Mon to Friday if available and LFTs at weekend) or LFTs or daily PCRs. Daily PCRs instead of LFDs **may only be considered following discussion with local testing laboratory and is dependent on laboratory capacity**.

Daily testing of staff using LAMP (Mon to Friday if available with LFTs at weekend) or LFTs.

*In choosing which form testing should take, OCT need to consider and discuss with local laboratory local PCR testing capacity, turnaround time for results and how results are incorporated into patients notes.

FINAL 24th January 2022

HSC Public Health Agency

12-22 Linenhall Street
Belfast
BT2 8BS

Email: Personal Information redacted by the USI
www.publichealth.hscni.net

Via email only

To: Chief Executives of the 6 Trusts

24 January 2021

Dear Colleagues,

Testing to reduce HCAI

I wrote to you on the 24th December 2021 regarding the risk of increased HCAIs as a result of Omicron. Northern Ireland is now averaging 10-12 new COVID HCAIs/day. In response to this we have developed a new testing protocol to be followed for regular testing of inpatients and healthcare workers and during an outbreak. In the event of a HCAI outbreak on a ward, following one round of PCR testing there is now a requirement to do daily testing of staff and patients using Lamp or Lateral Flow tests and results of patient daily testing should be entered into the clinical notes. The results of staff testing should be recorded in the same way as applies to regular testing. A copy of the new HCAI testing protocol is attached.

I would appreciate if this new testing protocol could be introduced with immediate effect.

Yours sincerely

Personal information redacted by USI

Dr Brid Farrell
Deputy Director of Public Health
Public Health Agency

ENC

CC: Trust Medical Directors
Trust Directors of Nursing
Dr Lourda Geohegan, DCMO
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HCAI working group

COVID-19 rapid guideline: Managing COVID-19

Main editor
NICE

Publishing, version history and subscription
20.0 published on 27.01.2022

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The National Institute for Health and Care Excellence (NICE)

Contact

Sections

Summary of recommendations

1. How to use this guideline

2. Introduction

3. Definition of disease severity

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 NHS every mind matters 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 Health Security Agency's stay at home: guidance for households with possible or confirmed coronavirus (COVID-19) infection and the UK government 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 Health Security Agency's stay at home: guidance for households with possible or confirmed coronavirus (COVID-19) infection
- 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 in primary and community care settings, to assess the severity of illness and detect early deterioration, use:

- NHS England's guide to pulse oximetry in people 18 years and over with COVID-19
- oxygen saturation levels below 91% in room air at rest in children and young people (17 years and under) with COVID-19.

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 judgement 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
- national guidance presented by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists
- advice on decision making under pandemic conditions by the Intensive Care Society, and
- advice on decision making and consent from the General Medical Council

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).

Remark:
Tools such as the British Medical Journal emergency care and resuscitation plan may be useful when making decisions about a treatment plan.

Consensus recommendation

Discuss treatment escalation with a multidisciplinary team of medical and allied health professional colleagues (such as from critical care, respiratory medicine, geriatric medicine and palliative care) when there is uncertainty about treatment escalation decisions.

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

Before escalating respiratory or other organ support, identify agreed treatment goals with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate). 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). Ensure this includes management plans for when there is further deterioration or no response to treatment.

Do not continue respiratory or other organ support if 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).

6.2.3 Delivering services in critical care and respiratory support units

Consensus recommendation

Trusts should review:

- their strategy on management for people who are deteriorating and
- use of the track-and-trigger system (NEWS2 has been endorsed by NHS England and Improvement).

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.

6.2.4 Non-invasive respiratory support

Info Box

Definitions

High-flow nasal oxygen (HFNO): involves the delivery of warm and humidified oxygen (up to 60 litres per minute) through a small nasal cannula. The delivered flow is higher than the flow of air when the person is breathing in (inspiratory flow). HFNO can also deliver a higher concentration of oxygen than supplemental oxygen alone.

Continuous positive airway pressure (CPAP): is a type of positive airway pressure that delivers a set pressure of airflow to the airways. This pressure is maintained throughout the respiratory cycle, both when the person is breathing in (inspiration) and breathing out (expiration). A CPAP device consists of a unit that generates airflow, which is delivered to the airway through a tight-fitting mask or other airtight interface.

Non-invasive ventilation (NIV): refers to a mode of positive pressure ventilation that delivers airflow to the airways through a tight-fitting mask or other airtight interface. Airflow is delivered at variable pressures that are higher than when the person is breathing in (inspiratory pressure) and lower than when the person is breathing out (expiratory pressure).

Non-invasive respiratory support: is a broad umbrella term for different types of non-invasive respiratory support, such as HFNO, CPAP and NIV. They are considered to be a more intensive intervention than oxygen therapy alone. The different types of support are not, however, interchangeable with each other because they have differing effects on a person's physiology. So, they typically have different indications for their use.

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'.

Info Box

For information on deciding when to escalate and de-escalate treatment, see the sections on deciding when to escalate treatment and escalating and de-escalating treatment. Also, consider factors such as:

- how much supplemental oxygen is needed to reach target oxygen saturation
- the overall clinical trajectory
- assessment of work of breathing
- how well treatment will be tolerated
- treatment preferences after discussion with the person, and their family and carers when appropriate.

Remark:
The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

Info Box

For information on how to manage COVID-19 in people who are having non-invasive respiratory support, see the sections on management and therapeutics for COVID-19.

Consensus recommendation

Ensure that pharmacological and non-pharmacological management strategies, including body positioning, are optimised before escalating treatment to non-invasive respiratory support.

Remark:
The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

Conditional recommendation against

Do not routinely offer high-flow nasal oxygen as the main form of respiratory support for people with COVID-19 and respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.

Conditional recommendation

Consider offering continuous positive airway pressure (CPAP) to people with COVID-19 when:

- they have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, **and**
- escalation to invasive mechanical ventilation would be an option but it is not immediately needed, **or**
- it is agreed that respiratory support should not be escalated beyond CPAP.

Remark:
In June 2021, the Medicines and Healthcare products Regulatory Agency issued a National Patient Safety Alert for Philips ventilator, CPAP and bilevel positive airway pressure devices because of a potential for harm from inhaled particles and volatile organic compounds. This applies to all devices manufactured before 26 April 2021.

For information on decision making and giving advice, see the British Thoracic Society risk stratification guidance on Philips ventilator, CPAP and bilevel positive airway pressure devices.

Consensus recommendation

For people with COVID-19 having continuous positive airway pressure, ensure:

- there is access to critical care providers for advice, review and prompt escalation of treatment if needed (such as when treatment has failed)
- regular review by an appropriate senior clinician (such as every 12 hours) and more frequent review if needed, in line with the British Thoracic Society guidance on respiratory support units and the Faculty of Intensive Care Medicine guidelines on the provision of intensive care services
- regular assessment and management of symptoms alongside non-invasive respiratory support.

Remark:
Staff caring for people with COVID-19 having CPAP should have appropriate skills and competencies and provide appropriate monitoring. For further information on standards of care and provision of services see the Faculty of Intensive Care Medicine and Intensive Care Society guidelines on the provision of intensive care services and the British Thoracic Society and Intensive Care Society guidance on development and implementation of respiratory support units.

Consensus recommendation

Consider using high-flow nasal oxygen for people having continuous positive airway pressure (CPAP) when they need:

- a break from CPAP, such as at mealtimes
- humidified oxygen
- weaning from CPAP.

7. Therapeutics for COVID-19

7.1 Neutralising monoclonal antibodies - for people not in hospital

Recommended New

Offer a neutralising monoclonal antibody (sotrovimab, or combination casirivimab plus imdevimab) for people aged 12 and over with COVID-19 who:

- are not in hospital, and
- are thought to be at high risk of progression to severe COVID-19. (NHS England's Interim Clinical Commissioning Policy provides a list of people at high-risk prioritised for access to neutralising monoclonal antibodies).

Be aware that the choice of neutralising monoclonal antibody may depend on availability as well as contextual factors (for example, emerging data on effectiveness of different antibodies against different SARS-CoV-2 variants).

Remark:
In vitro data suggests that the efficacy of casirivimab plus imdevimab is likely to be compromised against the Omicron (B.1.1.529) variant. NICE will review and update this recommendation as further evidence emerges.

The Interim Clinical Commissioning Policy published in December 2021 outlines the neutralising monoclonal antibodies with current UK access and details the risk factors and criteria to be used to guide treatment in people who are not in hospital. The policy states that patients must meet all the eligibility criteria and none of the exclusion criteria to have neutralising monoclonal antibodies.

7.2 Corticosteroids

Recommended

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.

Conditional recommendation against

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 Casirivimab and imdevimab - for people hospitalised because of COVID-19

Recommended

Offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative).

Remark:
This recommendation is informed by the results of the RECOVERY trial, which recruited people between 18 September 2020 and 22 May 2021. This was before the emergence of the Omicron (B.1.1.529) variant. In vitro data suggests that the efficacy of casirivimab and imdevimab is likely to be compromised against this variant. NICE will review and update this recommendation as further evidence emerges.

The criteria for accessing neutralising monoclonal antibodies (nMABs) for people hospitalised in the UK, and dosage to be used, are outlined in NHS England's Interim Clinical Commissioning Policy on neutralising monoclonal antibodies and intravenous antivirals in the treatment of COVID-19 in hospitalised patients, published in December 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given neutralising monoclonal antibodies.

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Not recommended

Do not offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19:

- who have detectable SARS-CoV-2 antibodies (seropositive), or
- whose serostatus is unknown.

Remark:
This recommendation is informed by the results of the RECOVERY trial, which recruited people between 18 September 2020 and 22 May 2021. This was before the emergence of the Omicron (B.1.1.529) variant. In vitro data suggests that the efficacy of casirivimab and imdevimab is likely to be compromised against this variant. NICE will review and update this recommendation as further evidence emerges.

The criteria for accessing neutralising monoclonal antibodies (nMABS) for people hospitalised in the UK, and dosage to be used, are outlined in NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 (aged 12 years and above, published in December 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given neutralising monoclonal antibodies.

7.4 Remdesivir

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'.

Low-flow oxygen supplementation: oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.

Conditional recommendation

Consider remdesivir for up to 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, in hospital and needing low-flow supplemental oxygen.

Remark:
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), which was updated in June 2021 to include eligibility criteria for remdesivir in people who are significantly immunocompromised.

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

The marketing authorisation for remdesivir for COVID-19 does not include children under 12 years or weighing less than 40 kg.

Only in research settings

Do not use remdesivir for COVID-19 pneumonia in adults, young people and children in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of a clinical trial.

7.5 Tocilizumab

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'.

Recommended

Offer tocilizumab to adults in hospital with COVID-19 if all 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:

- 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 October 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

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.

7.6 Sarilumab

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'.

Conditional recommendation

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

- 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 October 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.

7.7 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.

7.9 Antibiotics

Info Box

Antibiotics should not be used for preventing or treating COVID-19 unless there is clinical suspicion of additional bacterial co-infection. See the section on suspected or confirmed co-infection.

See also the recommendations on azithromycin and doxycycline in the section on therapeutics for COVID-19.

7.10 Azithromycin

Not recommended

Do not use azithromycin to treat COVID-19.

7.11 Budesonide (inhaled)

Only in research settings

Only use budesonide to treat COVID-19 as part of a clinical trial.

Remark:
People already on budesonide for conditions other than COVID-19 should continue treatment if they test positive for COVID-19.

7.12 Colchicine

Not recommended

Do not use colchicine to treat COVID-19.

7.13 Doxycycline

Not recommended

Do not use doxycycline to treat COVID-19 in the community.

7.14 Ivermectin

Only in research settings

Do not use ivermectin to treat COVID-19 except as part of a clinical trial.

7.15 Ongoing review of therapeutics for COVID-19

Info Box

We are currently reviewing new and existing therapeutics for treating COVID-19 as part of a living guidelines approach. New and updated recommendations will be published for this guideline as they become available (see Update information | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE).

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 the NICE guideline on intravenous fluid therapy in children and young people in hospital.

For information on managing renal replacement therapy for adults who are critically unwell with COVID-19, see the Renal Association's guidelines on renal replacement therapy for critically unwell adults.

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: 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: 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.

Standard prophylactic dose: the prophylactic dose of a low molecular weight heparin (LMWH), as listed in the medicine's summary of product characteristics, for medical patients.

Intermediate dose: double the standard prophylactic dose of an LMWH for medical patients.

A treatment dose: 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.

Remark:
The Department of Health VTE risk assessment tool is commonly used to develop treatment plans.

Recommended

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

See the NICE recommendation on low molecular weight heparin self-administration.

Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances.

Remark:
For people with COVID-19 who do not need low-flow oxygen, follow the recommendations in NICE's guideline on venous thromboembolism in over 16s.

In August 2021, using 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.

Only in research settings

Only offer an intermediate or treatment dose of a low molecular weight heparin to young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation as part of a clinical trial.

Consensus recommendation

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

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

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 low molecular weight heparins.

Consensus recommendation

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

8.3.1.1 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.

8.3.2 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.

8.3.3 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.

9. Identifying and managing co-infections

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).

9.1 Bacterial pneumonia

9.1.1 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.

9.1.2 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.

9.1.3 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.

9.1.4 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.

9.1.5 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.

9.2 COVID-19-associated pulmonary aspergillosis (CAPA)

Info Box New

For people who are critically ill and have, or have had, COVID-19 as part of their acute illness:

- CAPA is a recognised cause of someone's condition not improving despite treatment (for example, antibiotic therapy, ventilatory support)
- there are no specific combinations of signs or symptoms for diagnosing CAPA
- the risk of having CAPA may increase with age and chronic lung disease.

9.2.1 Diagnosing CAPA

Consensus recommendation

When deciding whether to suspect CAPA in someone who is critically ill and has, or has had, COVID-19 as part of their acute illness:

- base your decisions on individual risk factors and the person's clinical condition
- involve a multidisciplinary team, including infection specialists
- refer to local protocols on diagnosing and managing CAPA.

Remark:
Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

Not recommended

Do not do diagnostic tests for CAPA if there is low clinical suspicion of the condition.

Recommended

When investigating suspected CAPA:

- use a range of tests to increase the likelihood of making a confident diagnosis
- if possible, include bronchoalveolar lavage (BAL) as part of diagnostic testing, taking into account the risks of BAL in relation to the person's clinical condition
- discuss the diagnostic testing strategy and final diagnosis with a multidisciplinary team that includes infection specialists.

Consensus recommendation

Test for antifungal resistance if an Aspergillus isolate is cultured from a CAPA test sample.

Consensus recommendation

Commissioners and local trusts should ensure that results of diagnostic tests for CAPA are available in a timeframe that informs and supports clinical decision making.

Consensus recommendation

Monitor and report testing for, and diagnosis and management of, CAPA in line with local protocols.

Remark:
Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

9.2.2 Treating CAPA

Consensus recommendation

Only use antifungal treatments to treat CAPA if:

- diagnostic investigations support a diagnosis of CAPA or
- the results of diagnostic investigations are not available yet, but CAPA is suspected, and a multidisciplinary team or local protocols support starting treatment.

Remark:
See NICE's recommendations on diagnosing CAPA.

Recommended

When considering antifungal treatment for CAPA:

- discuss treatment options with a multidisciplinary team that includes infection specialists
- follow local protocols that include best practice guidance on treating invasive aspergillosis.

Remark:
There is not enough evidence to recommend specific antifungal treatments for CAPA.

The panel noted the importance of national antifungal stewardship guidance, such as NICE's guideline on antimicrobial stewardship.

Consensus recommendation

For people having antifungal treatment for suspected CAPA, stop treatment if the results of investigations do not support a diagnosis of CAPA and a multidisciplinary team agrees.

10. Discharge, follow up and rehabilitation

Info Box

NICE is monitoring evidence on follow up, discharge and rehabilitation. 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.

11. Palliative care

11.1 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.

11.2 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.

12. 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

Is high-flow nasal oxygen effective in reducing breathlessness compared with standard care or conventional oxygen therapy for people in hospital with COVID-19 and respiratory failure when it is agreed that treatment will not be escalated beyond non-invasive respiratory support or palliative care is needed?

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

P: adults over 18 years with COVID-19 having treatment for respiratory failure

I: high-flow nasal oxygen

C:

- standard care
- conventional oxygen therapy

O:

- patient experience
- symptom improvement
- frequency of coughing
- assessment of breathing pattern disorder
- impact of breathlessness on activities of daily living such as eating, drinking and movement
- recovery of sense of smell
- practicalities of maintaining high-flow nasal oxygen at home for patients who wish their end of life care to occur at home.

Subgroups: palliative care

Does a multidisciplinary team agreed approach to weaning from continuous positive airway pressure improve weaning times and result in stopping continuous positive airway pressure for people with COVID-19 and acute respiratory failure?

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

P: people with COVID-19 having continuous positive airway pressure for respiratory support

I: multidisciplinary team agreed approach to weaning

C:

- standard care
- different multidisciplinary team approaches

O:

- patient experience
- symptom improvement
- length of time to wean

What is the effectiveness, cost effectiveness and safety of using a combination of casirivimab and imdevimab at doses other than 8 g for treating COVID-19?

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

P: people hospitalised because of COVID-19

I: treatment with different doses of casirivimab and imdevimab

C:

- recommended dose against different doses
- standard care against recommended dose and/or different doses

O:

- mortality
- progression to invasive mechanical ventilation
- progression to non-invasive respiratory support
- duration of hospitalisation
- adverse events
- costs of treatment
- health-related quality of life

What is the effectiveness, cost effectiveness and safety of the combination of casirivimab and imdevimab for treating COVID-19 in people with particular clinical characteristics (for example, people who are seropositive, of unknown serostatus, immunocompromised, or with specific comorbidities and within both the seropositive and seronegative groups, according to vaccination status or history of natural infection)?

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

P: people hospitalised because of COVID-19

I: treatment with a combination of casirivimab and imdevimab

C:

- treatment in people with different clinical characteristics (for example, people who are seropositive, of unknown serostatus, immunocompromised, or with specific comorbidities and within both the seropositive and seronegative groups, according to vaccination status or history of natural infection)

O:

- mortality
- progression to invasive mechanical ventilation
- progression to non-invasive respiratory support
- duration of hospitalisation
- adverse events
- costs of treatment
- health-related quality of life

What is the clinical and cost effectiveness of budesonide for treating COVID-19 in the community in adults, young people and children?

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

P: Adults, young people and children who have COVID-19 and are not in hospital

Subgroups of particular interest:

- People 18 to 49 years
- Children and young people

I: Inhaled budesonide

C: Inhaled placebo (to accommodate blinding)

O:

- All-cause mortality
- Hospitalisation
- Need for oxygen therapy (including thresholds for this decision)
- Costs of treatment
- Time to recovery
- Health-related quality of life
- Adverse events

What risk factors in people who are critically ill and have, or have had, COVID-19 as part of their acute illness are associated with developing COVID-19-associated pulmonary aspergillosis (CAPA)?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness. Subgroups of particular interest include children and young people, and pregnant women.

Exposure: any

Outcomes:

- association of CAPA with individual factors (for example, age, sex, ethnicity, comorbidities, COVID-19 vaccination status,)
- association of CAPA with COVID-19 treatments (for example, respiratory support for COVID-19, high-dose corticosteroids, interleukin-6 inhibition)
- association of CAPA with length of stay in hospital

What are the possible outcomes for people who are critically ill and have COVID-19-associated pulmonary aspergillosis (CAPA)?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and who have CAPA. Subgroups of particular interest: young people and children, pregnant women, ethnicity, immunosuppression and subgroups who have higher rates of COVID-19

Outcomes:

- presence of fungal serum biomarkers (for example galactomannan and beta-D-glucan)
- measures of inflammation (for example C-reactive protein)
- need for respiratory support (for example, invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
- hospitalisation metrics (for example, mortality, length of hospital stay, admission to and length of stay in intensive care)
- long-term morbidity outcomes, functional measures and patient outcomes
- results may be stratified (for example, disease severity, use of ECMO)

In people with suspected COVID-19-associated pulmonary aspergillosis (CAPA), what are the most accurate tests for diagnosing the infection and when should they be done?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and suspected CAPA. Subgroups of particular interest include young people and children, and pregnant women.

Diagnostic tests:

- any methods used to diagnose pulmonary aspergillosis (for example, CT imaging, testing of bronchoalveolar lavage, non-bronchoscopic lavage, endotracheal aspirate, sputum samples, serum assays)

Reference standard:

- lung biopsy or postmortem diagnosis

Target condition:

- CAPA

Outcomes:

- sensitivity and specificity
- positive and negative likelihood ratios

Analysis:

- optimal time of diagnostic testing

What are the views, preferences and experiences of people with COVID-19-associated pulmonary aspergillosis (CAPA), and their families or carers, on:

- available tests for diagnosing CAPA
- available treatments for CAPA?

Remark:
Suggested PIC (Population, Interest, Context)

P: people who have been diagnosed with and treated for CAPA, and their families or carers. Subgroups of particular interest include young people and children, and pregnant women.

I: tests for diagnosing CAPA and treatments for CAPA

C: people who have been diagnosed with, and had treatment for, CAPA in hospital

What are the clinical and cost effectiveness, and the safety, of specific antifungal treatments for treating suspected or confirmed COVID-19-associated pulmonary aspergillosis (CAPA), and the optimal treatment duration? When should treatment be started, stopped or modified?

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

P: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness and have probable or diagnosed CAPA. Subgroups of particular interest: children and young people, pregnant women, ethnicity, immunosuppression, and subgroups who have higher rates of COVID-19.

I: voriconazole, isavuconazole, liposomal amphotericin B, posaconazole, echinocandins (for example, caspofungin, anidulafungin) and amphotericin B deoxycholate

C: Standard care (usually voriconazole)

O:

- all-cause mortality (at any time during treatment)
- number of people having 1 or more serious adverse events
- number of days without respiratory or organ support (organ support includes use of vasopressors and renal replacement therapy)
- length of stay in intensive care
- number of people having 1 or more adverse events
- treatment duration
- timing of starting treatment
- need for treatment modification
- length of hospital stays
- need for and duration of invasive mechanical ventilation
- need for switching, starting or restarting antifungal treatment

New

What is the effectiveness and safety of neutralising monoclonal antibodies against different SARS-CoV-2 variants?

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

P: people being treated for acute COVID-19 disease and who are not hospitalised with COVID-19

Subgroups of particular interest:

- ethnicity
- children and young people
- pregnant women
- vaccination status
- people with comorbidities
- people who are immunocompromised

I: neutralising monoclonal antibodies

- combination of casirivimab and imdevimab
- sotrovimab
- any neutralising monoclonal antibodies that are granted marketing authorisation in the future

C:

- standard care
- other neutralising monoclonal antibodies

O:

- health-related quality of life
- adverse events
- progression to invasive mechanical ventilation
- progression to non-invasive respiratory support
- hospitalisation and duration of hospitalisation
- mortality

13. Equality considerations

13.1 Equalities impact assessment during scoping - draft scope

13.2 Equalities impact assessment during scoping - final scope

13.3 Equalities impact assessment during guideline development

14. 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.

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

1. Recommendations

Recommendation for (Green)

A strong recommendation is given when there is high-certainty evidence, or lower-certainty evidence paired with consistent panel expertise, showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, patients will want the recommended intervention.

Recommendation against (Red)

A strong recommendation against the intervention is given when there is high-certainty evidence, or lower-certainty evidence paired with important contextual factors, showing that the overall disadvantages of the intervention are clearly greater than the benefits, or that the intervention is not effective. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.

Conditional Recommendation for (Yellow)

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

Conditional Recommendation against (Orange)

A conditional recommendation is given against the intervention when it is judged that the intervention may not be effective, but certainty is low. This recommendation is also used where the intervention is not likely to be effective, but it may be useful in specific settings or populations. Likewise, it is also used when patient preferences vary.

Only in research settings

A recommendation only for research settings is given where there is significant uncertainty about the effectiveness of an intervention, and it is not clear whether the benefits of the intervention are greater than the disadvantages or adverse effects.

Consensus Recommendation (Bluish-Purple)

A consensus recommendation can be given for or against an intervention, or may outline good practice or steps required to support other recommendations. This type of recommendation is used when there is not enough evidence to give an evidence-based recommendation, but the panel still regards it as important to give a recommendation.

2. Supporting information

Click on the recommendation to learn more about the basis of the recommendation. 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 are outlined in the World Health Organization's COVID-19 clinical management living guidance.

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 NHS every mind matters 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 Health Security Agency's stay at home: guidance for households with possible or confirmed coronavirus (COVID-19) infection and the UK government 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 Health Security Agency's stay at home: guidance for households with possible or confirmed coronavirus (COVID-19) infection
- 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 in primary and community care settings, to assess the severity of illness and detect early deterioration, use:

- NHS England's guide to pulse oximetry in people 18 years and over with COVID-19
- oxygen saturation levels below 91% in room air at rest in children and young people (17 years and under) with COVID-19.

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.

Rationale

This recommendation is based on the expert panel's consensus view. The panel agreed that using pulse oximetry to measure oxygen saturation threshold levels is appropriate for helping to identify people with acute COVID-19 in primary or community care, and to predict outcomes such as hospitalisation. NHS England has guidance on pulse oximetry in assessment in adults in the community. The panel agreed that it is appropriate to cross-refer to this guidance for adults but not for children. The panel's recommended oxygen saturation level for children and young people was based on their consensus view that oxygen saturation levels below 91% in room air at rest are appropriate to assess the severity of illness and detect early deterioration in this group.

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 judgement 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

Treatment	Dosage
Delirium and able to swallow: haloperidol tablets	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 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*
- *national guidance presented by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists*
- *advice on decision making under pandemic conditions by the Intensive Care Society, and*
- *advice on decision making and consent from the General Medical Council*

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).

Tools such as the British Medical Journal emergency care and resuscitation plan may be useful when making decisions about a treatment plan.

Consensus recommendation

Discuss treatment escalation with a multidisciplinary team of medical and allied health professional colleagues (such as from critical care, respiratory medicine, geriatric medicine and palliative care) when there is uncertainty about treatment escalation decisions.

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

Before escalating respiratory or other organ support, identify agreed treatment goals with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate). 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). Ensure this includes management plans for when there is further deterioration or no response to treatment.

Do not continue respiratory or other organ support if 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).

6.2.3 Delivering services in critical care and respiratory support units

Consensus recommendation

Trusts should review:

- their strategy on management for people who are deteriorating and
- use of the track-and-trigger system (NEWS2 has been endorsed by NHS England and Improvement).

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.

6.2.4 Non-invasive respiratory support

Info Box

Definitions

High-flow nasal oxygen (HFNO): involves the delivery of warm and humidified oxygen (up to 60 litres per minute) through a small nasal cannula. The delivered flow is higher than the flow of air when the person is breathing in (inspiratory flow). HFNO can also deliver a higher concentration of oxygen than supplemental oxygen alone.

Continuous positive airway pressure (CPAP): is a type of positive airway pressure that delivers a set pressure of airflow to the airways. This pressure is maintained throughout the respiratory cycle, both when the person is breathing in (inspiration) and breathing out (expiration). A CPAP device consists of a unit that generates airflow, which is delivered to the airway through a tight-fitting mask or other airtight interface.

Non-invasive ventilation (NIV): refers to a mode of positive pressure ventilation that delivers airflow to the airways through a tight-fitting mask or other airtight interface. Airflow is delivered at variable pressures that are higher than when the person is breathing in (inspiratory pressure) and lower than when the person is breathing out (expiratory pressure).

Non-invasive respiratory support: is a broad umbrella term for different types of non-invasive respiratory support, such as HFNO, CPAP and NIV. They are considered to be a more intensive intervention than oxygen therapy alone. The different types of support are not, however, interchangeable with each other because they have differing effects on a person's physiology. So, they typically have different indications for their use.

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'.

Info Box

For information on deciding when to escalate and de-escalate treatment, see the sections on deciding when to escalate treatment and escalating and de-escalating treatment. Also, consider factors such as:

- how much supplemental oxygen is needed to reach target oxygen saturation
- the overall clinical trajectory
- assessment of work of breathing
- how well treatment will be tolerated
- treatment preferences after discussion with the person, and their family and carers when appropriate.

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

Info Box

For information on how to manage COVID-19 in people who are having non-invasive respiratory support, see the sections on management and therapeutics for COVID-19.

Consensus recommendation

Ensure that pharmacological and non-pharmacological management strategies, including body positioning, are optimised before escalating treatment to non-invasive respiratory support.

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

Evidence To Decision

Benefits and harms

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

There is no evidence on optimising pharmacological and non-pharmacological management strategies before starting non-invasive respiratory support, but the panel noted that this is an important consideration. They made a consensus recommendation to optimise medical management (including pharmacological and non-pharmacological treatment) before starting non-invasive respiratory support.

Preference and values

Rationale

Based on their experience, the panel highlighted the importance of ensuring that existing management, including body positioning, is optimised before respiratory support is escalated.

Conditional recommendation against

Do not routinely offer high-flow nasal oxygen as the main form of respiratory support for people with COVID-19 and respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

They noted that evidence from the Recovery-RS trial does not show that using high-flow nasal oxygen (HFNO) has any benefits compared with conventional oxygen therapy. They made a recommendation to not routinely offer HFNO as the main form of respiratory support for people with respiratory failure due to COVID-19 in whom escalation to invasive mechanical ventilation would be appropriate.

The panel agreed that the evidence from the Recovery-RS trial shows that using continuous positive airway pressure (CPAP) reduces the number of people who need invasive ventilation and admission to critical care. Evidence from the HENIVOT trial shows that helmet non-invasive ventilation followed by HFNO significantly reduces the number of people who need invasive ventilation compared with HFNO alone. They also noted that evidence from the Recovery-RS trial suggests there is a small increase in the number of serious adverse events with CPAP compared with conventional oxygen therapy. However, they considered that there are uncertainties with the available evidence, including evidence on standard care, staffing ratios, and where people had CPAP and which staff gave it. The panel agreed that these uncertainties warranted a recommendation to consider offering CPAP for people with COVID-19 when they:

- have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 40% to 60%, and
- would be suitable for escalation to invasive mechanical ventilation but it is not immediately needed.

The panel noted that it is important for staff to have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a consensus recommendation to support this.

The panel discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this. The panel agreed not to define treatment failure to allow for individual clinical decision making.

The panel also made a consensus recommendation to optimise medical management (including pharmacological and non-pharmacological treatment) before starting non-invasive respiratory support.

Certainty of the Evidence

Low

The panel were aware that the certainty of the evidence for outcomes in the Recovery-RS trial and HENIVOT trial ranged from moderate to low and low to very low, respectively. They also noted that the Recovery-RS trial is currently only available as a pre-print publication. This means that the results have not been peer reviewed, so the panel interpreted the results with the appropriate caution.

Preference and values

No substantial variability expected

Lay members noted that people with COVID-19 may have different opinions on how acceptable non-invasive respiratory support is. Some people may be apprehensive of its use and others may be willing to accept it as an available treatment option. Patient preferences should be considered in a shared discussion.

The panel agreed that treatment plans, preferences and wishes should be discussed with patients, families and carers before starting non-invasive respiratory support. For this reason, information boxes linking to the existing guideline recommendations on escalation and de-escalation of treatment have been provided. The panel also considered that care of people who will not have care escalated should be supported by provision of an information box linking to existing recommendations on pharmacological and non-pharmacological treatment options.

The panel noted that outcomes, such as symptom control, would be important to people with COVID-19 and should be reported in future trials. The panel proposed to make a research recommendation to explore if high-flow nasal oxygen reduces breathlessness compared with standard care or conventional oxygen therapy to help improve the evidence base in this area.

Resources and other considerations

No important issues with the recommended alternative

The panel considered that using continuous positive airway pressure (CPAP) for people with COVID-19 in appropriate settings outside of the intensive care unit (ICU) has the potential to free up ICU capacity. Avoiding the need for invasive mechanical ventilation may also result in cost savings and avoid adverse outcomes from intubation. However, the panel were mindful that CPAP should be given by staff who have skills and competencies in CPAP and be accompanied by careful review and prompt recognition of when treatment has failed and further treatment escalation is needed.

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

Equity

Important issues, or potential issues not investigated

The scope of this evidence review was limited to adults and so no evidence in children and young people was included.

The panel noted that some people, including those with learning disabilities, dementia or delirium for example, may find it difficult to tolerate non-invasive respiratory support. As such, patient preferences should be considered in a shared discussion with the person and their family or carer.

Acceptability

Important issues, or potential issues not investigated

The panel discussed that some people can find that continuous positive airway pressure (CPAP) is uncomfortable. The panel commented that some people may find it difficult to tolerate non-invasive respiratory support. They noted that using high-flow nasal oxygen would allow people having CPAP to take treatment breaks for mealtimes and when CPAP is being gradually reduced. They made a consensus recommendation to support this. The panel proposed a research recommendation to explore which treatment methods are effective for weaning people with COVID-19 from CPAP and the acceptability and safety of these methods.

Feasibility

Important issues, or potential issues not investigated

Continuous positive airway pressure (CPAP) and high-flow nasal oxygen are established treatments in the NHS. However, the panel advised that context-specific factors influence when CPAP is used, for example staff skills and competencies, staffing ratios and the availability of different CPAP interfaces, so CPAP use may vary in practice.

Rationale

Evidence from a clinical trial does not show that high-flow nasal oxygen has treatment benefits over conventional oxygen therapy for people in whom escalation to invasive mechanical ventilation would be appropriate. So, the panel agreed that it

should not be used as the preferred treatment option in this situation.

The panel acknowledged that although high-flow nasal oxygen should not be offered as the main form of respiratory support routinely, it may be considered when people having continuous positive airway pressure (CPAP) need a break from CPAP, for example at mealtimes, or when they are being weaned from CPAP or when they need humidified oxygen.

Clinical Question/ PICO

Population: People with COVID-19
Intervention: CPAP
Comparator: Conventional oxygen

Summary

Evidence indicates that that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?
Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics
One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Greico 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?
Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of

intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen	**Intervention** CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 30 days	Odds Ratio 0.91 (CI 95% 0.59 — 1.39) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [1]	One study found no statistically significant difference in mortality with CPAP compared with conventional oxygen in people with COVID-19.
Tracheal intubation or mortality 30 days	Odds Ratio 0.67 (CI 95% 0.48 — 0.94) (Randomized controlled)			**Moderate** Due to serious risk of bias [2]	One study found a statistically significant reduction in the composite outcome of tracheal intubation or mortality with CPAP compared with conventional oxygen in people with COVID-19.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen	**Intervention** CPAP		**Plain language summary**
Intubation 30 days	Odds Ratio 0.66 (CI 95% 0.47 — 0.93) (Randomized controlled)			**Moderate** Due to serious risk of bias [3]	One study found a statistically significant reduction in intubation with CPAP compared with conventional oxygen in people with COVID-19.
Median time to intubation	Hazard Ratio 0.67 (CI 95% 0.52 — 0.86) (Randomized controlled)			**Moderate** Due to serious risk of bias [4]	One study found a statistically significant difference in median time to intubation with CPAP compared with conventional oxygen in people with COVID-19.
Admission to critical care	Odds Ratio 0.69 (CI 95% 0.49 — 0.96) (Randomized controlled)			**Moderate** Due to serious risk of bias [5]	One study found a statistically significant reduction in admission to critical care with CPAP compared with conventional oxygen in people with COVID-19.
Mean length of stay in hospital (days)	Lower better (Randomized controlled)	**17.3** days (Mean) Difference:	**16.4** days (Mean) **MD 0.97 fewer** (CI 95% 3.65 fewer — 1.71 more)	**Low** Due to serious risk of bias, Due to serious imprecision [6]	One study found no statistically significant difference in length of hospital stay with CPAP compared with conventional oxygen in people with COVID-19.
Mean length of stay in critical care (days)	Lower better (Randomized controlled)	**9.6** (Mean) Difference:	**9.5** (Mean) **MD 0.33 fewer** (CI 95% 2.44 fewer — 1.78 more)	**Low** Due to serious risk of bias, Due to serious imprecision [7]	One study found no statistically significant difference in length of critical care stay with CPAP compared with conventional oxygen in people with COVID-19.

1. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias,

inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

Clinical Question/ PICO

Population: People with COVID-19
Intervention: HFNO
Comparator: Conventional oxygen

Summary

Evidence indicates that that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?
Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics
One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Greico 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?
Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 30 days	Odds Ratio 0.96 (CI 95% 0.64 — 1.45) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [1]	One study found no statistically significant difference in mortality with HFNO compared with conventional oxygen in people with COVID-19.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Tracheal intubation or mortality 30 days	Odds Ratio 0.95 (CI 95% 0.69 — 1.3) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [2]	One study found no statistically significant difference in the composite outcome of tracheal intubation or mortality with HFNO compared with conventional oxygen in people with COVID-19.
Intubation 30 days	Odds Ratio 0.96 (CI 95% 0.7 — 1.31) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [3]	One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.
Median time to intubation	Hazard Ratio 0.91 (CI 95% 0.72 — 1.14) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [4]	One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.
Admission to critical care	Odds Ratio 1.06 (CI 95% 0.76 — 1.47) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [5]	One study found no statistically significant difference in admission to critical care with HFNO compared with conventional oxygen in people with COVID-19.
Mean length of stay in hospital (days)	Lower better (Randomized controlled)	17.1 (Mean) Difference:	18.3 (Mean) **MD 0.7 more** (CI 95% 1.93 fewer — 3.34 more)	**Low** Due to serious risk of bias, Due to serious imprecision [6]	One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.
Mean length of stay in critical care (days)	Lower better (Randomized controlled)	9.5 (Mean) Difference:	10.5 (Mean) **MD 0.69 more** (CI 95% 1.37 fewer — 2.75 more)	**Low** Due to serious risk of bias, Due to serious imprecision [7]	One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.

1. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias,

inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crossed line of no effect. **Publication bias: no serious.**
3. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
4. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
5. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

Clinical Question/ PICO

Population: People with COVID-19
Intervention: Helmet non-invasive ventilation followed by HFNO
Comparator: HFNO

Summary

Evidence indicates that that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?
Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics
One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Greico 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?
Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Helmet non-invasive ventilation following by HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality at 28 days	Relative risk 0.81 (CI 95% 0.35 — 1.91) Based on data from 109 participants in 1 studies. [1] (Randomized controlled)	182 per 1000 Difference:	147 per 1000 **35 fewer per 1000** (CI 95% 118 fewer — 166 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [2]	One study found no statistically significant difference in mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Mortality at 60 days	Relative risk 1.1 (CI 95% 0.55 — 2.2) Based on data from 109 participants in 1 studies. [3] (Randomized controlled)	218 per 1000 Difference:	240 per 1000 **22 more per 1000** (CI 95% 98 fewer — 262 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [4]	One study found no statistically significant difference in mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
In-hospital mortality	Relative risk 0.95 (CI 95% 0.49 — 1.82) Based on data from 109 participants in 1 studies. [5] (Randomized controlled)	255 per 1000 Difference:	242 per 1000 **13 fewer per 1000** (CI 95% 130 fewer — 209 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [6]	One study found no statistically significant difference in in-hospital mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
In–intensive care unit mortality	Relative risk 0.8 (CI 95% 0.4 — 1.6) Based on data from 109 participants in 1 studies. [7] (Randomized controlled)	255 per 1000 Difference:	204 per 1000 **51 fewer per 1000** (CI 95% 153 fewer — 153 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [8]	One study found no statistically significant difference in intensive care mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Intubation within 28 days from enrolment	Relative risk 0.58 (CI 95% 0.36 — 0.95) Based on data from 109 participants in 1 studies. [9] (Randomized controlled)	509 per 1000 Difference:	295 per 1000 **214 fewer per 1000** (CI 95% 326 fewer — 25 fewer)	Low Due to serious risk of bias, due to serious indirectness [10]	One study found a statistically significant reduction in intubation with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Intubation within 28 days from enrolment after adjudication of	Relative risk 0.55 (CI 95% 0.33 — 0.9) Based on data from 109 participants in 1 studies. [11] (Randomized controlled)	509 per 1000 Difference:	280 per 1000 **229 fewer per 1000**	Low Due to serious risk of bias, Due to serious indirectness [12]	One study found a statistically significant reduction in intubation with helmet non-invasive ventilation followed by HFNO

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Helmet non-invasive ventilation following by HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			(CI 95% 341 fewer — 51 fewer)		compared with HFNO in people with COVID-19.
		18 (Median) Difference:	20 (Median) **MD 2 more** (CI 95% 2 fewer — 6 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [13]	One study found no statistically significant difference in respiratory support free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
		25 (Median) Difference:	28 (Median) **MD 3 more** (CI 95% 0 more — 7 more)	**Low** Due to serious risk of bias, Due to serious indirectness [14]	One study found a statistically significant increase in invasive ventilation free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
		57 (Median) Difference:	60 (Median) **MD 6 more** (CI 95% 3 fewer — 15 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [15]	One study found no statistically significant difference in invasive ventilation free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
		22 days (Median) Difference:	21 days (Median) **MD 6 fewer** (CI 95% 14 fewer — 1 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [16]	One study found no statistically significant difference in duration of hospital stay with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
		10 (Median) Difference:	9 (Median) **MD 6 fewer** (CI 95% 13 fewer — 1 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [17]	One study found no statistically significant difference in duration of ICU stay with helmet non-invasive ventilation followed by HFNO compared with HFNO

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Helmet non-invasive ventilation following by HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					in people with COVID-19.

1. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
3. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
5. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
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7. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
9. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
11. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
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: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
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: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence

interval crosses line of no effect. **Publication bias: no serious.**
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: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
17. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

References

86. Respiratory support for COVID-19.

Conditional recommendation

Consider offering continuous positive airway pressure (CPAP) to people with COVID-19 when:

- they have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, **and**
- escalation to invasive mechanical ventilation would be an option but it is not immediately needed, **or**
- it is agreed that respiratory support should not be escalated beyond CPAP.

In June 2021, the Medicines and Healthcare products Regulatory Agency issued a National Patient Safety Alert for Philips ventilator, CPAP and bilevel positive airway pressure devices because of a potential for harm from inhaled particles and volatile organic compounds. This applies to all devices manufactured before 26 April 2021.

For information on decision making and giving advice, see the British Thoracic Society risk stratification guidance on Philips ventilator, CPAP and bilevel positive airway pressure devices.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

They noted that evidence from the Recovery-RS trial does not show that using high-flow nasal oxygen (HFNO) has any benefits compared with conventional oxygen therapy. They made a recommendation to not routinely offer HFNO as the main form of respiratory support for people with respiratory failure due to COVID-19 in whom escalation to invasive mechanical ventilation would be appropriate.

The panel agreed that the evidence from the Recovery-RS trial shows that using continuous positive airway pressure (CPAP) reduces the number of people who need invasive ventilation and admission to critical care. Evidence from the HENIVOT trial shows that helmet non-invasive ventilation followed by HFNO significantly reduces the number of people who need invasive ventilation compared with HFNO alone. They also noted that evidence from the Recovery-RS trial suggests there is a small increase in the number of serious adverse events with CPAP compared with conventional oxygen therapy. However, they considered that there are uncertainties with the available evidence, including evidence on standard care, staffing ratios, and where people had CPAP and which staff gave it. The panel agreed that these uncertainties warranted a recommendation to consider offering CPAP to people with COVID-19 when they:

- have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 40% to 60%,

and

- would be suitable for escalation to invasive mechanical ventilation but is not immediately needed.

The panel noted that it is important for staff to have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a consensus recommendation to support this.

The panel discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this. The panel agreed not to define treatment failure to allow for individual clinical decision making.

The panel also made a consensus recommendation to optimise medical management (including pharmacological and non-pharmacological treatment) before starting non-invasive respiratory support.

Certainty of the Evidence

Low

The panel were aware that the certainty of the evidence for outcomes in the Recovery-RS trial and HENIVOT trial ranged from moderate to low and low to very low, respectively. They also noted that the Recovery-RS trial is currently only available as a pre-print publication. This means that the results have not been peer reviewed, so the panel interpreted the results with the appropriate caution.

Preference and values

No substantial variability expected

Lay members noted that people with COVID-19 may have different opinions on how acceptable non-invasive respiratory support is. Some people may be apprehensive of its use and others may be willing to accept it as an available treatment option. Patient preferences should be considered in a shared discussion.

The panel agreed that treatment plans, preferences and wishes should be discussed with patients, families and carers before starting non-invasive respiratory support. For this reason, information boxes linking to the existing guideline recommendations on escalation and de-escalation of treatment have been provided. The panel also considered that care of people who will not have treatment escalation should be supported by provision of an information box linking to existing recommendations on pharmacological and non-pharmacological treatment options.

The panel noted that outcomes, such as symptom control, would be important to people with COVID-19 and should be reported in future trials. The panel proposed to make a research recommendation to explore if high-flow nasal oxygen reduces breathlessness compared with standard care or conventional oxygen therapy to help improve the evidence base in this area.

Resources and other considerations

No important issues with the recommended alternative

The panel considered that using continuous positive airway pressure (CPAP) for people with COVID-19 in appropriate settings outside of the intensive care unit (ICU) has the potential to free up ICU capacity. Avoiding the need for invasive mechanical intubation may also result in cost savings and avoid adverse outcomes from intubation. However, the panel were mindful that CPAP should be given by staff who have skills and competencies in CPAP, and be accompanied by careful review and prompt recognition of when treatment has failed and further treatment escalation is needed.

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

Equity

Important issues, or potential issues not investigated

The scope of this evidence review was limited to adults and so no evidence in children and young people was included.

The panel noted that some people, including those with learning disabilities, dementia or delirium for example, may find it difficult to tolerate non-invasive respiratory support. As such, patient preferences should be considered in a shared discussion with the person and their family or carer.

Acceptability

Important issues, or potential issues not investigated

The panel discussed that some people find that continuous positive airway pressure (CPAP) is uncomfortable. The panel commented that some people may find it difficult to tolerate non-invasive respiratory support. They noted that high-flow nasal oxygen would allow people having CPAP to take treatment breaks for mealtimes and when CPAP is being gradually reduced. They made a consensus recommendation to support this. The panel proposed a research recommendation to explore which treatment methods are effective for weaning people with COVID-19 from CPAP and the acceptability and safety of these methods.

Feasibility

Important issues, or potential issues not investigated

Continuous positive airway pressure (CPAP) and high-flow nasal oxygen are established treatments in the NHS. However, the panel advised that context-specific factors influence when CPAP may be used, for example staff skills and competencies, staffing ratios and the availability of different CPAP interfaces, so CPAP use may vary in practice.

Rationale

Evidence from a clinical trial suggests that there may be some treatment benefits with continuous positive airway pressure for people who have hypoxaemia and in whom escalation to invasive mechanical ventilation would be an option, particularly for intubation outcomes (including likelihood of requiring tracheal intubation and invasive mechanical ventilation). But, this is uncertain.

Clinical Question/ PICO

Population: People with COVID-19
Intervention: CPAP
Comparator: Conventional oxygen

Summary

Evidence indicates that that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?
Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics
One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute

respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Greico 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?
Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen	**Intervention** CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 30 days	Odds Ratio 0.91 (CI 95% 0.59 — 1.39) (Randomized controlled)			Low Due to serious risk of bias, Due to serious imprecision [1]	One study found no statistically significant difference in mortality with CPAP compared with conventional oxygen in people with COVID-19.
Tracheal intubation or mortality 30 days	Odds Ratio 0.67 (CI 95% 0.48 — 0.94) (Randomized controlled)			Moderate Due to serious risk of bias [2]	One study found a statistically significant reduction in the composite outcome of tracheal intubation or mortality with CPAP compared with conventional oxygen in people with COVID-19.
Intubation 30 days	Odds Ratio 0.66 (CI 95% 0.47 — 0.93) (Randomized controlled)			Moderate Due to serious risk of bias [3]	One study found a statistically significant reduction in intubation with CPAP compared with conventional oxygen in people with COVID-19.
Median time to intubation	Hazard Ratio 0.67 (CI 95% 0.52 — 0.86) (Randomized controlled)			Moderate Due to serious risk of bias [4]	One study found a statistically significant difference in median time to intubation with CPAP compared with conventional oxygen in people with COVID-19.
Admission to critical care	Odds Ratio 0.69 (CI 95% 0.49 — 0.96) (Randomized controlled)			Moderate Due to serious risk of bias [5]	One study found a statistically significant reduction in admission to critical care with CPAP compared with conventional oxygen in people with COVID-19.
Mean length of stay in hospital (days)	Lower better (Randomized controlled)	17.3 days (Mean) Difference:	16.4 days (Mean) **MD 0.97 fewer** (CI 95% 3.65 fewer — 1.71 more)	Low Due to serious risk of bias, Due to serious imprecision [6]	One study found no statistically significant difference in length of hospital stay with CPAP compared with conventional oxygen in people with COVID-19.

Outcome Timeframe	Study results and measurements	Comparator Conventional oxygen	Intervention CPAP	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mean length of stay in critical care (days)	Lower better (Randomized controlled)	9.6 (Mean) Difference:	9.5 (Mean) **MD 0.33 fewer** (CI 95% 2.44 fewer — 1.78 more)	Low Due to serious risk of bias, Due to serious imprecision [7]	One study found no statistically significant difference in length of critical care stay with CPAP compared with conventional oxygen in people with COVID-19.

1. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

Clinical Question/ PICO

Population: People with COVID-19
Intervention: HFNO
Comparator: Conventional oxygen

Summary

Evidence indicates that that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?
Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics
One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Greico 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?
Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or

mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 30 days	Odds Ratio 0.96 (CI 95% 0.64 — 1.45) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [1]	One study found no statistically significant difference in mortality with HFNO compared with conventional oxygen in people with COVID-19.
Tracheal intubation or mortality 30 days	Odds Ratio 0.95 (CI 95% 0.69 — 1.3) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [2]	One study found no statistically significant difference in the composite outcome of tracheal intubation or mortality with HFNO compared with conventional oxygen in people with COVID-19.
Intubation 30 days	Odds Ratio 0.96 (CI 95% 0.7 — 1.31) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [3]	One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.
Median time to intubation	Hazard Ratio 0.91 (CI 95% 0.72 — 1.14) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [4]	One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.
Admission to critical care	Odds Ratio 1.06 (CI 95% 0.76 — 1.47) (Randomized controlled)			**Low** Due to serious risk of bias, Due to serious imprecision [5]	One study found no statistically significant difference in admission to critical care with HFNO compared with conventional oxygen in

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					people with COVID-19.
Mean length of stay in hospital (days)	Lower better (Randomized controlled)	17.1 (Mean) Difference:	18.3 (Mean) **MD 0.7 more** (CI 95% 1.93 fewer — 3.34 more)	**Low** Due to serious risk of bias, Due to serious imprecision [6]	One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.
Mean length of stay in critical care (days)	Lower better (Randomized controlled)	9.5 (Mean) Difference:	10.5 (Mean) **MD 0.69 more** (CI 95% 1.37 fewer — 2.75 more)	**Low** Due to serious risk of bias, Due to serious imprecision [7]	One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.

1. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crossed line of no effect. **Publication bias: no serious.**
3. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
4. **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, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
5. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

Clinical Question/ PICO

Population: People with COVID-19

Intervention: Helmet non-invasive ventilation followed by HFNO
Comparator: HFNO

Summary

Evidence indicates that that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure. The evidence does not support the use of high-flow nasal oxygen (HFNO) as a main treatment option.

What is the evidence informing this recommendation?
Evidence comes from two randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2021 and Grieco 2021).

The 2 included RCTs allowed 3 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

As the comparisons differed between studies it was not possible to meta-analyse the included data.

Study characteristics
One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required (Perkins). The second RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

Mean age in Perkins 2021 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%.

The median and interquartile range for age in the Greico 2021 RCT was 66 (57-72) in the intervention group and 63 (55-69) in the comparator group and the proportion of women was 19%.

What are the main results?
Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (OR (adjusted) 0.67 (95% CI 0.48 - 0.94)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) and admission to critical care (OR (adjusted) 0.69 (95% CI 0.49 - 0.96)) were significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

No difference was observed between HFNO and conventional oxygen for any outcome measured.

Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation, admission to critical care mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Helmet non-invasive ventilation following by HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality at 28 days	Relative risk 0.81 (CI 95% 0.35 — 1.91) Based on data from 109 participants in 1 studies. [1] (Randomized controlled)	182 per 1000 Difference:	147 per 1000 **35 fewer per 1000** (CI 95% 118 fewer — 166 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [2]	One study found no statistically significant difference in mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Mortality at 60 days	Relative risk 1.1 (CI 95% 0.55 — 2.2) Based on data from 109 participants in 1 studies. [3] (Randomized controlled)	218 per 1000 Difference:	240 per 1000 **22 more per 1000** (CI 95% 98 fewer — 262 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [4]	One study found no statistically significant difference in mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
In-hospital mortality	Relative risk 0.95 (CI 95% 0.49 — 1.82) Based on data from 109 participants in 1 studies. [5] (Randomized	255 per 1000 Difference:	242 per 1000 **13 fewer per 1000**	**Very low** Due to serious risk of bias, Due to serious imprecision, Due	One study found no statistically significant difference in in-hospital mortality with helmet non-invasive ventilation followed by HFNO

Outcome Timeframe	Study results and measurements	Comparator HFNO	Intervention Helmet non-invasive ventilation following by HFNO		Plain language summary
	controlled)		(CI 95% 130 fewer — 209 more)	to serious indirectness [6]	compared with HFNO in people with COVID-19.
In–intensive care unit mortality	Relative risk 0.8 (CI 95% 0.4 — 1.6) Based on data from 109 participants in 1 studies. [7] (Randomized controlled)	**255** per 1000 Difference:	**204** per 1000 **51 fewer per 1000** (CI 95% 153 fewer — 153 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [8]	One study found no statistically significant difference in intensive care mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Intubation within 28 days from enrolment	Relative risk 0.58 (CI 95% 0.36 — 0.95) Based on data from 109 participants in 1 studies. [9] (Randomized controlled)	**509** per 1000 Difference:	**295** per 1000 **214 fewer per 1000** (CI 95% 326 fewer — 25 fewer)	**Low** Due to serious risk of bias, due to serious indirectness [10]	One study found a statistically significant reduction in intubation with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Intubation within 28 days from enrolment after adjudication of intubation criteria by external experts	Relative risk 0.55 (CI 95% 0.33 — 0.9) Based on data from 109 participants in 1 studies. [11] (Randomized controlled)	**509** per 1000 Difference:	**280** per 1000 **229 fewer per 1000** (CI 95% 341 fewer — 51 fewer)	**Low** Due to serious risk of bias, Due to serious indirectness [12]	One study found a statistically significant reduction in intubation with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Respiratory support free days	High better (Randomized controlled)	**18** (Median) Difference:	**20** (Median) **MD 2 more** (CI 95% 2 fewer — 6 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [13]	One study found no statistically significant difference in respiratory support free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
Invasive ventilation free days 28 days	High better (Randomized controlled)	**25** (Median) Difference:	**28** (Median) **MD 3 more** (CI 95% 0 more — 7 more)	**Low** Due to serious risk of bias, Due to serious indirectness [14]	One study found a statistically significant increase in invasive ventilation free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with

				Plain language summary
				COVID-19.
	57 (Median)	60 (Median)	Difference: **MD 6 more** (CI 95% 3 fewer — 15 more)	One study found no statistically significant difference in invasive ventilation free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
	22 days (Median)	21 days (Median)	Difference: **MD 6 fewer** (CI 95% 14 fewer — 1 more)	One study found no statistically significant difference in duration of hospital stay with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.
	10 (Median)	9 (Median)	Difference: **MD 6 fewer** (CI 95% 13 fewer — 1 more)	One study found no statistically significant difference in duration of ICU stay with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.

1. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
3. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
5. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
7. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.

8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
9. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
11. Systematic review [86] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
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: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**
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: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
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: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
17. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

References

86. Respiratory support for COVID-19.

Consensus recommendation

For people with COVID-19 having continuous positive airway pressure, ensure:

- there is access to critical care providers for advice, review and prompt escalation of treatment if needed (such as when treatment has failed)
- regular review by an appropriate senior clinician (such as every 12 hours) and more frequent review if needed, in line with the British Thoracic Society guidance on respiratory support units and the Faculty of Intensive Care Medicine guidelines on the provision of intensive care services
- regular assessment and management of symptoms alongside non-invasive respiratory support.

Staff caring for people with COVID-19 having CPAP should have appropriate skills and competencies and provide appropriate monitoring. For further information on standards of care and provision of services see the Faculty of Intensive Care Medicine and Intensive Care Society guidelines on the provision of intensive care services and the British Thoracic Society and Intensive Care Society guidance on development and implementation of respiratory support units.

Evidence To Decision

Benefits and harms

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the evidence review.

There is no evidence on reviewing and monitoring people having continuous positive airway pressure (CPAP). However, the panel noted that it is important that staff have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a consensus recommendation to support this.

The panel also discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this.

Preference and values

Rationale

Based on their experience, the panel agreed that it is important to closely review people with COVID-19 having continuous positive airway pressure and recognise the need for escalation of treatment.

Consensus recommendation

Consider using high-flow nasal oxygen for people having continuous positive airway pressure (CPAP) when they need:

- a break from CPAP, such as at mealtimes
- humidified oxygen
- weaning from CPAP.

Evidence To Decision

Benefits and harms

The panel discussed the findings from the 2 randomised controlled trials (Recovery-RS and HENIVOT) included in the

evidence review.

Although there is no evidence on treatment breaks from continuous positive airway pressure (CPAP), the panel noted this was an important consideration. The panel discussed that people can find CPAP uncomfortable. The panel commented that some people may find it difficult to tolerate non-invasive respiratory support. They noted that using high-flow nasal oxygen would allow people having CPAP to take breaks from treatment, for example at mealtimes and when CPAP is being gradually reduced. They made a consensus recommendation to support this.

Preference and values

Rationale

Based on their experience, the panel recognised that prolonged use of continuous positive airway pressure (CPAP) can be uncomfortable, and that there needs to be an appropriate alternative to CPAP when needed.

7. Therapeutics for COVID-19

7.1 Neutralising monoclonal antibodies - for people not in hospital

Recommended

New

Offer a neutralising monoclonal antibody (sotrovimab, or combination casirivimab plus imdevimab) for people aged 12 and over with COVID-19 who:

- are not in hospital, and
- are thought to be at high risk of progression to severe COVID-19. (NHS England's Interim Clinical Commissioning Policy provides a list of people at high-risk prioritised for access to neutralising monoclonal antibodies).

Be aware that the choice of neutralising monoclonal antibody may depend on availability as well as contextual factors (for example, emerging data on effectiveness of different antibodies against different SARS-CoV-2 variants).

In vitro data suggests that the efficacy of casirivimab plus imdevimab is likely to be compromised against the Omicron (B.1.1.529) variant. NICE will review and update this recommendation as further evidence emerges.

The Interim Clinical Commissioning Policy published in December 2021 outlines the neutralising monoclonal antibodies with current UK access and details the risk factors and criteria to be used to guide treatment in people who are not in hospital. The policy states that patients must meet all the eligibility criteria and none of the exclusion criteria to have neutralising monoclonal antibodies.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Five studies were considered as part of the evidence review for neutralising monoclonal antibodies in non-hospitalised patients. One study evaluated the effectiveness of sotrovimab in non-hospitalised patients (Gupta 2021) and four studies evaluated the effectiveness of the combination of casirivimab and imdevimab (O'Brien 2022, Portal-Celhay 2021, Weinreich 2021a and Weinreich 2021b).

The panel noted that most of these studies were conducted in populations with at least one risk factor for severe COVID-19 disease (for example obesity, chronic lung disease, chronic kidney disease and cardiovascular disease). They also agreed that the evidence suggests that treatment with either sotrovimab, or the combination of casirivimab and imdevimab showed clinical benefit in these populations, with minimal adverse events.

Unlike the other trials on casirivimab and imdevimab, Portal-Celhay 2021 was carried out in asymptomatic participants with no risk factors for severe COVID-19.

The panel discussed that there were benefits seen in the composite outcome of hospitalisation or death for people treated in the community. The panel acknowledged that hospitalisations made up a higher number of events in this outcome than deaths, which is anticipated in community settings.

As most of the evidence was from trials in high-risk populations the panel agreed that these patients would benefit the most from treatment but that the benefit could be of most clinical importance in those that are at the highest risk of progression to severe disease as outlined in the NHSE Clinical Commissioning Policy for neutralising monoclonal antibodies in non-hospitalised patients.

For the majority of the outcomes in the trials, there was no statistically significant difference between the analysed subgroups (including seronegative, seropositive, unknown serostatus). The overall treatment effect in all participants in the treatment and placebo groups was unchanged by differences in the effects of the subgroups. So the panel agreed that recommendations by serostatus would not be clinically useful.

The differences in the route of administration of some of the monoclonal antibodies (for example subcutaneous, intravenous) was considered by the panel. The panel noted that one of the studies that used subcutaneous administration (Portal-Celhay 2021), had lower quality evidence than those that administered the drugs intravenously. The evidence

presented to the panel did not compare the efficacy of the administration routes to one another as it was outside the scope of the review question.

The panel acknowledged that immunodeficient people were underrepresented in the study populations and so the effects of these drugs on these participants cannot be evaluated. However, based on some panel members' experience with immunodeficiency, it was agreed that neutralising monoclonal antibodies are likely to be particularly clinically effective for immunosuppressed people. The panel also considered that in all the trials, vaccination status was not reported and so the role of vaccination could not be elucidated.

The panel addressed the fact that neutralising monoclonal antibodies as a class have shown clinical benefit against SARS-CoV-2 infection. In light of the emergence of the Omicron (B.1.1.529) variant, the panel were presented with research data on the biological efficacy of sotrovimab and the combination of casirivimab and imdevimab against Omicron in vitro. The in vitro data suggested that the efficacy of casirivimab and imdevimab is likely to be compromised against the Omicron variant. It also suggested that the efficacy of sotrovimab against Omicron may be maintained however there remains uncertainty around the clinical effectiveness of sotrovimab without pragmatic trial data.

In order to apply the evidence to the changing context of the pandemic, further studies on emerging variants need to be carried out to determine the clinical efficacy and safety of neutralising monoclonal antibodies. The panel acknowledged that there was a gap in the published evidence and made a research recommendation to assess the effectiveness of neutralising monoclonal antibodies against different SARS-CoV-2 variants.

Certainty of the Evidence

Moderate

The certainty of the evidence in the Gupta 2021 study assessing sotrovimab was rated as high to moderate for most outcomes. The panel highlighted that due to the few numbers of events in some outcomes, there was serious risk of imprecision and uncertainty.

The certainty of the evidence in studies assessing intravenous casirivimab and imdevimab (Portal-Celhay 2021; Weinreich 2021a; Weinreich 2021b) was rated between high to moderate for most outcomes. The panel noted that some issues with imprecision and uncertainty are due to few event numbers in some outcomes, as well as wide confidence intervals.

The certainty of the evidence in studies assessing subcutaneous casirivimab and imdevimab (O'Brien 2022; Portal-Celhay 2021) was rated between moderate to very low for most outcomes. The evidence highlighted that some issues with risk of bias, imprecision and uncertainty were due to few event numbers and wide confidence intervals in some outcomes, as well as inconsistent reporting of data for some outcomes.

The certainty of the evidence for the outcomes was impacted by considerations for the different study populations, treatments, routes of administration and COVID-19 disease severity.

The panel discussed that in some studies the number of serious adverse events was lower in the treatment arm than in the placebo arm. However, some panel members noted that in clinical trials adverse events are reported in the analysis regardless of whether they were adverse events resulting from the disease itself (for example COVID-19 pneumonia) or from the drug received. The panel agreed that this may account for variations in these outcomes.

The panel also noted that all the studies included in the evidence review were funded by pharmaceutical companies that manufactured the individual drugs.

Preference and values

No substantial variability expected

The panel recognised that some outcomes, like hospitalisations, mortality and treatment-emergent adverse events, may be important for decision-making. It is likely that these outcomes would also be of similar importance to people with COVID-19.

Resources and other considerations

Important issues, or potential issues not investigated

The panel discussed that in line with the Interim clinical commissioning policy for neutralising monoclonal antibodies in non-

hospitalised patients published in December 2021, a positive PCR test would be used to guide treatment.

The panel agreed that depending on emerging evidence of benefit, treatment with different neutralising monoclonal antibodies may be guided by the SARS-CoV-2 variant that is more probable or proven in patients. The panel noted that to optimise the potential benefits of this intervention, a system for rapid identification of the variant strain would need to be established and be made accessible.

The panel were made aware that COVID-19 Medicine Delivery Units (CMDUs) will be the main hub to administer neutralising monoclonal antibodies as patients will have to be monitored after administration.

The panel noted that this would incur costs. For example, it requires PCR positive patients to travel, which may also pose a risk to others (unwell patients driving and drivers or family members exposed to COVID-19). Alternatively, a specialist team may be required to visit people at home to administer and monitor treatment, which may incur further costs.

Equity

Important issues, or potential issues not investigated

The panel noted that children aged 12 and over were included in these trials. One study included pregnant women in its protocol. The panel also noted that 3% of participants included in the Weinreich 2021b study were immunodeficient. However, no subgroup analyses or further evidence on the effects of sotrovimab and casirivimab and imdevimab on these groups was reported.

The panel discussed that there may be potential issues with access to treatment, as people may need to travel to specialist centres to receive it. The panel highlighted that there may be challenges to delivering this treatment to certain patient groups (for example older people, people from lower socioeconomic backgrounds and people with mobility and learning difficulties).

No other equity issues were identified.

Acceptability

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about acceptability.

Due to the benefit and clinical efficacy of these treatments, it is likely that the patients, their clinicians and families, would accept the use of neutralising monoclonal antibodies.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

The panel discussed the availability and feasibility of administering these medications in different areas in the UK. The panel noted that COVID-19 Medicine Delivery Units (CMDU) will be the main hub for people to receive these treatments.

The panel highlighted that it may not be easy to access CMDUs for some patient groups, for example, older people or people with learning disabilities or those who live in rural areas. As such, special provisions need to be put in place by local centres to ensure ease of access to treatments for all (for example a specialist team that can be dispatched to administer treatment and monitor patients).

The panel also discussed the feasibility of testing and detecting COVID-19 and emerging variants, such as the Omicron B.1.1.529 variant to guide treatment. The panel noted that at present PCR testing is used to confirm SARS-CoV-2 infection. Further testing, such as S-gene target failure, is used to distinguish the Omicron variant in patients who are PCR positive with COVID-19.

NHS England's Interim clinical commissioning policy outlines UK access and eligibility criteria for neutralising monoclonal antibodies in non-hospitalised patients.

Rationale

There is evidence that neutralising monoclonal antibodies (sotrovimab, and the combination of casirivimab and imdevimab) reduce the combined outcome of hospitalisation or death, and clinical progression to severe disease, in people who are not in hospital with COVID-19 but are thought to be at high risk of progression to severe disease.

In vitro research data on the efficacy of sotrovimab, and the combination of casirivimab and imdevimab against the new Omicron (B.1.1.529) variant, suggests that neutralising monoclonal antibodies have varying biological efficacy against Omicron. The results suggest this may also be the case with future emerging SARS-CoV-2 variants. The panel agreed that more research into this area is needed to guide treatment and made a research recommendation to address this gap in the published evidence.

Clinical Question/ PICO

Population: People with COVID-19 (Community)
Intervention: Sotrovimab
Comparator: Placebo

Summary

Key results

Evidence from one study showed that sotrovimab reduced the combined outcome of hospitalisation or death and clinical progression to critical COVID-19 disease compared to placebo, in symptomatic people with risk factors for developing severe COVID-19.

What is the evidence informing this conclusion?

Evidence comes from 1 randomised controlled trial that compared sotrovimab with placebo in 1057 adults with confirmed COVID-19 who were not hospitalised at baseline (Gupta 2021). Participants had mild-moderate COVID-19 disease but had at least one risk factor that made them susceptible to severe COVID-19 disease.

Participants received a single intravenous dose of sotrovimab (500mg) and were monitored to determine the clinical progression of COVID-19 disease in high-risk participant groups. Analysis of serostatus was not reported/conducted in participants.

The study evaluated the clinical efficacy and safety of sotrovimab compared to placebo.

Publication status

This study is only available as a preprint posted to medRxiv on 8 November 2021 (Gupta et al. (COMET-ICE)) and is therefore not peer-reviewed.

Study characteristics

The median age of participants was 53 years and women made up the majority of the study population (54%). The severity of COVID-19 in study participants ranged from mild-moderate disease. One of the key inclusion criteria of the study was for participants to have at least one risk factor for severe COVID-19 disease (for example obesity, chronic kidney disease, chronic lung disease, cardiovascular disease).

The participants received a single dose of sotrovimab (500mg) or placebo (saline) intravenously. Participants aged below 18 years were excluded, alongside pregnant women.

The study was funded by Vir Biotechnology and GlaxoSmithKline.

What are the main results?

Sotrovimab significantly reduces mortality, hospitalisation and clinical progression to severe COVID-19 disease in people who are high risk for severe disease and are RT-PCR positive for SARS-CoV-2 infection. Safety evidence from the trial suggests that sotrovimab does not increase the incidence of adverse events in people who receive it.

For further details see the evidence review.

Our confidence in the results

This study was rated as low risk of bias due to there being very few concerns around study design and results. The study was appropriately randomised with appropriate allocation concealment. The study sample size was large, and baseline characteristics were balanced across both treatment groups.

Some outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect as well as a small number of events in the outcome.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality Day 29 9 Critical	Relative risk 0.2 (CI 95% 0.01 — 4.16) Based on data from 1,057 participants in 1 studies. [1] (Randomized controlled)	4 per 1000 Difference:	0 per 1000 **46 fewer per 1000** (CI 95% 56 fewer — 180 more)	**Low** Due to very serious imprecision [2]	One study found no statistically significant difference in mortality at day 29 in people with COVID-19 who were treated with sotrovimab compared to placebo.
Hospitalised >24 hours for any cause Day 29 9 Critical	Relative risk 0.21 (CI 95% 0.09 — 0.5) Based on data from 1,057 participants in 1 studies. [3] (Randomized controlled)	55 per 1000 Difference:	12 per 1000 **43 fewer per 1000** (CI 95% 50 fewer — 28 fewer)	**High**	One study found a statistically significant reduction in the number of people who were hospitalised for >24 hours who had COVID-19 and were treated with sotrovimab compared to placebo.
Hospitalised >24 hours for any cause or death Day 29 9 Critical	Relative risk 0.19 (CI 95% 0.08 — 0.46) Based on data from 1,057 participants in 1 studies. [4] (Randomized controlled)	57 per 1000 Difference:	11 per 1000 **46 fewer per 1000** (CI 95% 52 fewer — 31 fewer)	**High**	One study found a statistically significant reduction in people who were hospitalised for >24 hours for any cause or death who had COVID-19 and were treated with sotrovimab compared to placebo.
Emergency room visit, hospitalisation, or death for any cause Day 29 6 Important	Relative risk 0.33 (CI 95% 0.18 — 0.62) Based on data from 1,057 participants in 1 studies. [5] (Randomized controlled)	74 per 1000 Difference:	24 per 1000 **50 fewer per 1000** (CI 95% 61 fewer — 28 fewer)	**High**	One study found a statistically significant reduction in emergency room visits, hospitalisation or death for any cause in people who had COVID-19 and were treated with sotrovimab compared to placebo.
Admission to intensive care for any cause Day 29	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [6] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer	**Moderate** Due to serious imprecision [7]	One study found a statistically significant reduction in admission to intensive care for any cause who had COVID-19 and were treated with sotrovimab

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Sotrovimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important			— 4 fewer)		compared to placebo.
Low flow nasal cannula/face mask Day 29 6 Important	Relative risk 0.58 (CI 95% 0.23 — 1.47) Based on data from 1,057 participants in 1 studies. [8] (Randomized controlled)	23 per 1000 Difference:	13 per 1000 **10 fewer per 1000** (CI 95% 18 fewer — 11 more)	Moderate Due to serious imprecision [9]	One study found no statistically significant difference in progression to low flow nasal cannula or face masks for COVID-19 in people who were treated with sotrovimab compared to placebo.
Non-rebreather mask, high-flow nasal cannula, or noninvasive ventilation Day 29 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [10] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	Moderate Due to serious imprecision [11]	One study found a statistically significant reduction in progression to non-rebreather mask or high-flow nasal cannula or non-invasive ventilation for COVID-19 in people who were treated with sotrovimab compared to placebo.
Invasive mechanical ventilation Day 29 6 Important	Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 1,057 participants in 1 studies. [12] (Randomized controlled)	8 per 1000 Difference:	1 per 1000 **7 fewer per 1000** (CI 95% 8 fewer — 8 more)	Low Due to very serious imprecision [13]	One study found no statistically significant difference in progression to invasive mechanical ventilation for COVID-19 in people who were treated with sotrovimab compared to placebo.
Adverse events - Any adverse event Day 29 6 Important	Relative risk 0.93 (CI 95% 0.74 — 1.17) Based on data from 1,049 participants in 1 studies. [14] (Randomized controlled)	234 per 1000 Difference:	218 per 1000 **16 fewer per 1000** (CI 95% 61 fewer — 40 more)	Moderate Due to serious imprecision [15]	One study found no statistically significant difference in the incidence of adverse events in people with COVID-19 and who were treated with sotrovimab compared to placebo.
Adverse events - Any serious adverse event Day 29 6 Important	Relative risk 0.35 (CI 95% 0.18 — 0.68) Based on data from 1,049 participants in 1 studies. [16] (Randomized controlled)	61 per 1000 Difference:	21 per 1000 **40 fewer per 1000** (CI 95% 50 fewer — 20 fewer)	High	One study found a statistically significant reduction in the incidence of serious adverse events in people who had COVID-19 and were treated with sotrovimab compared to placebo.
Adverse events - Any infusion-	Relative risk 1.01 (CI 95% 0.33 — 3.1)	11	11	Moderate Due to serious	One study found no statistically significant

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Sotrovimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
related reaction Day 29	Based on data from 1,049 participants in 1 studies. [17] (Randomized controlled)	per 1000 Difference:	per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 23 more)	imprecision [18]	difference in the incidence of infusion-related adverse events in people with COVID-19 and who were treated with sotrovimab compared to placebo.

1. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very low number of events and confidence interval includes line of no effect. **Publication bias: no serious.**
3. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Low number of events. **Publication bias: no serious.**
8. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**
10. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Low number of events. **Publication bias: no serious.**
12. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence interval includes line of no effect and very small number of events. **Publication bias: no serious.**
14. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**
16. Systematic review [154] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [155] with included studies: Gupta 2021. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect . **Publication bias: no serious.**

References

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164. Gupta A, Gonzalez-Rojas Y, Juarez E, Casal MC, Moya J, Falci DR, et al. : Effect of the Neutralizing SARS-CoV-2 Antibody Sotrovimab in Preventing Progression of COVID-19: A Randomized Clinical Trial. medRxiv 2021/01/01;

2021.11.03.21265533 Journal Website

Clinical Question/ PICO

Population: People with COVID-19 (Community)
Intervention: Casirivimab and Imdevimab (IV)
Comparator: Placebo

Summary

Key results

In outpatient settings, the evidence suggests that intravenous combination of casirivimab and imdevimab may reduce hospitalisation or death compared to placebo in people who are symptomatic and at high risk of developing severe COVID-19 disease.

What is the evidence informing this conclusion?

Evidence comes from 3 randomised controlled trials that compared different doses of intravenous casirivimab and imdevimab (300mg, 600mg, 1200mg, 2400mg) (Portal-Celhay 2021; Weinreich 2021a; Weinreich 2021b). Weinreich 2021a was the phase 1 and 2 analysis of the same trial that had phase 3 results published in Weinreich 2021b.

Most data are from the Weinreich 2021b study (n=4057), with Weinreich 2021a contributing 275 participants and Portal-Celhay 2021 contributing 815 participants.

The majority of participants in the Weinreich studies included participants with high-risk factors for developing severe COVID-19 (73%), whereas Portal-Celhay mostly included participants who were at low risk of developing severe COVID-19.

Both studies included a majority of symptomatic participants (95%), however, a minority of participants from Portal-Celhay were asymptomatic (9%). Where possible, outcomes from the three studies were combined and effect sizes were estimated.

All studies were conducted in outpatient settings. Study sites were mostly based in the United States, with some based in Mexico.

Publication status

Two studies were published and peer-reviewed manuscripts (Weinreich 2021a and Weinreich 2021b). One study, Portal-Celhay (2021), was only available as a preprint posted on medRxiv on 10 November 2021 and is therefore not peer-reviewed.

Study characteristics

The mean age in the studies ranged between 34 and 44 years and the proportion of women ranged between 50 and 56% of the overall study populations. The severity of COVID-19 across all studies was mild-moderate. All the studies were conducted in outpatient settings. All of the studies excluded breastfeeding and pregnant women. Of the included study participants, across all three trials, 55.5% of participants were seronegative at baseline.

The phase 3 trial (Weinreich 2021b) used a modified full analysis set to determine the efficacy and safety of the treatments in people with at least one risk factor for severe COVID-19 disease.

Participants in Weinreich 2021a received 2400mg or 8000mg casirivimab and imdevimab intravenously (single-dose), whereas in phase 3 (Weinreich 2021b) participants received 1200mg or 2400mg casirivimab or imdevimab intravenously.

As Portal-Celhay (2021) was a dose-ranging study, participants were randomised to 300mg, 600mg, 1200mg, 2400mg casirivimab and imdevimab intravenously. This review only reports outcomes for 1200mg and 2400mg casirivimab and

imdevimab. All studies compared the efficacy of the intervention to a placebo.

All 3 studies were funded by Regeneron Pharmaceuticals.

What are the main results?

The combination of casirivimab and imdevimab (intravenous) significantly reduced the composite outcome of hospitalisation and death, intensive care unit admission and median time to symptom resolution in people with mild to moderate COVID-19. Similar to subcutaneous administration of casirivimab and imdevimab, the evidence suggests that intravenous administration of the drugs does not increase the incidence of adverse events.

For further details see the evidence review.

Our confidence in the results

The Weinreich studies (2021a and 2021b) were rated as low risk of bias due to there being very few concerns around study design and results. The studies were appropriately randomised with appropriate allocation concealment. Weinreich 2021b had a large sample size, and baseline characteristics were balanced across both treatment groups.

There were some concerns around the risk of bias in Portal-Celhay (2021) due to insufficient reporting on their methods of blinding and allocation concealment. Therefore, the study was rated as high risk of bias.

All outcomes from the Portal-Celhay study were downgraded for risk of bias due to insufficient detail of the randomisation process or allocation concealment. Some outcomes were also downgraded for small numbers of events and when the 95% CI included the line of no effect. Outcomes were also downgraded for imprecision if the 95% CI was not reported.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Casirivimab and Imdevimab IV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation or death - 1200mg Day 29 9 Critical	Relative risk 0.3 (CI 95% 0.13 — 0.68) Based on data from 1,484 participants in 1 studies. [1] (Randomized controlled)	32 per 1000 Difference:	10 per 1000 **22 fewer per 1000** (CI 95% 28 fewer — 10 fewer)	**High**	One study found a statistically significant reduction in hospitalisation or death at day 29 in people with COVID-19, who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Hospitalisation or death - Baseline viral load >10^6 copies/ml 1200mg Day 29 9 Critical	Relative risk 0.29 (CI 95% 0.12 — 0.72) Based on data from 953 participants in 1 studies. [2] (Randomized controlled)	42 per 1000 Difference:	12 per 1000 **30 fewer per 1000** (CI 95% 37 fewer — 12 fewer)	**High**	One study found a statistically significant reduction in hospitalisation or death in people with COVID-19 and a baseline viral load >10^6 copies/ml, who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Hospitalisation or death - Seronegative 1200mg Day 29	Relative risk 0.17 (CI 95% 0.05 — 0.58) Based on data from 1,019 participants in 1 studies. [3] (Randomized controlled)	35 per 1000 Difference:	6 per 1000 **29 fewer per 1000**	**High**	One study found a statistically significant reduction in hospitalisation or death in people who are seronegative, and have

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab and Imdevimab IV	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical			(CI 95% 33 fewer — 15 fewer)		COVID-19, who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Hospitalisation or death - Seropositive 1200mg Day 29 9 Critical	Relative risk 0.15 (CI 95% 0.02 — 1.27) Based on data from 341 participants in 1 studies. [4] (Randomized controlled)	37 per 1000 Difference:	6 per 1000 **31 fewer per 1000** (CI 95% 36 fewer — 10 more)	Moderate Due to serious imprecision [5]	One study found no statistically significant difference in hospitalisation or death in people who are seropositive and have COVID-19, who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Hospitalisation or death - 2400mg Day 29 9 Critical	Relative risk 0.29 (CI 95% 0.17 — 0.48) Based on data from 2,696 participants in 1 studies. [6] (Randomized controlled)	46 per 1000 Difference:	13 per 1000 **33 fewer per 1000** (CI 95% 38 fewer — 24 fewer)	High	One study found a statistically significant reduction in hospitalisation or death in people with COVID-19, who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Hospitalisation or death - Baseline viral load >10^6 copies/ml 2400mg Day 29 9 Critical	Relative risk 0.22 (CI 95% 0.12 — 0.41) Based on data from 1,800 participants in 1 studies. [7] (Randomized controlled)	63 per 1000 Difference:	14 per 1000 **49 fewer per 1000** (CI 95% 55 fewer — 37 fewer)	High	One study found a statistically significant reduction in hospitalisation or death in people with COVID-19 and a baseline viral load >10^6 copies/ml, who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Hospitalisation or death - Seronegative 2400mg Day 29 9 Critical	Relative risk 0.24 (CI 95% 0.13 — 0.45) Based on data from 1,870 participants in 1 studies. [8] (Randomized controlled)	53 per 1000 Difference:	13 per 1000 **40 fewer per 1000** (CI 95% 46 fewer — 29 fewer)	High	One study found a statistically significant reduction in hospitalisation or death in people who are seronegative and have COVID-19, who were treated with casirivimab and imdevimab 2400mg compared to placebo.
		40 per 1000 Difference:	12 per 1000 **28 fewer per 1000** (CI 95% 36 fewer — 2 fewer)	High	One study found a statistically significant reduction in hospitalisation or death in people who are seropositive and have COVID-19, who were treated with casirivimab and imdevimab 2400mg compared to placebo.

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab and Imdevimab IV	Certainty of the Evidence (Quality of evidence)	Plain language summary
≥1 COVID-19 related medical visit - 1200mg within 29 days 6 Important		36 per 1000 Difference:	18 per 1000 **18 fewer per 1000** (CI 95% 27 fewer — 2 fewer)	High	One study found a statistically significant reduction in the number of people with COVID-19 related medical visits, who were treated with casirivimab and imdevimab 1200mg compared to placebo.
≥1 COVID-19 related medical visit - 2400mg within 29 days 6 Important		39 per 1000 Difference:	20 per 1000 **19 fewer per 1000** (CI 95% 26 fewer — 7 fewer)	High	One study found a statistically significant reduction in the number of people with COVID-19 related medical visits, who were treated with casirivimab and imdevimab 2400mg compared to placebo.
≥1 COVID-19 related medical visit 2400mg - Seronegative within 29 days 6 Important		152 per 1000 Difference:	49 per 1000 **103 fewer per 1000** (CI 95% 141 fewer — 84 more)	Low Due to very serious imprecision [12]	One study found no statistically significant difference in the number of seronegative people with COVID-19 related medical visits, who were treated with casirivimab and imdevimab 2400mg compared to placebo.
≥1 COVID-19 related medical visit 2400mg - Seropositive within 29 days 6 Important		21 per 1000 Difference:	27 per 1000 **6 more per 1000** (CI 95% 19 fewer — 391 more)	Low Due to very serious imprecision [14]	One study found no statistically significant difference in the number of seropositive people with COVID-19 related medical visits, who were treated with casirivimab and imdevimab 2400mg compared to placebo.
COVID-19 related hospitalisation, emergency room visit or all cause death - 1200mg 6 Important		45 per 1000 Difference:	12 per 1000 **33 fewer per 1000** (CI 95% 39 fewer — 20 fewer)	High	One study found a statistically significant reduction in the number of COVID-19 related hospitalisation, emergency room visit or all-cause death in people with COVID-19, who were treated with casirivimab and imdevimab 1200mg compared to placebo.
		58 per 1000 Difference:	20 per 1000 **38 fewer per 1000** (CI 95% 45 fewer	High	One study found a statistically significant reduction in the number of COVID-19 related hospitalisation, emergency room visit or

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab and Imdevimab IV	Certainty of the Evidence (Quality of evidence)	Plain language summary
2400mg 6 Important			— 27 fewer)		all cause death in people with COVID-19, who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Intensive care unit admission - 1200mg Day 29 9 Critical	Relative risk 0.44 (CI 95% 0.11 — 1.68) Based on data from 1,484 participants in 1 studies. [17] (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000** (CI 95% 8 fewer — 6 more)	Moderate Due to serious imprecision [18]	One study found no statistically significant difference in admission to intensive care units in people with COVID-19 who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Intensive care unit admission - 2400mg Day 29 9 Critical	Relative risk 0.33 (CI 95% 0.13 — 0.83) Based on data from 2,696 participants in 1 studies. [19] (Randomized controlled)	13 per 1000 Difference:	4 per 1000 **9 fewer per 1000** (CI 95% 11 fewer — 2 fewer)	High	One study found a statistically significant reduction in admission to intensive care units in people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Invasive mechanical ventilation - 1200mg Day 29 9 Critical	Relative risk 0.51 (CI 95% 0.05 — 5.59) Based on data from 1,484 participants in 1 studies. [20] (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000** (CI 95% 3 fewer — 14 more)	Moderate Due to serious imprecision [21]	One study found no statistically significant difference in progression to invasive mechanical ventilation in people with COVID-19 who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Invasive mechanical ventilation - 2400mg Day 29 9 Critical	Relative risk 0.16 (CI 95% 0.02 — 1.37) Based on data from 2,696 participants in 1 studies. [22] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 1 more)	Moderate Due to serious imprecision [23]	One study found no statistically significant difference in progression to invasive mechanical ventilation in people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
		331 per 1000 Difference:	122 per 1000 **209 fewer per 1000** (CI 95% 318 fewer — 688 more)	Moderate Due to serious imprecision [24]	One study found no statistically significant difference in the number of serious adverse events that occurred in people who were treated with casirivimab and imdevimab 1200mg compared to placebo during the observation

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab and Imdevimab IV	Certainty of the Evidence (Quality of evidence)	Plain language summary
					period
Adverse events - Any serious adverse event 2400mg 6 Important	Relative risk 0.33 (CI 95% 0.21 — 0.51) Based on data from 3,873 participants in 2 studies. [25] (Randomized controlled)	105 per 1000 Difference:	35 per 1000 **70 fewer per 1000** (CI 95% 83 fewer — 51 fewer)	High	Two studies found a statistically significant reduction in the number of serious adverse events that occurred in people with COVID-19 and were treated with casirivimab and imdevimab 2400mg compared to placebo during the observation period.
Adverse events - Treatment emergent adverse event 1200mg 6 Important	Relative risk 0.9 (CI 95% 0.48 — 1.69) Based on data from 173 participants in 1 studies. [26] (Randomized controlled)	211 per 1000 Difference:	190 per 1000 **21 fewer per 1000** (CI 95% 110 fewer — 146 more)	Low Due to serious risk of bias, Due to serious imprecision [27]	One study found no statistically significant difference in the number of treatment-emergent adverse events in people with COVID-19 who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Adverse events - Treatment emergent adverse event 2400mg 6 Important	Relative risk 0.45 (CI 95% 0.19 — 1.04) Based on data from 172 participants in 1 studies. [28] (Randomized controlled)	175 per 1000 Difference:	79 per 1000 **96 fewer per 1000** (CI 95% 142 fewer — 7 more)	Low Due to serious risk of bias, Due to serious imprecision [29]	One study found no statistically significant difference in the number of treatment-emergent adverse events in people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Median time to resolution of symptoms - 1200mg days 6 Important	Lower better Based on data from: 1,353 participants in 1 studies. [30] (Randomized controlled)	14 (Median) Difference:	10 (Median) **4 fewer** (CI 95% 4 fewer — 4 fewer)	Moderate Due to serious imprecision [31]	One study found a statistically significant reduction in median time to symptom resolution in people with COVID-19 who were treated with casirivimab and imdevimab 1200mg compared to placebo.
		14 (Median) Difference:	10 (Median) **4 fewer** (CI 95% 4 fewer — 13 fewer)	Moderate Due to serious imprecision [32]	One study found a statistically significant reduction in median time to symptom resolution in seronegative people with COVID-19 who were treated with casirivimab and imdevimab 1200mg compared to placebo.

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab and Imdevimab IV	Certainty of the Evidence (Quality of evidence)	Plain language summary
Median time to resolution of symptoms - Seropositive 1200mg days 6 Important	Lower better Based on data from: 308 participants in 1 studies. (Randomized controlled)	15 (Median) Difference:	11 (Median) **4 fewer** (CI 95% 3 fewer — 4 fewer)	**Moderate** Due to serious imprecision [33]	One study found a statistically significant reduction in median time to symptom resolution in seropositive people with COVID-19 who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Median time to resolution of symptoms - 2400mg days 6 Important	Lower better Based on data from: 2,411 participants in 1 studies. [34] (Randomized controlled)	14 (Median) Difference:	10 (Median) **4 fewer** (CI 95% 3 fewer — 4 fewer)	**Moderate** Due to serious imprecision [35]	One study found a statistically significant reduction in median time to symptom resolution in people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Median time to resolution of symptoms - Seronegative 2400mg days 6 Important	Lower better Based on data from: 1,672 participants in 1 studies. (Randomized controlled)	13 (Median) Difference:	10 (Median) **3 fewer** (CI 95% 2 fewer — 4 fewer)	**Moderate** Due to serious imprecision [36]	One study found a statistically significant reduction in median time to symptom resolution in seronegative people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Median time to resolution of symptoms - Seropositive 2400mg days 6 Important	Lower better Based on data from: 552 participants in 1 studies. (Randomized controlled)	14 (Median) Difference:	10 (Median) **4 fewer** (CI 95% 2 fewer — 7 fewer)	**Moderate** Due to serious imprecision [37]	One study found a statistically significant reduction in median time to symptom resolution in seropositive people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Virologic efficacy - 1200mg Change in baseline viral load day 1-7 6 Important	High better Based on data from: 1,484 participants in 1 studies. (Randomized controlled)	2.64 (Mean) Difference:	3.35 (Mean) **MD 1.04 fewer** (CI 95% 0.9 fewer — 0.53 fewer)	**High**	One study found a statistically significant reduction in viral load at day 7 people with COVID-19 who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Virologic efficacy (seronegative) - 1200mg Change in baseline viral load day 1-7	High better Based on data from: 956 participants in 1 studies. (Randomized controlled)	2.7 (Mean) Difference:	3.56 (Mean) **MD 0.86 fewer** (CI 95% 1.09 fewer — 0.64	**High**	One study found a statistically significant reduction in viral load at day 7 in seronegative people with COVID-19 who were treated with casirivimab and

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab and Imdevimab IV	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important			fewer)		imdevimab 1200mg compared to placebo.
Virologic efficacy (seropositive) - 1200mg Change in baseline viral load day 1-7 6 Important	High better Based on data from: 341 participants in 1 studies. (Randomized controlled)	2.36 (Mean) Difference:	2.53 (Mean) **MD 0.17 fewer** (CI 95% 0.53 fewer — 0.2 fewer)	Moderate Due to serious imprecision [38]	One study found no statistically significant difference in viral load at day 7 in seropositive people with COVID-19 who were treated with casirivimab and imdevimab 1200mg compared to placebo.
Virologic efficacy - 2400mg Change in baseline viral load day 1-7 6 Important	High better Based on data from: 2,696 participants in 1 studies. (Randomized controlled)	2.47 (Mean) Difference:	3.32 (Mean) **MD 0.86 fewer** (CI 95% 1 fewer — 0.72 fewer)	High	One study found a statistically significant reduction in viral load at day 7 in people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Virologic efficacy (seronegative) - 2400mg Change in baseline viral load day 1-7 6 Important	High better Based on data from: 1,870 participants in 1 studies. (Randomized controlled)	2.55 (Mean) Difference:	3.58 (Mean) **MD 1.04 fewer** (CI 95% 1.2 fewer — 0.87 fewer)	High	One study found a statistically significant reduction in viral load at day 7 in seronegative people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Virologic efficacy (seropositive) - 2400mg Change in baseline viral load day 1-7 6 Important	High better Based on data from: 620 participants in 1 studies. (Randomized controlled)	1.94 (Mean) Difference:	2.36 (Mean) **MD 0.43 fewer** (CI 95% 0.7 fewer — 0.15 more)	High	One study found a statistically significant reduction in viral load at day 7 in seropositive people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.
Virologic efficacy in low risk participants - 1200mg Change in baseline viral load day 1-7 6 Important	High better Based on data from: 149 participants in 1 studies. [39] (Randomized controlled)	0.66 (Mean) Difference:	0.56 (Mean) **MD 0.1 more** (CI 95% 0.24 fewer — 0.89 fewer)	Low Due to serious risk of bias, Due to serious imprecision [40]	One study found a statistically significant greater reduction in viral load at day 7 in symptomatic people with COVID-19 who were treated with placebo compared to casirivimab and imdevimab 1200mg.

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab and Imdevimab IV	Certainty of the Evidence (Quality of evidence)	Plain language summary
Virologic efficacy in low risk participants - 2400mg Change in baseline viral load day 1-7 6 Important	High better Based on data from: 116 participants in 1 studies. (Randomized controlled)	**0.53** (Mean) Difference:	**0.71** (Mean) **MD 0.22 more** (CI 95% 1.05 fewer — 0.38 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision [41]	One study found a statistically significant reduction in viral load at day 7 in symptomatic people with COVID-19 who were treated with casirivimab and imdevimab 2400mg compared to placebo.

1. Systematic review [153] with included studies: Weinreich III 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [158] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [159] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [159] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**
6. Systematic review [153] with included studies: Weinreich III 2021. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [158] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
8. Systematic review [159] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
9. Systematic review [159] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [158] with included studies: Weinreich 2021b, Weinreich 2021a, Weinreich 2021a, Weinreich 2021a, Weinreich 2021a. **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [158] with included studies: Weinreich 2021a. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence interval includes the line of no effect and the outcome has a small number of participants and events. **Publication bias: no serious.**
13. Systematic review [158] with included studies: Weinreich 2021a. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence interval includes the line of no effect and small numbers of events and participants. **Publication bias: no serious.**
15. Systematic review [158] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
16. Systematic review [158] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
17. Systematic review [158] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**
19. Systematic review [158] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
20. Systematic review [158] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
21. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**

22. Systematic review [158] with included studies: Weinreich 2021b. **Baseline/comparator:** Control arm of reference used for intervention.
23. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**
24. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**
25. Systematic review [153] with included studies: Portal-Celhay 2021, Weinreich III 2021. **Baseline/comparator:** Control arm of reference used for intervention.
26. Systematic review [159] with included studies: Portal-Celhay 2021. **Baseline/comparator:** Control arm of reference used for intervention.
27. **Risk of Bias: serious.** Insufficient detail on randomisation and allocation concealment of study participants . **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**
28. Systematic review [159] with included studies: Portal-Celhay 2021. **Baseline/comparator:** Control arm of reference used for intervention.
29. **Risk of Bias: serious.** Insufficient detail on randomisation and allocation concealment of study participants . **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**
30. Systematic review [153] with included studies: Weinreich III 2021. **Baseline/comparator:** Control arm of reference used for intervention.
31. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs were not possible to calculate. **Publication bias: no serious.**
32. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Not possible to calculate CIs. **Publication bias: no serious.**
33. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Not possible to calculate CIs. **Publication bias: no serious.**
34. Systematic review [153] with included studies: Weinreich III 2021. **Baseline/comparator:** Control arm of reference used for intervention.
35. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Not possible to calculate CIs. **Publication bias: no serious.**
36. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Not possible to calculate CIs. **Publication bias: no serious.**
37. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Not possible to calculate CIs. **Publication bias: no serious.**
38. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**
39. Systematic review [158] with included studies: Portal-Celhay 2021. **Baseline/comparator:** Control arm of reference used for intervention.
40. **Risk of Bias: serious.** Randomisation and allocation concealment information was not reported in enough detail in the study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small number of participants. **Publication bias: no serious.**
41. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small number of participants . **Publication bias: no serious.**

References

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Clinical Question/ PICO

Population: People with COVID-19 (Community)
Intervention: Casirivimab and Imdevimab (SC)
Comparator: Placebo

Summary

Key results

Evidence from two studies shows there is uncertainty about the effect of subcutaneous use of the combination of casirivimab and imdevimab for people with COVID-19 who are asymptomatic and at low risk of developing severe COVID-19 disease.

What is the evidence informing this conclusion?

Evidence comes from 2 randomised controlled trials that compared different doses of subcutaneous casirivimab and imdevimab with placebo in adults with COVID-19 (O'Brien 2022; Portal-Celhay 2021). O'Brien used a 1200mg dose of casirivimab and imdevimab, whereas Portal-Celhay used 600mg and 1200mg doses to determine dose efficacy.

Both studies compared the effect of casirivimab and imdevimab to saline placebo. The majority of study sites in both studies were based in the United States, with a minority of sites in Moldova and Romania (O'Brien 2022). The studies included asymptomatic participants, with some who were at a high-risk of developing severe COVID-19 disease.

Primary analyses for both studies were in the seronegative population.

Publication status

O'Brien (2022) is a peer-reviewed manuscript and was published on 14 January 2022. Portal-Celhay (2021) was posted to medRxiv on 10 November 2021) and is not peer-reviewed.

Study characteristics

The mean age in the studies ranged between 24 and 41 years and women made up the majority of the study populations ranging between 45.6% and 56.4%. The severity of COVID-19 in both studies was mild-moderate, with both studies including asymptomatic participants and Portal-Celhay included those with symptoms within 7 days of randomisation. O'Brien 2021 included pregnant and breastfeeding women in the analysis whereas Portal-Celhay 2021 excluded high risk groups from the analysis.

The majority of the participants included in the O'Brien study (66%) were seronegative for SARS-CoV-2 antibodies upon enrolment to study. Portal-Celhay reported that 44% of their study participants were seronegative at baseline.

Portal-Celhay 2021 was a dose-ranging study to test the virologic efficacy and safety of casirivimab and imdevimab 600mg (subcutaneous) and 1200mg (subcutaneous).

Both of the studies were funded by Regeneron Pharmaceuticals.

What are the main results?

The evidence suggests that the combination of casirivimab and imdevimab (subcutaneous) may reduce the viral load and duration of symptomatic infection in people with COVID-19. Similar to intravenous administration of casirivimab and imdevimab, evidence on the safety and tolerability of the drugs does not suggest that casirivimab and imdevimab are

associated with higher incidents of adverse events.

For further details see the evidence review.

Our confidence in the results

There were some concerns about the risk of bias in Portal-Celhay 2021. The study did not report the methods of blinding and allocation concealment. Therefore, Portal-Celhay was reported as high risk of bias due to inconsistency in the reporting of outcomes, as well as insufficient information on the randomisation and allocation concealment process.

All outcomes for Portal-Celhay 2021 were downgraded for risk of bias due to insufficient detail of the randomisation process or allocation concealment. Some outcomes in both the studies were also downgraded for small numbers of events and where the 95% CI included the line of no effect.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Casirivimab + Imdevimab (SC)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Participants who developed symptoms (all participants) within 14 days of positive RT-PCR 9 Critical	Relative risk 0.65 (CI 95% 0.45 — 0.93) Based on data from 311 participants in 1 studies. [1] (Randomized controlled)	340 per 1000 Difference:	221 per 1000 **119 fewer per 1000** (CI 95% 187 fewer — 24 fewer)	High	One study found a statistically significant reduction in the number of people who developed symptoms within 14 days of a positive PCR test when treated with casirivimab and imdevimab compared to placebo.
Participants who developed symptoms (seronegative) within 14 days of positive RT-PCR 9 Critical	Relative risk 0.69 (CI 95% 0.47 — 1) Based on data from 204 participants in 1 studies. [2] (Randomized controlled)	423 per 1000 Difference:	292 per 1000 **131 fewer per 1000** (CI 95% 224 fewer — 0 fewer)	Low Due to very serious imprecision [3]	One study found no statistically significant difference in the number of seronegative people who developed symptoms within 14 days of a positive PCR test when treated with casirivimab and imdevimab compared to placebo.
Participants who developed symptoms (seropositive) within 14 days of positive RT-PCR 9 Critical	Relative risk 0.66 (CI 95% 0.19 — 2.29) Based on data from 84 participants in 1 studies. (Randomized controlled)	132 per 1000 Difference:	87 per 1000 **41 fewer per 1000** (CI 95% 104 fewer — 126 more)	Very low Due to serious risk of bias, Due to very serious imprecision [4]	One study found no statistically significant difference in the number of seropositive people who developed symptoms within 14 days of a positive PCR test when treated with casirivimab and imdevimab compared to placebo.
COVID-19 related hospitalisation (seronegative)	Relative risk 0.15 (CI 95% 0.01 — 2.84) Based on data from 204 participants in 1 studies.	29 per 1000 Difference:	0 per 1000 **25 fewer per**	Low Due to very serious imprecision [5]	One study found no statistically significant difference in the number of COVID-19 related

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab + Imdevimab (SC)	Certainty of the Evidence (Quality of evidence)	Plain language summary
Within 29 days 6 Important	(Randomized controlled)		**1000** (CI 95% 29 fewer — 53 more)		hospitalisation in people who were treated with 1200mg casirivimab and imdevimab compared to placebo.
COVID-19 related hospitalisation or Emergency department visit (seronegative) 6 Important	Relative risk 0.08 (CI 95% 0 — 1.4) Based on data from 204 participants in 1 studies. (Randomized controlled)	58 per 1000 Difference:	5 per 1000 **53 fewer per 1000** (CI 95% 58 fewer — 23 more)	**Low** Due to very serious imprecision [6]	One study found no statistically significant difference in the number of COVID-19 related hospitalisations or emergency department visits in people who were treated with 1200mg casirivimab and imdevimab compared to placebo.
Adverse events - Any treatment-emergent adverse event 1200mg 6 Important	Relative risk 0.72 (CI 95% 0.56 — 0.94) Based on data from 482 participants in 2 studies. [7] (Randomized controlled)	380 per 1000 Difference:	274 per 1000 **106 fewer per 1000** (CI 95% 167 fewer — 23 fewer)	**Moderate** Due to serious risk of bias [8]	One study found a statistically significant reduction in treatment emergent adverse events in people who were treated with 1200mg casirivimab and imdevimab compared to placebo.
Adverse event - Any serious treatment emergent adverse events 1200mg 6 Important	Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 156 participants in 1 studies. (Randomized controlled)	25 per 1000 Difference:	3 per 1000 **22 fewer per 1000** (CI 95% 25 fewer — 27 more)	**Low** Due to very serious imprecision, [9]	One study found no statistically significant difference in the number of serious treatment emergent adverse events in people who were treated with 1200mg casirivimab and imdevimab compared to placebo.
Adverse events - Injection-site reaction grade ≥3 1200mg 6 Important	Relative risk 0.2 (CI 95% 0.02 — 1.7) Based on data from 311 participants in 1 studies. [10] (Randomized controlled)	32 per 1000 Difference:	6 per 1000 **26 fewer per 1000** (CI 95% 31 fewer — 22 more)	**Moderate** Due to serious imprecision [11]	One study found no statistically significant difference in the number of injection-site reaction adverse events in people who were treated with casirivimab and imdevimab compared to placebo.
Duration of symptomatic SARS-CoV-2 infection Mean weeks per symptomatic participant 6 Important	Based on data from: 87 participants in 1 studies. [12] (Randomized controlled)	3.9 (Mean) Difference:	3 (Mean) **MD 0.9 fewer** (CI 95% 1.98 fewer — 0.38 more)	**Low** Due to very serious imprecision [13]	One study found no statistically significant difference in the mean number of weeks per symptomatic participant of clinical recovery in people who were treated with casirivimab and imdevimab compared to placebo.

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab + Imdevimab (SC)	Certainty of the Evidence (Quality of evidence)	Plain language summary
Duration of symptomatic SARS-CoV-2 infection (seronegative) Mean weeks per symptomatic participant 6 Important	Based on data from: 73 participants in 1 studies. [14] (Randomized controlled)	3.9 (Mean) Difference:	3.1 (Mean) **MD 0.8 fewer** (CI 95% 2.78 fewer — 0.98 more)	**Low** Due to very serious imprecision [15]	One study found no statistically significant difference in the mean number of weeks per symptomatic participant of clinical recovery in people who were treated with casirivimab and imdevimab compared to placebo.
Duration of symptomatic SARS-CoV-2 infection (seropositive) Mean weeks per symptomatic participant 6 Important	Based on data from: 9 participants in 1 studies. [16] (Randomized controlled)	6.1 (Mean) Difference:	2.5 (Mean) **MD 3.6 fewer** (CI 95% 6.46 fewer — 0.74 fewer)	**Low** Due to very serious imprecision [17]	One study found a statistically significant reduction in the mean number of weeks per symptomatic participant of clinical recovery in people who were treated with casirivimab and imdevimab compared to placebo.
Weeks of high viral load (all randomised participants) Mean per participant 6 Important	Based on data from: 303 participants in 1 studies. (Randomized controlled)	0.6 (Mean) Difference:	0.4 (Mean) **MD 0.2 fewer** (CI 95% 1 more — 0.8 more)	**Moderate** Due to serious imprecision [18]	One study found a statistically significant reduction in the mean number of weeks of high viral load in seropositive people who were treated with casirivimab and imdevimab compared to placebo.
Weeks of high viral load (seronegative) Mean per participant 6 Important	Based on data from: 209 participants in 1 studies. (Randomized controlled)	0.8 (Mean) Difference:	0.5 (Mean) **MD 0.3 fewer** (CI 95% 0.28 fewer — 0.32 fewer)	**Moderate** Due to serious imprecision [19]	One study found a statistically significant reduction in the mean number of weeks of high viral load in seronegative people who were treated with casirivimab and imdevimab compared to placebo.
Weeks of high viral load (seropositive) Mean per participant 6 Important	Based on data from: 82 participants in 1 studies. (Randomized controlled)	0.2 (Mean) Difference:	0.1 (Mean) **MD 0.1 fewer** (CI 95% 0.05 more — 0.11 fewer)	**Low** Due to very serious imprecision [20]	One study found no statistically significant difference in the mean number of weeks of high viral load in seropositive people who were treated with casirivimab and imdevimab compared to placebo.
Weeks of confirmed SARS-CoV-2	Based on data from: 311 participants in 1 studies.	1.7 (Mean)	1.3 (Mean)	**High**	One study found a statistically significant reduction in the number of weeks of confirmed

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Casirivimab + Imdevimab (SC)	Certainty of the Evidence (Quality of evidence)	Plain language summary
infection - all randomised participants Mean per participant 6 Important	[21] (Randomized controlled)	Difference:	**MD 0.4 fewer** (CI 95% 0.36 fewer — 0.44 fewer)		SARS-CoV-2 infection in all randomised participants who were treated with casirivimab and imdevimab compared to placebo.
Weeks of confirmed SARS-CoV-2 infection - Seronegative Mean per participant 6 Important	Based on data from: 204 participants in 1 studies. [22] (Randomized controlled)	1.9 (Mean) Difference:	1.3 (Mean) **MD 0.6 fewer** (CI 95% 0.57 fewer — 0.63 fewer)	Moderate Due to serious imprecision [23]	One study found a statistically significant reduction in the number of weeks of confirmed SARS-CoV-2 infection in seronegative people who were treated with casirivimab and imdevimab compared to placebo.
Weeks of confirmed SARS-CoV-2 infection - Seropositive Mean per participant 6 Important	Based on data from: 84 participants in 1 studies. [24] (Randomized controlled)	1.2 (Mean) Difference:	1.1 (Mean) **MD 0.1 fewer** (CI 95% 0.03 more — 0.23 fewer)	Very low Due to very serious imprecision [25]	One study found no statistically significant difference in the number of weeks of confirmed SARS-CoV-2 infection in seronegative people who were treated with casirivimab and imdevimab compared to placebo.
Virologic efficacy (symptomatic participants) Change in viral load between day 1-7 6 Important	Based on data from: 150 participants in 1 studies. (Randomized controlled)	0.49 (Mean) Difference:	0.56 (Mean) **MD 0.07 more** (CI 95% 0.87 fewer — 0.24 fewer)	Low Due to serious risk of bias, Due to serious imprecision [26]	One study found a statistically significant reduction in viral load in symptomatic participants who were treated with casirivimab and imdevimab compared to placebo.
Virologic efficacy (asymptomatic participants) Change in viral load between day 1-7 6 Important	Based on data from: 191 participants in 1 studies. (Randomized controlled)	2.5 (Mean) Difference:	3.7 (Mean) **MD 1.2 more** (CI 95% 1.3 fewer — 0.6 fewer)	Moderate Due to serious imprecision [27]	One study found a statistically significant reduction in viral load in asymptomatic participants who were treated with casirivimab and imdevimab compared to placebo.

1. Systematic review [156] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [152] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.

3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** CI includes line of no effect and small number of participants . **Publication bias: no serious.**
4. **Risk of Bias: serious.** The study was downgraded as there was insufficient information on their randomisation methodology and allocation concealment. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence interval includes line of no effect and small number of participants . **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Small number of events and confidence interval includes line of no effect. **Publication bias: no serious.**
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Small number of events and confidence interval includes line of no effect. **Publication bias: no serious.**
7. Systematic review [152] with included studies: O'Brien 2021, Portal-Celhay 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** There was insufficient information on their randomisation methodology and allocation concealment. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence interval includes line of no effect and small number of participants . **Publication bias: no serious.**
10. Systematic review [156] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**
12. Systematic review [152] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Small number of participants and confidence interval includes line of no effect. **Publication bias: no serious.**
14. Systematic review [152] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Small number of participants and confidence interval includes line of no effect. **Publication bias: no serious.**
16. Systematic review [152] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.
17. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Small number of events and participants, and confidence intervals include the line of no effect. **Publication bias: no serious.**
18. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small number of participants. **Publication bias: no serious.**
19. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small number of participants . **Publication bias: no serious.**
20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Small number of participants and wide confidence intervals . **Publication bias: no serious.**
21. Systematic review [157] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.
22. Systematic review [157] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.
23. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small number of participants. **Publication bias: no serious.**
24. Systematic review [157] with included studies: O'Brien 2021. **Baseline/comparator:** Control arm of reference used for intervention.
25. **Inconsistency: serious. Indirectness: no serious. Imprecision: very serious.** Confidence interval includes line of no effect and small number of participants. **Publication bias: no serious.**
26. **Risk of Bias: serious.** There was insufficient information on their randomisation methodology and allocation concealment. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small number of participants. **Publication bias: no serious.**
27. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small number of participants. **Publication bias: no serious.**

References

152. Neutralising antibodies for non-hospitalised adults, young people and children with COVID-19.

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163. O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan K-C, et al. : Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial. JAMA 2022; Pubmed Journal

7.2 Corticosteroids

Recommended

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 mg/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 and other considerations

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 *[9]* of seven randomised controlled trials (RCTs) of patients with critical COVID-19 *[10][20][11][17][16][10][15]*, one study of patients with moderate, severe and critical COVID-19 *[14]*, and one study of patients with severe COVID-19 *[13]*. 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 *[18]* and sepsis *[21]* – provided indirect evidence for serious adverse events.

Study characteristics
Three RCTs compared dexamethasone with standard care *[10][17][14]*, three compared hydrocortisone with standard care *[16][11][12]* and three compared methylprednisolone with standard care *[20][15][13]*.

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	Comparator Control		Certainty of the Evidence (Quality of evidence)	Plain language 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 participants in 9 studies. [1] (Randomized controlled)	316 per 1000 Difference:	265 per 1000 **51 fewer per 1000** (CI 95% 85 fewer — 6 fewer)	**Moderate** Due to some inconsistency [2]	Nine studies found a statistically significantly lower incidence of all-cause mortality at day 28 with corticosteroids compared with standard care 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 participants in 1 studies. [3] (Randomized controlled)	140 per 1000 Difference:	178 per 1000 **38 more per 1000** (CI 95% 0 fewer — 85 more)	**Moderate** Only data from one study	One study found no statistically significant difference in all cause mortality at day 28 with corticosteroids compared with placebo.
	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. [5] (Randomized controlled)	320 per 1000 Difference:	282 per 1000 **38 fewer per 1000** (CI 95% 67 fewer — 10 fewer)	**Moderate** Due to only one study	One study found a statistically significant reduction in death or the need for invasive mechanical ventilation at day 28 with corticosteroids compared with standard care in adults who require oxygen.
	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. [6] (Randomized controlled)	155 per 1000 Difference:	194 per 1000 **39 more per 1000** (CI 95% 0 fewer — 88 more)	**Moderate** Due to only one study [7]	One study found no statistically significant reduction in death or the need for invasive mechanical ventilation at day 28 with corticosteroids compared with standard care in adults who do not require oxygen.
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. [8] (Randomized controlled)	804 per 1000 Difference:	772 per 1000 **32 fewer per 1000** (CI 95% 80 fewer — 8 more)	**Moderate** Due to only one study [9]	One study found no statistically significant difference in discharge from hospital at day 28 with corticosteroids compared with standard care in adults who do not require oxygen.

	Study results and measurements	Comparator Control	Intervention Corticosteroids		
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical		582 per 1000	640 per 1000	Moderate Due to serious inconsistency [11]	Two studies found a statistically significant increase in discharge from hospital at day 28 with corticosteroids compared with standard care in adults who require oxygen.
		Difference:	**58 more per 1000** (CI 95% 35 more — 87 more)		
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important		234 per 1000	187 per 1000	Moderate Due to serious inconsistency [13]	Six studies found no statistically significant difference in serious adverse events at day 28 with corticosteroids compared with standard care in adults who require oxygen.
		Difference:	**47 fewer per 1000** (CI 95% 110 fewer — 44 more)		
Gastrointestinal bleeding End of treatment 6 Important		48 per 1000	51 per 1000	Low Due to serious indirectness and imprecision	Thirty studies found no statistically significant difference in gastrointestinal bleeding with corticosteroids compared with standard care.
		Difference:	**3 more per 1000** (CI 95% 9 fewer — 16 more)		
Bacterial co-infections End of treatment 6 Important		186 per 1000	188 per 1000	Low Due to serious indirectness and imprecision	Thirty two studies found no statistically significant difference in the incidence of bacterial coinfections with corticosteroids compared with standard care.
		Difference:	**2 more per 1000** (CI 95% 19 fewer — 24 more)		
		286 per 1000	332 per 1000	Moderate Due to serious indirectness	Twenty four studies found a statistically significant increase in the incidence of hyperglycaemia with corticosteroids compared with standard care.
		Difference:	**46 more per 1000** (CI 95% 23 more — 72 more)		
		69 per 1000	75 per 1000	Low Due to serious indirectness and imprecision	Eight studies found no statistically significant difference in the incidence of neuromuscular weakness
		Difference:	**6 more per 1000**		

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important			(CI 95% 10 fewer — 27 more) 28 per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)		with corticosteroids compared with standard care.
		35 per 1000 Difference:			

1. Systematic review [9] with included studies: RECOVERY, CAPE COVID 2020, Steroids-SARI 2020, CoDEX 2020, Edalatifard 2020, COVID STEROID 2020, REMAP-CAP 2020, METCOVID 2020, RECOVERY, DEXA-COVID 19 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 [9] 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 [9] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [9] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Imprecision: serious.** Only data from one study.
8. Systematic review [9] with included studies: RECOVERY. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Imprecision: serious.** Only data from one study.
10. Systematic review [9] 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 [9] with included studies: Steroids-SARI 2020, REMAP-CAP 2020, COVID STEROID 2020, CAPE COVID 2020, CoDEX 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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Conditional recommendation against

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 and other considerations

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 Casirivimab and imdevimab - for people hospitalised because of COVID-19

Recommended

Offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative).

This recommendation is informed by the results of the RECOVERY trial, which recruited people between 18 September 2020 and 22 May 2021. This was before the emergence of the Omicron (B.1.1.529) variant. In vitro data suggests that the efficacy of casirivimab and imdevimab is likely to be compromised against this variant. NICE will review and update this recommendation as further evidence emerges.

The criteria for accessing neutralising monoclonal antibodies (nMABs) for people hospitalised in the UK, and dosage to be used, are outlined in NHS England's Interim Clinical Commissioning Policy on neutralising monoclonal antibodies and intravenous antivirals in the treatment of COVID-19 in hospitalised patients, published in December 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given neutralising monoclonal antibodies.

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Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

The panel were presented with evidence from 1 randomised controlled trial (RECOVERY – Horby and Landray 2021). This study looked at people aged 12 and over who were hospitalised because of COVID-19. The treatment was casirivimab and imdevimab (also called Ronapreve, REGEN-COV or REGEN-COV2).

The panel agreed that the evidence from this study showed that there was no marked difference or benefit in the overall population when treated with casirivimab and imdevimab compared to usual care (critical outcomes were mortality, duration of hospitalisation, and progression to invasive mechanical ventilation).

The panel also discussed whether there were significant differences in benefit between and within subgroups of the treatment population. The evidence showed that in people who were seropositive, there was no benefit. However, in people who were seronegative there was a statistically significant reduction in mortality when treated with casirivimab and imdevimab compared to usual care (NNT = around 20). The difference between the results for seronegative and seropositive groups was statistically significant.

The panel discussed the fact that in accordance with protocol, early safety outcomes were not collected throughout the study period. However it was noted that at lower doses side effects are rare. The panel therefore decided that it was likely that the benefit outweighed the risks of treatment based on the available evidence on adverse events.

Based on the evidence, the panel agreed to make a recommendation to offer casirivimab and imdevimab to hospitalised seronegative COVID-19 patients aged 12 and over. The panel discussed whether there was any further evidence to support stratification by different subgroups within the seronegative population, of which there was none. The panel considered subgroups within the seronegative group (for example, age, sex, ethnicity, level of respiratory support, days since symptom onset and use of corticosteroids). Further heterogeneity tests confirmed that no statistically significant differences between subgroups were observed, so the panel agreed that the recommendation could not be further stratified according to subgroups.

The panel acknowledged the need for a serological assay to determine whether someone is seronegative or seropositive. They discussed whether such assays are readily available in the NHS and what the turnaround of these investigations is likely to be. They concluded that they were not aware of any barriers currently to use of serological assays for this purpose in a hospital setting.

The panel also noted the high dosage used in this study population and acknowledged that, at present, there is a lack of evidence about different treatment dosages in people hospitalised with COVID-19. The panel noted that the study did not collect data on whether patients were immunocompromised or vaccinated at baseline and so could not present outcomes for these patient groups. They therefore decided to make a recommendation for research in these areas.

The panel discussed the cost effectiveness of this treatment. However, it was acknowledged that this was out of scope and the panel made recommendations based on the effectiveness and safety evidence.

Certainty of the Evidence

Moderate

The certainty of the evidence was rated as moderate for most outcomes because of serious imprecision. The panel discussed that the issues with imprecision result from few event numbers in some outcomes. Some outcomes within the seronegative subgroup were rated as high certainty.

The panel also noted that safety outcomes were not collected throughout the study period in accordance with study protocol, and early safety data was reported for 30% of the study population. Therefore, the panel concluded that the safety profile of the drugs is not fully understood.

The panel highlighted that the evidence around people who are seronegative was of high certainty and clinical benefit. The panel therefore recommended that this population should be offered the treatment.

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on peoples' preferences and values for treatment with casirivimab and imdevimab. They 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.

Resources and other considerations

Important issues, or potential issues not investigated

The panel discussed the need for prompt testing to determine antibody status and concluded that they were not aware of any barriers currently to use of serological assays for this purpose in a hospital setting. The panel were also aware that the drug could be in short supply. A link to the Interim clinical commissioning policy outlines the eligibility criteria NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 (aged 12 years and above), published in December 2021.

Equity

Important issues, or potential issues not investigated

The panel noted that pregnant and children aged 12 and over were included in the RECOVERY trial, however, no further evidence on the clinical benefit and safety of casirivimab and imdevimab was reported in these participant groups.

No other equity issues were identified.

Acceptability

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about acceptability.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

As of 16 December 2021, NHS England outlined certain criteria for accessing casirivimab and imdevimab in the UK for people hospitalised with COVID-19 (aged 12 years and above). The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given casirivimab and imdevimab.

Rationale

Evidence from 1 randomised, controlled trial in people aged 12 years and over who were hospitalised because of COVID-19 and receiving casirivimab and imdevimab suggests possible benefit of this treatment when compared to usual care for seronegative people. The results from this trial suggest that casirivimab and imdevimab reduced mortality for seronegative people who were hospitalised with COVID-19 when compared to usual care.

The panel decided that the benefits outweighed the risks of treatment based on the available evidence on adverse events in the study and known side effects from the Summary of Product Characteristics (SmPC). As such, this treatment was recommended for seronegative people aged 12 years and over with COVID-19 infection.

Clinical Question/ PICO

Population: People with COVID-19 (Hospitalised)
Intervention: Casirivimab + Imdevimab
Comparator: Usual Care

Summary

What is the evidence informing this recommendation?

Evidence comes from 1 randomised controlled trial with 9,785 participants included. Results from one study, the RECOVERY trial, were reported in Horby and Landray 2021.

The study compared a single dose of intravenous casirivimab (4g) imdevimab (4g) (n=4,839) with usual care (n=4,946). Usual care treatment varied but included corticosteroids (94%), aspirin (28%), remdesivir (25%), colchicine (23%) and tocilizumab or sarilumab (16%).

Study characteristics

The study population was derived from 127 sites in the United Kingdom. Participants aged >12 years, who were hospitalised with COVID-19 were recruited between 18 September 2020 and 22 May 2021. COVID-19 diagnosis was confirmed by a positive polymerase chain reaction (PCR) test. The mean age in the study was around 62 years and 63% of participants were male. Approximately 77% of participants were White, 13% Black, Asian, and minority ethnic groups, and the remainder of unknown ethnicity. It was a median of 9 [IQR 6-12] days since symptom onset, and median 2 (IQR 1-3) days since admission to hospital. Approximately 7% of participants received no oxygen, 62% simple oxygen, 26% non-invasive ventilation and 6% invasive mechanical ventilation. Approximately 54% of participants were positive for SARS-CoV-2 antibody, 32% negative and in 14% these data were missing. Approximately 53% of participants reported comorbidity (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus (HIV), severe liver disease requiring ongoing specialist care, or severe kidney impairment with estimated glomerular filtration rate <30 mL/min per 1·73 m^2). Approximately 94% of participants in both groups were treated with corticosteroids 25% with remdesivir and 16% with tocilizumab or sarilumab. Lastly, pregnant or breastfeeding women were eligible for inclusion.

Exclusion criteria varied, but patients who received intravenous immunoglobulin treatment during the current admission and children weighing less than 40kg and were younger than 12 years old were excluded.

Outcomes were assessed within 28 days after randomisation.

What are the main results?

Mortality – All patients

Moderate quality evidence from 1 study found no statistically significant reduction in overall mortality at 28 days in all participants hospitalised with COVID-19, who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 0.94, CI 95% 0.87 - 1.02; 9,785 people in 1 study].

Mortality - Seropositive

Moderate quality evidence from 1 study found no statistically significant reduction in mortality at 28 days in seropositive people, hospitalised with COVID-19, who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 1.07, CI 95% 0.94 - 1.22; 5,272 people in 1 study].

Mortality - Seronegative

High quality evidence from 1 study found a statistically significant reduction in mortality at 28 days in seronegative people, hospitalised with COVID-19 who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 0.82, CI 95% 0.73 - 0.92; 3,153 people in 1 study].

Invasive mechanical ventilation - All patients

Moderate quality evidence from 1 study found no statistically significant difference in progression to invasive mechanical ventilation at 28 days in all study participants who were hospitalised with COVID-19, and who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 1.00, CI 95% 0.89 - 1.13; 9,198 people in 1 study].

Invasive mechanical ventilation - Seropositive

High quality evidence from 1 study found a statistically significant increase in progression to invasive mechanical ventilation at 28 days in people who were seropositive and treated with casirivimab and imdevimab compared to usual care. [Relative risk 1.17, CI 95% 1.01 - 1.36; 4,989 people in 1 study].

Invasive mechanical ventilation - Seronegative

High quality evidence from 1 study found a statistically significant reduction in progression to invasive mechanical ventilation at 28 days in people who were seropositive and treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.76, CI 95% 0.66 - 0.88; 3,083 people in 1 study].

Non-invasive ventilation - All patients

High quality evidence from 1 study found no statistically significant difference in progression to non-invasive ventilation at 28 days in all study participants who were treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.94, CI 95% 0.84 - 1.05; 6,637 people in 1 study].

Non-invasive ventilation - Seronegative

High quality evidence from 1 study found a statistically significant reduction in progression to non-invasive ventilation at 28 days in people who were seronegative and treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.80, CI 95% 0.67 - 0.96; 2,410 people in 1 study].

Adverse Events - Severe allergic reaction

Low quality evidence from 1 study found no statistically significant difference in severe allergic reactions in people who were hospitalised with COVID-19, and who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 3.83, CI 95% 0.43 - 34.20; 3,506 people in 1 study].

Duration of hospitalisation - All patients

Low quality evidence from 1 study is uncertain about whether treatment with casirivimab and imdevimab in all patients has an effect on the duration of hospitalisation compared to usual care. [Median 10 (IQR: 22) days and Median 10 (IQR: 23) days; 9,785 people in 1 study].

Duration of hospitalisation - Seronegative

Low quality evidence from 1 study is uncertain about whether treatment with casirivimab and imdevimab in the seronegative subgroup has an effect on the duration of hospitalisation compared to usual care. [Median 13 (IQR: 21) days and Median 17 (IQR: 21) days; 3,153 people in 1 study].

Our confidence in the results

Evidence includes one open-label RCT with 9,785 participants (4,839 in treatment arm and 4,946 in control arm). While there are clear reasons for this, it is unlikely to affect the incidence of objective outcomes such as death, invasive ventilation and duration of hospitalisation. The included study was a pre-print and as such was not peer-reviewed.

The strengths of this trial included: appropriate randomisation with allocation concealment, similarity between baseline characteristics in both treatment and control groups and lastly the study population was large and included broad eligibility criteria and the study population was large. Overall it was rated as low risk of bias in all outcomes and domains.

The limitations of the study include the fact that the dose of casirivimab (4g) and imdevimab (4g) used was high compared to similar studies conducted in community settings. Moreover, data on factors such virological load, physiological outcomes, number of patients with clinical deterioration or development of long-term effects of COVID-19 were not collected.

Further subgroup analyses for outcomes within the seronegative population were conducted to identify evidence of marked treatment benefit in specific groups. However, there were no statistically significant differences within these subgroups.

Certainty of the evidence is low for median duration of hospitalisation in all patients and seronegative subgroup, as well as severe allergic reactions, due to very serious imprecision (confidence interval included the line of no effect and low numbers of participants).

Certainty of the evidence is moderate for mortality in all patients in the study and mortality in the seropositive subgroup, progression to invasive mechanical ventilation in all patients and the seropositive subgroup, due to serious imprecision (confidence intervals included the line of no effect).

Certainty of the evidence is high for mortality in people who were seronegative, as well as progression to invasive mechanical ventilation for the seropositive and seronegative subgroups, progression to non-invasive mechanical ventilation in all patients and in the seronegative subgroup.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Casirivimab + Imdevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality [All patients] Within 28 days of randomisation	Relative risk 0.94 (CI 95% 0.87 — 1.02) Based on data from 9,785 participants in 1	207 per 1000	195 per 1000	Moderate Due to serious imprecision [2]	One study found no statistically significant difference in mortality for all participants

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical		Difference:	**12 fewer per 1000** (CI 95% 27 fewer — 4 more)		included in the study who were hospitalised with COVID-19 infection and treated with casirivimab and imdevimab compared to usual care.
Mortality [Seropositive] Within 28 days of randomisation 9 Critical		145 per 1000 Difference:	155 per 1000 **10 more per 1000** (CI 95% 9 fewer — 32 more)	**Moderate** Due to serious imprecision [4]	One study found no statistically significant difference in mortality in people who were seropositive for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Mortality [Seronegative] Within 28 days of randomisation 9 Critical		297 per 1000 Difference:	244 per 1000 **53 fewer per 1000** (CI 95% 80 fewer — 24 fewer)	**High**	One study found a statistically significant reduction in mortality for people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [All patients] Within 28 days of randomisation 9 Critical		105 per 1000 Difference:	105 per 1000 **0 fewer per 1000** (CI 95% 12 fewer — 14 more)	**Moderate** Due to serious imprecision [7]	One study found no statistically significant difference in progression to invasive mechanical ventilation for overall study participants who were not on invasive mechanical ventilation at randomisation and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [Seropositive] Within 28 days of randomisation 9 Critical		163 per 1000 Difference:	185 per 1000 **23 more per 1000** (CI 95% 1 more — 46 more)	**High**	One study found a statistically significant increase in the progression to invasive mechanical ventilation among people who were seropositive for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
		365 per 1000	304 per 1000	**High**	One study found a statistically significant reduction in progression

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
[Seronegative] Within 28 days of randomisation 9 Critical	3,083 participants in 1 studies. [9] (Randomized controlled)	Difference:	**61 fewer per 1000** (CI 95% 90 fewer — 29 fewer)		to invasive mechanical ventilation in people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Non-invasive ventilation [All patients] Within 28 days of randomisation 6 Important	Odds Ratio 0.94 (CI 95% 0.84 — 1.05) Based on data from 6,637 participants in 1 studies. [10] (Randomized controlled)	230 per 1000 Difference:	219 per 1000 **11 fewer per 1000** (CI 95% 29 fewer — 9 more)	High	One study found no statistically significant difference in progression to non-invasive ventilation in all hospitalised patients who were treated with casirivimab and imdevimab compared to usual care.
Non-invasive ventilation [Seronegative] Within 28 days of randomisation 6 Important	Odds Ratio 0.8 (CI 95% 0.67 — 0.96) Based on data from 2,410 participants in 1 studies. [11] (Randomized controlled)	315 per 1000 Difference:	268 per 1000 **46 fewer per 1000** (CI 95% 79 fewer — 9 fewer)	High	One study found a statistically significant reduction in progression to non-invasive mechanical ventilation in people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Adverse events [Severe allergic reaction] 72 hours 6 Important	Relative risk 3.83 (CI 95% 0.43 — 34.2) Based on data from 3,506 participants in 1 studies. [12] (Randomized controlled)	1 per 1000 Difference:	4 per 1000 **3 more per 1000** (CI 95% 1 fewer — 33 more)	**Low** Due to very serious imprecision [13]	One study found no statistically significant difference in severe allergic reactions in hospitalised people treated with casirivimab+imdevimab compared to usual care.
Median duration of hospitalisation [All patients] Days 6 Important	Lower better Based on data from: 9,785 participants in 1 studies. (Randomized controlled)	10 (Median)	10 (Median) CI 95%	**Low** Due to very serious imprecision [14]	It is uncertain whether treatment with casirivimab and imdevimab has an effect on the median duration of hospitalisation in all patients included in the study compared to usual care.
		17 (Median)	13 (Median) CI 95%	**Low** Due to very serious imprecision [15]	It is uncertain whether treatment with casirivimab and imdevimab has an effect on the median duration of hospitalisation in all patients included in the

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Casirivimab + Imdevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important					study compared to usual care.

1. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI cross the line of no effect. **Publication bias: no serious.**
3. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included the line of no effect. **Publication bias: no serious.**
5. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included the line of no effect. **Publication bias: no serious.**
8. Systematic review [100] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
9. Systematic review [100] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [103] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [103] with included studies: Horby 2021, Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** CI included the line of no effect and wide confidence intervals due to small number of events. **Publication bias: no serious.**
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Outcome is not comparable . **Publication bias: no serious.**
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Outcome is not comparable. **Publication bias: no serious.**

References

87. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

100. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

101. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

102. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

103. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

Not recommended

Do not offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19:

- who have detectable SARS-CoV-2 antibodies (seropositive), or
- whose serostatus is unknown.

This recommendation is informed by the results of the RECOVERY trial, which recruited people between 18 September 2020 and 22 May 2021. This was before the emergence of the Omicron (B.1.1.529) variant. In vitro data suggests that the efficacy of casirivimab and imdevimab is likely to be compromised against this variant. NICE will review and update this recommendation as further evidence emerges.

The criteria for accessing neutralising monoclonal antibodies (nMABS) for people hospitalised in the UK, and dosage to be used, are outlined in NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 (aged 12 years and above, published in December 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given neutralising monoclonal antibodies.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel were presented with evidence from 1 randomised controlled trial (RECOVERY – Horby and Landray 2021). This study looked at people aged 12 and over who were hospitalised because of COVID-19. The treatment was casirivimab and imdevimab (also called Ronapreve, REGEN-COV or REGEN-COV2).

The panel agreed that the results from this study showed no marked difference or benefit in the overall population when treated with casirivimab and imdevimab compared to usual care (critical outcomes were: mortality, duration of hospitalisation, progression to invasive mechanical ventilation). The panel also noted the high dosage used in this study population and that at present, there is a lack of evidence about different treatment dosages in people hospitalised with COVID-19.

The panel noted that the proportion of seropositive people hospitalised with COVID-19 is expected to be higher because of the high numbers of the population vaccinated against SARS-CoV-2 and possibly because of previous infection with COVID-19. The panel noted that the study did not account for immunocompromised patients, patients who are vaccinated and patients with unknown serostatus and the outcomes within these specific patient groups. They therefore decided to make a recommendation for research in these areas.

The panel discussed whether there were significant differences in benefit between and within subgroups of the treatment population. The study reported serostatus of subgroups, and the evidence from the study showed that in people who were seropositive or of unknown serostatus there was no benefit in treatment with casirivimab and imdevimab when compared to usual care.

The panel discussed the fact that early safety outcomes were not collected throughout the full study period, in accordance with the study protocol. However, it was noted that at lower doses than those used in the RECOVERY trial, side effects are rare. However, the panel agreed that in seropositive or unknown serostatus groups risk of adverse events could not be determined based on the data reported in the RECOVERY trial.

Certainty of the Evidence

Moderate

The certainty of the evidence was rated as moderate for most outcomes because of serious imprecision. The panel discussed that these issues with imprecision result from few event numbers in some outcomes.

The panel also noted that safety outcomes were not collected throughout the study period in accordance with study protocol. Early safety data was reported for 30% of the study population and so the safety profile of the drugs is not fully understood.

The panel discussed that the evidence around people who were seropositive or of unknown serostatus was less certain but indicated a potential harm of the treatment. The panel therefore recommended that they should not be offered the treatment.

Preference and values

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values for treatment with casirivimab and imdevimab. They 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.

The panel inferred that, in view of the evidence provided, most people who are seropositive or with an unknown serostatus for SARS-CoV-2 antibodies would not choose treatment with casirivimab and imdevimab.

Resources and other considerations

Important issues, or potential issues not investigated

The panel discussed the need for prompt testing to determine antibody status and concluded that they were not aware of any barriers currently to use of serological assays for this purpose in a hospital setting. The panel were also aware that the drug could be in short supply. A link to the Interim clinical commissioning policy outlines the eligibility criteria NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 (aged 12 years and above), published in December 2021.

Equity

Important issues, or potential issues not investigated

The panel noted that pregnant and children aged 12 and over were included in the RECOVERY trial, however, no further evidence on the clinical benefit and safety of casirivimab and imdevimab was reported in these participant groups.

No other equity issues were identified.

Acceptability

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about acceptability.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

As of 16 December2021, NHS England outlined certain criteria for accessing casirivimab and imdevimab in the UK for people hospitalised with COVID-19 (aged 12 years and above). The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given casirivimab and imdevimab.

Rationale

Evidence from 1 randomised, controlled trial did not suggest benefit from treatment with casirivimab and imdevimab for people aged over 12 years who are hospitalised because of COVID-19 and who are seropositive or of an unknown serostatus. The results showed that, compared with usual care, casirivimab and imdevimab did not reduce incidence of mortality, duration of hospitalisation, progression to invasive mechanical ventilation or adverse events incidence in people who are seropositive or of an unknown serostatus.

The panel agreed not to recommend treatment with casirivimab and imdevimab for people who are seropositive or of an unknown serostatus.

Clinical Question/ PICO

Population: People with COVID-19 (Hospitalised)
Intervention: Casirivimab + Imdevimab
Comparator: Usual Care

Summary

What is the evidence informing this recommendation?

Evidence comes from 1 randomised controlled trial with 9,785 participants included. Results from one study, the RECOVERY trial, were reported in Horby and Landray 2021.

The study compared a single dose of intravenous casirivimab (4g) imdevimab (4g) (n=4,839) with usual care (n=4,946). Usual care treatment varied but included corticosteroids (94%), aspirin (28%), remdesivir (25%), colchicine (23%) and tocilizumab or sarilumab (16%).

Study characteristics

The study population was derived from 127 sites in the United Kingdom. Participants aged >12 years, who were hospitalised with COVID-19 were recruited between 18 September 2020 and 22 May 2021. COVID-19 diagnosis was confirmed by a positive polymerase chain reaction (PCR) test. The mean age in the study was around 62 years and 63% of participants were male. Approximately 77% of participants were White, 13% Black, Asian, and minority ethnic groups, and the remainder of unknown ethnicity. It was a median of 9 [IQR 6-12] days since symptom onset, and median 2 (IQR 1-3) days since admission to hospital. Approximately 7% of participants received no oxygen, 62% simple oxygen, 26% non-invasive ventilation and 6% invasive mechanical ventilation. Approximately 54% of participants were positive for SARS-CoV-2 antibody, 32% negative and in 14% these data were missing. Approximately 53% of participants reported comorbidity (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus (HIV), severe liver disease requiring ongoing specialist care, or severe kidney impairment with estimated glomerular filtration rate <30 mL/min per 1·73 m^2). Approximately 94% of participants in both groups were treated with corticosteroids 25% with remdesivir and 16% with tocilizumab or sarilumab. Lastly, pregnant or breastfeeding women were eligible for inclusion.

Exclusion criteria varied, but patients who received intravenous immunoglobulin treatment during the current admission and children weighing less than 40kg and were younger than 12 years old were excluded.

Outcomes were assessed within 28 days after randomisation.

What are the main results?

Mortality – All patients

Moderate quality evidence from 1 study found no statistically significant reduction in overall mortality at 28 days in all participants hospitalised with COVID-19, who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 0.94, CI 95% 0.87 - 1.02; 9,785 people in 1 study].

Mortality - Seropositive

Moderate quality evidence from 1 study found no statistically significant reduction in mortality at 28 days in seropositive people, hospitalised with COVID-19, who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 1.07, CI 95% 0.94 - 1.22; 5,272 people in 1 study].

Mortality - Seronegative

High quality evidence from 1 study found a statistically significant reduction in mortality at 28 days in seronegative

people, hospitalised with COVID-19 who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 0.82, CI 95% 0.73 - 0.92; 3,153 people in 1 study].

Invasive mechanical ventilation - All patients

Moderate quality evidence from 1 study found no statistically significant difference in progression to invasive mechanical ventilation at 28 days in all study participants who were hospitalised with COVID-19, and who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 1.00, CI 95% 0.89 - 1.13; 9,198 people in 1 study].

Invasive mechanical ventilation - Seropositive

High quality evidence from 1 study found a statistically significant increase in progression to invasive mechanical ventilation at 28 days in people who were seropositive and treated with casirivimab and imdevimab compared to usual care. [Relative risk 1.17, CI 95% 1.01 - 1.36; 4,989 people in 1 study].

Invasive mechanical ventilation - Seronegative

High quality evidence from 1 study found a statistically significant reduction in progression to invasive mechanical ventilation at 28 days in people who were seropositive and treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.76, CI 95% 0.66 - 0.88; 3,083 people in 1 study].

Non-invasive ventilation - All patients

High quality evidence from 1 study found no statistically significant difference in progression to non-invasive ventilation at 28 days in all study participants who were treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.94, CI 95% 0.84 - 1.05; 6,637 people in 1 study].

Non-invasive ventilation - Seronegative

High quality evidence from 1 study found a statistically significant reduction in progression to non-invasive ventilation at 28 days in people who were seronegative and treated with casirivimab and imdevimab compared to usual care. [Relative risk 0.80, CI 95% 0.67 - 0.96; 2,410 people in 1 study].

Adverse Events - Severe allergic reaction

Low quality evidence from 1 study found no statistically significant difference in severe allergic reactions in people who were hospitalised with COVID-19, and who were treated with casirivimab + imdevimab compared to usual care. [Relative risk 3.83, CI 95% 0.43 - 34.20; 3,506 people in 1 study].

Duration of hospitalisation - All patients

Low quality evidence from 1 study is uncertain about whether treatment with casirivimab and imdevimab in all patients has an effect on the duration of hospitalisation compared to usual care. [Median 10 (IQR: 22) days and Median 10 (IQR: 23) days; 9,785 people in 1 study].

Duration of hospitalisation - Seronegative

Low quality evidence from 1 study is uncertain about whether treatment with casirivimab and imdevimab in the seronegative subgroup has an effect on the duration of hospitalisation compared to usual care. [Median 13 (IQR: 21) days and Median 17 (IQR: 21) days; 3,153 people in 1 study].

Our confidence in the results

Evidence includes one open-label RCT with 9,785 participants (4,839 in treatment arm and 4,946 in control arm). While there are clear reasons for this, it is unlikely to affect the incidence of objective outcomes such as death, invasive ventilation and duration of hospitalisation. The included study was a pre-print and as such was not peer-reviewed.

The strengths of this trial included: appropriate randomisation with allocation concealment, similarity between baseline characteristics in both treatment and control groups and lastly the study population was large and included broad eligibility criteria and the study population was large. Overall it was rated as low risk of bias in all outcomes and domains.

The limitations of the study include the fact that the dose of casirivimab (4g) and imdevimab (4g) used was high compared to similar studies conducted in community settings. Moreover, data on factors such virological load, physiological outcomes, number of patients with clinical deterioration or development of long-term effects of COVID-19 were not collected.

Further subgroup analyses for outcomes within the seronegative population were conducted to identify evidence of marked treatment benefit in specific groups. However, there were no statistically significant differences within these subgroups.

Certainty of the evidence is low for median duration of hospitalisation in all patients and seronegative subgroup, as well as severe allergic reactions, due to very serious imprecision (confidence interval included the line of no effect and low numbers of participants).

Certainty of the evidence is moderate for mortality in all patients in the study and mortality in the seropositive subgroup, progression to invasive mechanical ventilation in all patients and the seropositive subgroup, due to serious imprecision (confidence intervals included the line of no effect).

Certainty of the evidence is high for mortality in people who were seronegative, as well as progression to invasive mechanical ventilation for the seropositive and seronegative subgroups, progression to non-invasive mechanical ventilation in all patients and in the seronegative subgroup.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual Care	**Intervention** Casirivimab + Imdevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality [All patients] Within 28 days of randomisation 9 Critical	Relative risk 0.94 (CI 95% 0.87 — 1.02) Based on data from 9,785 participants in 1 studies. [1] (Randomized controlled)	207 per 1000 Difference:	195 per 1000 **12 fewer per 1000** (CI 95% 27 fewer — 4 more)	**Moderate** Due to serious imprecision [2]	One study found no statistically significant difference in mortality for all participants included in the study who were hospitalised with COVID-19 infection and treated with casirivimab and imdevimab compared to usual care.
Mortality [Seropositive]	Relative risk 1.07 (CI 95% 0.94 — 1.22)	145	155	**Moderate** Due to serious	One study found no statistically significant

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Within 28 days of randomisation 9 Critical		per 1000 Difference:	per 1000 **10 more per 1000** (CI 95% 9 fewer — 32 more)	imprecision [4]	difference in mortality in people who were seropositive for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Mortality [Seronegative] Within 28 days of randomisation 9 Critical		**297** per 1000 Difference:	**244** per 1000 **53 fewer per 1000** (CI 95% 80 fewer — 24 fewer)	**High**	One study found a statistically significant reduction in mortality for people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [All patients] Within 28 days of randomisation 9 Critical		**105** per 1000 Difference:	**105** per 1000 **0 fewer per 1000** (CI 95% 12 fewer — 14 more)	**Moderate** Due to serious imprecision [7]	One study found no statistically significant difference in progression to invasive mechanical ventilation for overall study participants who were not on invasive mechanical ventilation at randomisation and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [Seropositive] Within 28 days of randomisation 9 Critical		**163** per 1000 Difference:	**185** per 1000 **23 more per 1000** (CI 95% 1 more — 46 more)	**High**	One study found a statistically significant increase in the progression to invasive mechanical ventilation among people who were seropositive for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Invasive mechanical ventilation [Seronegative] Within 28 days of randomisation 9 Critical		**365** per 1000 Difference:	**304** per 1000 **61 fewer per 1000** (CI 95% 90 fewer — 29 fewer)	**High**	One study found a statistically significant reduction in progression to invasive mechanical ventilation in people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
		230	**219**	**High**	One study found no

Outcome Timeframe	Study results and measurements	Comparator Usual Care	Intervention Casirivimab + Imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
ventilation [All patients] Within 28 days of randomisation 6 Important	(CI 95% 0.84 — 1.05) Based on data from 6,637 participants in 1 studies. [10] (Randomized controlled)	per 1000 Difference:	per 1000 **11 fewer per 1000** (CI 95% 29 fewer — 9 more)		statistically significant difference in progression to non-invasive ventilation in all hospitalised patients who were treated with casirivimab and imdevimab compared to usual care.
Non-invasive ventilation [Seronegative] Within 28 days of randomisation 6 Important	Odds Ratio 0.8 (CI 95% 0.67 — 0.96) Based on data from 2,410 participants in 1 studies. [11] (Randomized controlled)	315 per 1000 Difference:	268 per 1000 **46 fewer per 1000** (CI 95% 79 fewer — 9 fewer)	High	One study found a statistically significant reduction in progression to non-invasive mechanical ventilation in people who were seronegative for SARS-CoV-2 antibodies and were treated with casirivimab and imdevimab compared to usual care.
Adverse events [Severe allergic reaction] 72 hours 6 Important	Relative risk 3.83 (CI 95% 0.43 — 34.2) Based on data from 3,506 participants in 1 studies. [12] (Randomized controlled)	1 per 1000 Difference:	4 per 1000 **3 more per 1000** (CI 95% 1 fewer — 33 more)	**Low** Due to very serious imprecision [13]	One study found no statistically significant difference in severe allergic reactions in hospitalised people treated with casirivimab+imdevimab compared to usual care.
Median duration of hospitalisation [All patients] Days 6 Important	Lower better Based on data from: 9,785 participants in 1 studies. (Randomized controlled)	10 (Median)	10 (Median) CI 95%	**Low** Due to very serious imprecision [14]	It is uncertain whether treatment with casirivimab and imdevimab has an effect on the median duration of hospitalisation in all patients included in the study compared to usual care.
		17 (Median)	13 (Median) CI 95%	**Low** Due to very serious imprecision [15]	It is uncertain whether treatment with casirivimab and imdevimab has an effect on the median duration of hospitalisation in all patients included in the study compared to usual care.

1. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI cross the line of no effect. **Publication bias: no serious.**
3. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included the line of no effect. **Publication bias: no serious.**
5. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included the line of no effect. **Publication bias: no serious.**
8. Systematic review [100] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
9. Systematic review [100] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [103] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [103] with included studies: Horby 2021, Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. Systematic review [87] with included studies: Horby 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** CI included the line of no effect and wide confidence intervals due to small number of events. **Publication bias: no serious.**
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Outcome is not comparable . **Publication bias: no serious.**
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Outcome is not comparable. **Publication bias: no serious.**

References

87. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

100. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

101. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

102. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

103. Neutralising antibodies (REGEN-COV) for adults, young people and children hospitalised with COVID-19.

7.4 Remdesivir

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'.

Low-flow oxygen supplementation: oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.

Conditional recommendation

Consider remdesivir for up to 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, in hospital and needing low-flow supplemental oxygen.

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), which was updated in June 2021 to include eligibility criteria for remdesivir in people who are significantly immunocompromised.

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

The marketing authorisation for remdesivir for COVID-19 does not include children under 12 years or weighing less than 40 kg.

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 high-flow oxygen, non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV), which showed a trend towards higher all-cause mortality, and people receiving low-flow oxygen supplementation or no oxygen, which showed a trend towards lower all-cause mortality. The duration and severity of disease was considered the explanation. The panel were presented with a clinical rationale for antiviral treatment, which supports the thinking that antivirals are expected to be most effective early in the disease course, when viral replication is a driver of disease. Antivirals are less likely to be effective in the later stages in the disease course when it enters the hyperinflammatory phase. This phase is often associated with the need for more respiratory support. Although not always described in the evidence, the panel considered that continuous positive airway pressure (CPAP) was included as a type of NIV.

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 provides the optimal treatment duration. The current evidence does not suggest any greater benefit for a 10-day duration but suggests an increased risk of harm. The panel also acknowledged that, if disease progression resulted in the need for more respiratory support while using remdesivir, there may be no benefit in completing the full course. For these reasons, along with resource impact considerations (see also Resources), the panel agreed to recommend remdesivir for up to 5 days.

The panel noted the unclear additive benefit of remdesivir when used with dexamethasone, particularly because 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 need low-flow oxygen supplementation or no oxygen, and people who need high-flow oxygen supplementation, NIV or 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 NIV and IMV. However, the panel agreed that subgroup data should be distinguished between high-flow oxygen, NIV or IMV and low-flow oxygen 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 receiving low-flow oxygen or no oxygen. They agreed that a 'consider' recommendation for people on low-flow supplementary oxygen and not on high-flow oxygen, NIV or 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), and 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. They identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for IMV 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.

The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need low-flow oxygen supplementation, most would choose remdesivir.

Resources and other considerations

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 showing 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 treatment duration. See also the benefits and harms section.

Equity

Important issues, or potential issues not investigated

The panel noted an absence of evidence from randomised trials on remdesivir use 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, weighing 40 kg or more, and 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 their treatment 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, they considered it unlikely that it would be used outside the hospital setting because the criteria for accessing remdesivir in the UK currently stipulate hospitalisation with COVID-19.

No evidence for using remdesivir in pregnancy was identified. The marketing authorisation confirms the lack of evidence, and notes that remdesivir should be avoided in pregnancy unless 'the clinical condition of the women requires treatment with it'. Any decisions to use remdesivir in someone who is pregnant should involve them and a multidisciplinary team, if possible.

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 for those on lower levels of respiratory support.

It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and need low-flow oxygen supplementation would choose 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

There is limited evidence suggesting that remdesivir probably reduces the risk of death in people in hospital with COVID-19 pneumonia needing low-flow oxygen supplementation. This is likely because it is being given early in the disease course (that is, before the need for high-flow oxygen supplementation, non-invasive ventilation or invasive mechanical ventilation) when viral replication is a driver of disease.

The evidence for remdesivir in children and young people is limited. However, the panel were aware that the marketing authorisation for remdesivir for COVID-19 includes young people aged 12 years and over weighing 40 kg or more.

The evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but suggests an increased risk of harm. There may also be no benefit in completing the full course of remdesivir if there is progression to high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation during treatment. The panel also acknowledged that using remdesivir for longer would have greater resource implications.

Clinical Question/ PICO

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

Summary

Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised people who require no or low-flow oxygen.

Compared with standard care, remdesivir probably increases death at day 28 in people who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care.

What is the evidence informing this recommendation?
Evidence comes from 4 randomised controlled trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 (Beigel 2020, Pan 2020, Spinner 2020, Wang 2020). 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 (Pan 2020, Beigel 2020).

The evidence for mortality was divided into 2 analyses based on the level of respiratory support required. This is because it is expected that antivirals will most likely be more effective in the early stages of disease progression. The levels of respiratory support have been used as a proxy to measure disease progression in the trials. Low levels of

respiratory support were considered to be no oxygen supplementation or low-flow oxygen supplementation. Higher levels of respiratory support included, high-flow oxygen supplementation, non-invasive ventilation (NIV) [such as Bilevel Positive Airway Pressure (BiPAP) and Continuous Positive Airway Pressure (CPAP)] and invasive ventilation.

The ACTT-1 trial was conducted very early in the pandemic and may not be reflective of current standard care practices. A sensitivity analysis was conducted for key outcomes.

Study characteristics
Mean or median age ranged from 56 to 66 years and women comprised 32 to 44% of patients across the studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more. There was variability in levels of respiratory support among patients included in the trials (see table).

Levels of respiratory support in trial participants

Level of respiratory support	Biegel 2020 (n=1062)	Wang 2020 (n=236)	Spinner 2020 (n=584)	Pan 2020 (n=5451)
No oxygen or low-flow oxygen supplementation	573 (54%)	197 (83%)	584 (100%)	4964 (91%)
High-flow oxygen supplementation or NIV	193 (18%)	39 (17%)	0 (0%)	0 (0%)
Invasive mechanical ventilation	285 (27%)	0 (0%)	0 (0%)	487 (9%)

What are the main results?
Critical outcomes

All-cause mortality
Moderate quality evidence from 4 studies found that remdesivir reduces death at day 28 in hospitalised people who require no or low-flow oxygen compared to standard care but the estimate is not statistically significant (25 fewer deaths per 1000 people [RR 0.72, 95% CI 0.52 to 1.01; 6318 people in 4 studies]).

Moderate quality evidence from 3 studies found that remdesivir increases death at day 28 in people who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care but the estimate is not statistically significant (50 more deaths per 1000 people [RR 1.20 CI 95% 0.98 to 1.47; 1004 people in 3 studies]).

Sensitivity analyses for mortality which removed the ACTT-1 trial did not change the overall findings in the full analysis. However, it removed evidence of statistical heterogeneity in the no oxygen/low-flow oxygen supplementation analysis. This could be attributed to the expected differences in the trial based on it it being conducted early in the pandemic.

Need for invasive mechanical ventilation of ECMO
Low quality evidence from 1 study found that remdesivir significantly reduced the need for invasive mechanical ventilation (IMV) or ECMO at day 28 with remdesivir compared to standard care in people not receiving IMV at baseline (97 fewer events per 1000 people [RR 0.57 95% CI 0.42 to 0.79; 6192 people in 1 study]).

Serious adverse events
Moderate quality evidence from 3 studies found that remdesivir significantly reduced serious adverse events compared to standard care (63 fewer events per 1000 people [RR 0.75, CI 95% 0.63 to 0.89; 1865 people in 3 studies]).

Important outcomes

Respiratory failure or ARDS
Low quality evidence from 2 studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline (30 fewer events per 1000 people [RR 0.79 95% CI 0.35 to 1.78; 1296 people in 2 studies]).

Septic shock
Very low quality evidence from 2 studies found no statistically significant difference in septic shock at day 28 between remdesivir and standard care. (0 fewer events per 1000 people [RR 1.02 95% CI 0.34 to 3.01; 1296 people from 2 studies]).

Clinical recovery
Low quality evidence from 3 studies found no statistically significant difference in clinical recovery at day 28 between

remdesivir and standard care (7 fewer events per 1000 people [RR 0.99 95% CI 0.86 to 1.14; 1876 people from 3 studies]). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale (Beigel 2020) or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale (Spinner 2020).

Adverse events
Low quality evidence from 3 studies found no statistically significant difference in adverse events at end of follow up between remdesivir and standard care. (22 more events per 1000 people [RR 1.04 95% CI 0.89 to 1.21; 1880 people from 3 studies]).

Discontinuation due to adverse events
Very low quality evidence from 3 studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care. (68 more events per 1000 people [RR 1.73 95% CI 0.57 to 5.28; 1880 people from 3 studies]).

Discharge from hospital
Compared with standard care, remdesivir may have no effect on discharge from hospital at day 28 (7 fewer events per 1000 people [RR 0.99 95% CI 0.96 to 1.03; 5451 people in 1 study]).

Time to recovery
Moderate quality evidence from 1 study found a statistically significant decrease in time to recovery with remdesivir compared with standard care. (HR 1.24, 95% CI 1.08 to 1.42; 1643 people in 2 studies).

Time to improvement
Moderate quality evidence from 2 studies found a borderline statistically significant difference in time to improvement between remdesivir and standard care. (HR 1.17, 95% CI 1.00 to 1.38; 810 people in 2 studies. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale (Spinner 2020) or 6-point ordinal scale (Wang 2020).

Our confidence in the results

Certainty of the evidence is moderate for death in both subgroups (patients who require no oxygen or low-flow oxygen supplementation, and patients who require high-flow oxygen supplementation, NIV or 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**	**Comparator** Placebo or standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality (No oxygen or low flow oxygen) [1] Within 28 days of commencing treatment 9 Critical	Relative risk 0.72 (CI 95% 0.52 — 1.01) Based on data from 6,318 participants in 4 studies. [2] (Randomized controlled)	90 per 1000 Difference:	65 per 1000 **25 fewer per 1000** (CI 95% 43 fewer — 1 more)	Moderate Due to serious imprecision [3]	A pooled analysis of 6 studies found a non-statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (High flow oxygen, NIV or IMV) [4] Within 28 days of commencing treatment 9 Critical		248 per 1000 Difference:	298 per 1000 **50 more per 1000** (CI 95% 5 fewer — 117 more)	**Moderate** Due to serious imprecision [6]	A pooled analysis of 4 studies found a non-statistically significant increase in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV.
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical		225 per 1000 Difference:	128 per 1000 **97 fewer per 1000** (CI 95% 130 fewer — 47 fewer)	**Low** Due to serious imprecision and serious risk of bias [8]	One study found a statistically significant reduction in the need for invasive mechanical ventilation or ECMO at day 28 with remdesivir compared with standard care, in hospitalised patients not on invasive ventilation at baseline.
Serious adverse events [9] End of follow-up 9 Critical		253 per 1000 Difference:	190 per 1000 **63 fewer per 1000** (CI 95% 94 fewer — 28 fewer)	**Moderate** Due to serious risk of bias [11]	Three studies found a statistically significant reduction in serious adverse events at end of follow up between remdesivir and standard care.
Respiratory failure or ARDS Within 28 days of commencing treatment 6 Important		143 per 1000 Difference:	113 per 1000 **30 fewer per 1000** (CI 95% 93 fewer — 112 more)	**Low** Due to serious inconsistency and serious imprecision [13]	Two studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline.
Patients requiring ventilation [14] Within 28 days of commencing treatment 6 Important		115 per 1000 Difference:	118 per 1000 **3 more per 1000** (CI 95% 13 fewer — 23 more)	**Moderate** Due to serious imprecision [16]	One study found no statistically significant difference in the number of patients requiring mechanical ventilation at day 28 between remdesivir and standard care.
		10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 20 more)	**Very low** Due to serious risk of bias, serious inconsistency and serious	Two studies found no statistically significant difference in septic shock at day 28 between remdesivir and standard care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
				imprecision [18]	
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 participants in 3 studies. [19] (Randomized controlled)	711 per 1000 Difference:	704 per 1000 **7 fewer per 1000** (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [20]	Three studies found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 1,880 participants in 3 studies. [21] (Randomized controlled)	548 per 1000 Difference:	570 per 1000 **22 more per 1000** (CI 95% 60 fewer — 115 more)	**Low** Due to serious risk of bias and serious inconsistency [22]	Three studies found no statistically significant difference in adverse events at end of follow up between remdesivir and standard care.
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 participants in 3 studies. [23] (Randomized controlled)	93 per 1000 Difference:	161 per 1000 **68 more per 1000** (CI 95% 40 fewer — 398 more)	**Very low** Due to serious risk of bias, serious inconsistency and serious imprecision [24]	Three studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care.
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 participants in 1 studies. [25] (Randomized controlled)	720 per 1000 Difference:	713 per 1000 **7 fewer per 1000** (CI 95% 29 fewer — 22 more)	**Moderate** Due to serious imprecision [26]	One study found no statistically significant difference in discharge from hospital at day 28 between remdesivir and standard care.
Time to recovery Days 6 Important	Hazard Ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 participants in 2 studies. [27] (Randomized controlled)			**Moderate** Due to serious risk of bias [28]	Two studies found a statistically significant decrease in time to recovery with remdesivir compared with standard care.
Time to improvement Days 6 Important	Hazard Ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 participants in 2 studies. [29] (Randomized controlled)			**Moderate** Due to serious risk of bias [30]	Two studies found a borderline statistically significant difference in time to improvement between remdesivir and standard care.

1. People not receiving oxygen or receiving low flow oxygen at baseline only
2. Systematic review [29] with included studies: SOLIDARITY 2020 no O2, SOLIDARITY 2020 low/hi flow, Wang 2020 low flow, Spinner 2020, Beigel 2020 lo-flow, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.

3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
4. People who were receiving high flow oxygen, non-invasive ventilation or invasive mechanical ventilation at baseline
5. Systematic review [29] with included studies: SOLIDARITY 2020 ventilation, Beigel 2020 Inv vent, Beigel 2020 hi flow or NIV, Wang 2020 high flow or ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
7. Systematic review [29] 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 [29] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. Systematic review [29] with included studies: Wang 2020, Beigel 2020, Wang 2020, Beigel 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. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
14. Listed as critical in PICO
15. Systematic review [29] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
17. Systematic review [29] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
19. Systematic review [29] with included studies: Spinner 2020, Wang 2020, Spinner 2020, Beigel 2020, Beigel 2020, Wang 2020, Spinner 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **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.**
21. Systematic review [29] with included studies: Beigel 2020, Wang 2020, Spinner 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: no serious. Publication bias: no serious.**
23. Systematic review [29] with included studies: Spinner 2020, Wang 2020, Spinner 2020, Beigel 2020. **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **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.**
25. Systematic review [29] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
26. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
27. Systematic review [29] . **Baseline/comparator:** Control arm of reference used for intervention.

28. **Risk of Bias: serious.** Inadequate/lack of 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.**
29. Systematic review [29] . **Baseline/comparator:** Control arm of reference used for intervention.
30. **Risk of Bias: serious.** Inadequate/lack of 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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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 moderate to critical COVID-19 (Goldman 2020; Spinner 2020).

Study characteristics
Mean or median age ranged between 56 to 62 years and women comprised 32 to 40% of patients across both studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more.

The majority of people (84%) in 1 trial (Spinner 2020) were not receiving oxygen supplementation at baseline. In the second trial 55% were receiving oxygen supplementation at baseline and 30.5% were ventilated (Goldman 2020).

What are the main results?

Critical outcomes

All-cause mortality
Moderate quality evidence from 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment (16 fewer deaths per 1000 people [RR 0.73 95% CI 0.40 to 1.33; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment (5 fewer deaths per 1000 people [RR 0.67 95% CI 0.11 to 3.99; 384 people in 1 study]).

Serious adverse events
Moderate quality evidence from 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment (72 fewer events per 1000 people [RR 0.64 95% CI 0.47 to 0.87; 781 people in 2 studies]).

Important outcomes

Acute respiratory failure or ARDS
Low quality evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment (62 fewer events per 1000 people [RR 0.47 95% CI 0.24 to 0.94; 397 people in 1 study]).

Septic shock
Very low-quality evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment compared to 10-day treatment (15 fewer events per 1000 people [RR 0.39 95% CI 0.08 to 2.01; 397 people in 1 study]).

Clinical recovery
Low quality evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment (108 more events per 1000 people [RR 1.20 95% CI 1.02 to 1.14; 397 people in 1 study]).

Adverse events
Moderate quality evidence from 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment (46 fewer events per 1000 people [RR 0.93 95% CI 0.84 to 1.03; 781 people in 2 studies]) .

Discontinuation due to adverse events
Low quality evidence from 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment (23 fewer events per 1000 people [RR 0.59 95% CI 0.30 to 1.15; 781 people in 2 studies]).

Discharge from hospital
Moderate quality evidence from 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment (38 more events per 1000 people [RR 1.06 95% CI 0.93 to 1.20; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment (9 fewer events per 1000 people [RR 0.99 95% CI 0.92 to 1.06; 384 people in 1 study]).

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, lack of blinding), serious imprecision (low event rate for the outcome of death within 14 days) 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir 10 days	**Intervention** Remdesivir 5 days	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 14 days of commencing treatment	Relative risk 0.73 (CI 95% 0.4 — 1.33) Based on data from 781 participants in 2 studies. [1] (Randomized	59 per 1000 Difference:	43 per 1000 **16 fewer per**	**Moderate** Due to serious imprecision [2]	A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 14 days with

Outcome Timeframe	Study results and measurements	Comparator Remdesivir 10 days	Intervention Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical	controlled)		**1000** (CI 95% 35 fewer — 19 more)		
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 participants in 1 studies. [3] (Randomized controlled)	**16** per 1000 Difference:	**11** per 1000 **5 fewer per 1000** (CI 95% 14 fewer — 48 more)	**Low** Due to very serious imprecision [4]	Evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment.
Serious adverse events End of follow-up 9 Critical	Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 participants in 2 studies. [5] (Randomized controlled)	**200** per 1000 Difference:	**128** per 1000 **72 fewer per 1000** (CI 95% 106 fewer — 26 fewer)	**Moderate** Due to serious risk of bias [6]	A pooled analysis of 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment.
Acute respiratory failure or ARDS Within 30 days of commencing treatment 6 Important	Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 participants in 1 studies. [7] (Randomized controlled)	**117** per 1000 Difference:	**55** per 1000 **62 fewer per 1000** (CI 95% 89 fewer — 7 fewer)	**Low** Due to very serious imprecision [8]	Evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment 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 participants in 1 studies. [9] (Randomized controlled)	**25** per 1000 Difference:	**10** per 1000 **15 fewer per 1000** (CI 95% 23 fewer — 25 more)	**Very low** Due to very serious imprecision and serious risk of bias [10]	Evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment 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 participants in 1 studies. [11] (Randomized controlled)	**538** per 1000 Difference:	**646** per 1000 **108 more per 1000** (CI 95% 11 more — 221 more)	**Low** Due to serious risk of bias and serious imprecision [12]	Evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
		662 per 1000 Difference:	**616** per 1000 **46 fewer per 1000**	**Moderate** Due to serious risk of bias [14]	A pooled analysis of 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment

Outcome Timeframe	Study results and measurements	Comparator Remdesivir 10 days	Intervention Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain language summary
			(CI 95% 106 fewer — 20 more)		compared to 10-day treatment.
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 participants in 2 studies. [15] (Randomized controlled)	56 per 1000 Difference:	33 per 1000 **23 fewer per 1000** (CI 95% 39 fewer — 8 more)	**Low** Due to serious risk of bias and serious imprecision [16]	A pooled analysis of 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment 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 participants in 2 studies. [17] (Randomized controlled)	638 per 1000 Difference:	676 per 1000 **38 more per 1000** (CI 95% 45 fewer — 128 more)	**Moderate** Due to serious risk of bias [18]	A pooled analysis of 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
		902 per 1000 Difference:	893 per 1000 **9 fewer per 1000** (CI 95% 72 fewer — 54 more)	**Low** Due to very serious imprecision [20]	Evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment.

1. Systematic review [22] with included studies: Spinner 2020, Goldman 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 [22] 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 [22] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **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 [22] 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: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
11. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for

intervention.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
13. Systematic review [22] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
15. Systematic review [22] 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 [22] 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 [22] 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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26. 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 in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of a clinical trial.

Evidence To Decision

Benefits and harms

Important harms

The panel noted the opposing directions of effect between people receiving high-flow oxygen, non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV), which showed a trend towards higher all-cause mortality, and people receiving low-flow oxygen supplementation or no oxygen, which showed a trend towards lower all-cause mortality. The duration and severity of disease was considered the explanation. The panel were presented with a clinical rationale for antiviral treatment, which supports the thinking that antivirals are expected to be most effective early in the disease course, when viral replication is a driver of disease. Antivirals are less likely to be effective in the later stages in the disease course, which include the hyperinflammatory phase and the need for more respiratory support.

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 high-flow oxygen supplementation, NIV or 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 provides the optimal duration of treatment. The current evidence does not suggest any greater benefit for 10-day duration but increased risk of harm. The panel also acknowledged that, if the disease progression resulted in the need for more respiratory support while using remdesivir, there may be no benefit in completing the full course. For these reasons, along with resource impact considerations (see also Resources), the panel agreed to recommend remdesivir for up to 5 days.

The panel noted the unclear additive benefit of remdesivir when used with dexamethasone, particularly because 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 need low-flow oxygen supplementation or no oxygen, and people who need high-flow oxygen supplementation, NIV or 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 NIV and IMV. However, the panel agreed that subgroup data should be distinguished between high-flow oxygen, NIV or IMV and low-flow oxygen 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 high-flow oxygen, NIV or 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), and 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

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values. They identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for IMV 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.

The panel inferred that, in view of the potential harm for people with COVID-19 receiving high-flow oxygen supplementation, NIV or IMV, most would not choose remdesivir.

Resources and other considerations

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 showing 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 treatment duration. See also the benefits and harms section.

Equity

Important issues, or potential issues not investigated

The panel noted an absence of evidence on remdesivir use in children. However, they 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, weighing 40 kg or more, and 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 their treatment should be discussed on a case-by-case basis with the paediatric infectious diseases team.

Children are often excluded from clinical trials. It was suggested that the recommendation could lead to inequity if adults could have remdesivir as part of a trial, but children could not. However, the proposed inequity is outweighed by the possibility of harm from remdesivir use in people who need high-flow or more intensive oxygen therapy.

The panel also noted the absence of evidence on the use of remdesivir in community settings. However, they considered it unlikely that it would be used outside the hospital setting because the criteria for accessing remdesivir in the UK currently stipulate hospitalisation with COVID-19.

No evidence for using remdesivir in pregnancy was identified. The marketing authorisation confirms the lack of evidence and notes that remdesivir should be avoided in pregnancy unless 'the clinical condition of the women requires treatment with it'. People who are pregnant are often excluded from clinical trials, which could lead to inequity if some adults could have remdesivir as part of a clinical trial but people who are pregnant could not. However, the proposed inequity is outweighed by the possibility of harm from remdesivir use in people who need high-flow or more intensive oxygen therapy.

No other equity issues were identified.

Acceptability

Intervention is likely poorly accepted

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 standard care for those on higher levels of respiratory support.

It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and need high-flow oxygen supplementation, NIV or IMV 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

There is evidence that shows remdesivir may increase the risk of death in people who are on high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation. However, the panel were aware of ongoing trials of remdesivir that include this group of people. The panel agreed that remdesivir should only be used for COVID-19 pneumonia in this group as part of a clinical trial to support recruitment into these trials.

Clinical Question/ PICO

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

Summary

Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised people who require no or low-flow oxygen.

Compared with standard care, remdesivir probably increases death at day 28 in people who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care.

What is the evidence informing this recommendation?
Evidence comes from 4 randomised controlled trials that compared remdesivir with standard care in 7333 adults hospitalised with COVID-19 (Beigel 2020, Pan 2020, Spinner 2020, Wang 2020). 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 (Pan 2020, Beigel 2020).

The evidence for mortality was divided into 2 analyses based on the level of respiratory support required. This is because it is expected that antivirals will most likely be more effective in the early stages of disease progression. The levels of respiratory support have been used as a proxy to measure disease progression in the trials. Low levels of respiratory support were considered to be no oxygen supplementation or low-flow oxygen supplementation. Higher levels of respiratory support included, high-flow oxygen supplementation, non-invasive ventilation (NIV) [such as Bilevel Positive Airway Pressure (BiPAP) and Continuous Positive Airway Pressure (CPAP)] and invasive ventilation.

The ACTT-1 trial was conducted very early in the pandemic and may not be reflective of current standard care practices. A sensitivity analysis was conducted for key outcomes.

Study characteristics
Mean or median age ranged from 56 to 66 years and women comprised 32 to 44% of patients across the studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more. There was variability in levels of respiratory support among patients included in the trials (see table).

Levels of respiratory support in trial participants

Level of respiratory support	Biegel 2020 (n=1062)	Wang 2020 (n=236)	Spinner 2020 (n=584)	Pan 2020 (n=5451)
No oxygen or low-flow oxygen supplementation	573 (54%)	197 (83%)	584 (100%)	4964 (91%)
High-flow oxygen supplementation or NIV	193 (18%)	39 (17%)	0 (0%)	0 (0%)
Invasive mechanical ventilation	285 (27%)	0 (0%)	0 (0%)	487 (9%)

What are the main results?
Critical outcomes

All-cause mortality
Moderate quality evidence from 4 studies found that remdesivir reduces death at day 28 in hospitalised people who require no or low-flow oxygen compared to standard care but the estimate is not statistically significant (25 fewer deaths per 1000 people [RR 0.72, 95% CI 0.52 to 1.01; 6318 people in 4 studies]).

Moderate quality evidence from 3 studies found that remdesivir increases death at day 28 in people who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care but the estimate is not statistically significant (50 more deaths per 1000 people [RR 1.20 CI 95% 0.98 to 1.47; 1004 people in 3 studies]).

Sensitivity analyses for mortality which removed the ACTT-1 trial did not change the overall findings in the full analysis. However, it removed evidence of statistical heterogeneity in the no oxygen/low-flow oxygen supplementation analysis. This could be attributed to the expected differences in the trial based on it it being conducted early in the pandemic.

Need for invasive mechanical ventilation of ECMO
Low quality evidence from 1 study found that remdesivir significantly reduced the need for invasive mechanical ventilation (IMV) or ECMO at day 28 with remdesivir compared to standard care in people not receiving IMV at baseline (97 fewer events per 1000 people [RR 0.57 95% CI 0.42 to 0.79; 6192 people in 1 study]).

Serious adverse events
Moderate quality evidence from 3 studies found that remdesivir significantly reduced serious adverse events compared to standard care (63 fewer events per 1000 people [RR 0.75, CI 95% 0.63 to 0.89; 1865 people in 3 studies]).

Important outcomes

Respiratory failure or ARDS
Low quality evidence from 2 studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline (30 fewer events per 1000 people [RR 0.79 95% CI 0.35 to 1.78; 1296 people in 2 studies]).

Septic shock
Very low quality evidence from 2 studies found no statistically significant difference in septic shock at day 28 between remdesivir and standard care. (0 fewer events per 1000 people [RR 1.02 95% CI 0.34 to 3.01; 1296 people from 2 studies]).

Clinical recovery
Low quality evidence from 3 studies found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care (7 fewer events per 1000 people [RR 0.99 95% CI 0.86 to 1.14; 1876 people from 3 studies]). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale (Beigel 2020) or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale (Spinner 2020).

Adverse events
Low quality evidence from 3 studies found no statistically significant difference in adverse events at end of follow up between remdesivir and standard care. (22 more events per 1000 people [RR 1.04 95% CI 0.89 to 1.21; 1880 people from 3 studies]).

Discontinuation due to adverse events
Very low quality evidence from 3 studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care. (68 more events per 1000 people [RR 1.73 95% CI 0.57 to 5.28; 1880 people from 3 studies]).

Discharge from hospital
Compared with standard care, remdesivir may have no effect on discharge from hospital at day 28 (7 fewer events per 1000 people [RR 0.99 95% CI 0.96 to 1.03; 5451 people in 1 study]).

Time to recovery
Moderate quality evidence from 1 study found a statistically significant decrease in time to recovery with remdesivir compared with standard care. (HR 1.24, 95% CI 1.08 to 1.42; 1643 people in 2 studies).

Time to improvement
Moderate quality evidence from 2 studies found a borderline statistically significant difference in time to improvement between remdesivir and standard care. (HR 1.17, 95% CI 1.00 to 1.38; 810 people in 2 studies. Clinical improvement was defined as an improvement of 2 or more points on a 7-point ordinal scale (Spinner 2020) or 6-point ordinal scale (Wang 2020).

Our confidence in the results

Certainty of the evidence is moderate for death in both subgroups (patients who require no oxygen or low-flow oxygen supplementation, and patients who require high-flow oxygen supplementation, NIV or 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	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (No oxygen or low flow oxygen) [1] Within 28 days of commencing treatment 9 Critical	Relative risk 0.72 (CI 95% 0.52 — 1.01) Based on data from 6,318 participants in 4 studies. [2] (Randomized controlled)	90 per 1000 Difference:	65 per 1000 **25 fewer per 1000** (CI 95% 43 fewer — 1 more)	Moderate Due to serious imprecision [3]	A pooled analysis of 6 studies found a non-statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation
All-cause mortality (High flow oxygen, NIV or IMV) [4] Within 28 days of commencing treatment 9 Critical	Relative risk 1.2 (CI 95% 0.98 — 1.47) Based on data from 1,004 participants in 3 studies. [5]	248 per 1000 Difference:	298 per 1000 **50 more per 1000** (CI 95% 5 fewer — 117 more)	Moderate Due to serious imprecision [6]	A pooled analysis of 4 studies found a non-statistically significant increase in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV.
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 participants in 1 studies. [7] (Randomized controlled)	225 per 1000 Difference:	128 per 1000 **97 fewer per 1000** (CI 95% 130 fewer — 47 fewer)	Low Due to serious imprecision and serious risk of bias [8]	One study found a statistically significant reduction in the need for invasive mechanical ventilation or ECMO at day 28 with remdesivir compared with standard care, in hospitalised patients not on invasive ventilation at baseline.
Serious adverse events [9] End of follow-up 9 Critical	Relative risk 0.75 (CI 95% 0.63 — 0.89) Based on data from 1,865 participants in 3 studies. [10] (Randomized controlled)	253 per 1000 Difference:	190 per 1000 **63 fewer per 1000** (CI 95% 94 fewer — 28 fewer)	Moderate Due to serious risk of bias [11]	Three studies found a statistically significant reduction in serious adverse events at end of follow up between remdesivir and standard care.
Respiratory failure or ARDS Within 28 days of commencing treatment 6 Important	Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 participants in 2 studies. [12] (Randomized controlled)	143 per 1000 Difference:	113 per 1000 **30 fewer per 1000** (CI 95% 93 fewer — 112 more)	Low Due to serious inconsistency and serious imprecision [13]	Two studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline.

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Patients requiring ventilation [14] Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.89 — 1.2) Based on data from 4,964 participants in 1 studies. [15] (Randomized controlled)	115 per 1000 Difference:	118 per 1000 **3 more per 1000** (CI 95% 13 fewer — 23 more)	Moderate Due to serious imprecision [16]	One study found no statistically significant difference in the number of patients requiring mechanical ventilation at day 28 between remdesivir and standard care.
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 participants in 2 studies. [17] (Randomized controlled)	10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 20 more)	Very low Due to serious risk of bias, serious inconsistency and serious imprecision [18]	
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 participants in 3 studies. [19] (Randomized controlled)	711 per 1000 Difference:	704 per 1000 **7 fewer per 1000** (CI 95% 100 fewer — 100 more)	Low Due to serious risk of bias and serious inconsistency [20]	
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 1,880 participants in 3 studies. [21] (Randomized controlled)	548 per 1000 Difference:	570 per 1000 **22 more per 1000** (CI 95% 60 fewer — 115 more)	Low Due to serious risk of bias and serious inconsistency [22]	
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 participants in 3 studies. [23] (Randomized controlled)	93 per 1000 Difference:	161 per 1000 **68 more per 1000** (CI 95% 40 fewer — 398 more)	Very low Due to serious risk of bias, serious inconsistency and serious imprecision [24]	Three studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care.
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 participants in 1 studies. [25] (Randomized controlled)	720 per 1000 Difference:	713 per 1000 **7 fewer per 1000** (CI 95% 29 fewer — 22 more)	Moderate Due to serious imprecision [26]	One study found no statistically significant difference in discharge from hospital at day 28 between remdesivir and standard care.
				Moderate Due to serious risk of bias [28]	Two studies found a statistically significant decrease in time to recovery with remdesivir

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important	studies. [27] (Randomized controlled)				compared with standard care.

1. People not receiving oxygen or receiving low flow oxygen at baseline only
2. Systematic review [29] with included studies: SOLIDARITY 2020 no O2, SOLIDARITY 2020 low/hi flow, Wang 2020 low flow, Spinner 2020, Beigel 2020 lo-flow, Beigel 2020 no O2. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
4. People who were receiving high flow oxygen, non-invasive ventilation or invasive mechanical ventilation at baseline
5. Systematic review [29] with included studies: SOLIDARITY 2020 ventilation, Beigel 2020 Inv vent, Beigel 2020 hi flow or NIV, Wang 2020 high flow or ventilation. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
7. Systematic review [29] 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 [29] with included studies: Beigel 2020, Spinner 2020, Wang 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. Systematic review [29] with included studies: Wang 2020, Beigel 2020, Wang 2020, Beigel 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. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
14. Listed as critical in PICO
15. Systematic review [29] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
17. Systematic review [29] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
19. Systematic review [29] with included studies: Spinner 2020, Wang 2020, Spinner 2020, Beigel 2020, Beigel 2020, Wang 2020, Spinner 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance

bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **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.**

21. Systematic review [29] with included studies: Beigel 2020, Wang 2020, Spinner 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: no serious. Publication bias: no serious.**

23. Systematic review [29] with included studies: Spinner 2020, Wang 2020, Spinner 2020, Beigel 2020. **Baseline/ comparator:** Control arm of reference used for intervention.

24. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **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.**

25. Systematic review [29] with included studies: SOLIDARITY 2020. **Baseline/comparator:** Control arm of reference used for intervention.

26. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**

27. Systematic review [29] . **Baseline/comparator:** Control arm of reference used for intervention.

28. **Risk of Bias: serious.** Inadequate/lack of 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.**

29. Systematic review [29] . **Baseline/comparator:** Control arm of reference used for intervention.

30. **Risk of Bias: serious.** Inadequate/lack of 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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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 moderate to critical COVID-19 (Goldman 2020; Spinner 2020).

Study characteristics
Mean or median age ranged between 56 to 62 years and women comprised 32 to 40% of patients across both studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more.

The majority of people (84%) in 1 trial (Spinner 2020) were not receiving oxygen supplementation at baseline. In the second trial 55% were receiving oxygen supplementation at baseline and 30.5% were ventilated (Goldman 2020).

What are the main results?

Critical outcomes

All-cause mortality
Moderate quality evidence from 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment (16 fewer deaths per 1000 people [RR 0.73 95% CI 0.40 to 1.33; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment (5 fewer deaths per 1000 people [RR 0.67 95% CI 0.11 to 3.99; 384 people in 1 study]).

Serious adverse events
Moderate quality evidence from 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment (72 fewer events per 1000 people [RR 0.64 95% CI 0.47 to 0.87; 781 people in 2 studies]).

Important outcomes

Acute respiratory failure or ARDS
Low quality evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment (62 fewer events per 1000 people [RR 0.47 95% CI 0.24 to 0.94; 397 people in 1 study]).

Septic shock
Very low-quality evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment compared to 10-day treatment (15 fewer events per 1000 people [RR 0.39 95% CI 0.08 to 2.01; 397 people in 1 study]).

Clinical recovery
Low quality evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment (108 more events per 1000 people [RR 1.20 95% CI 1.02 to 1.14; 397 people in 1 study]).

Adverse events
Moderate quality evidence from 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment (46 fewer events per 1000 people [RR 0.93 95% CI 0.84 to 1.03; 781 people in 2 studies]) .

Discontinuation due to adverse events
Low quality evidence from 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment (23 fewer events per 1000 people [RR 0.59 95% CI 0.30 to 1.15; 781 people in 2 studies]).

Discharge from hospital
Moderate quality evidence from 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment (38 more events per 1000 people [RR 1.06 95% CI 0.93 to 1.20; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment (9 fewer events per 1000 people [RR 0.99 95% CI 0.92 to 1.06; 384 people in 1 study]).

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, lack of blinding), serious imprecision (low event rate for the outcome of death within 14 days) 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir 10 days	**Intervention** Remdesivir 5 days	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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 participants in 2 studies. [1] (Randomized controlled)	59 per 1000 Difference:	43 per 1000 **16 fewer per 1000** (CI 95% 35 fewer — 19 more)	Moderate Due to serious imprecision [2]	A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
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 participants in 1 studies. [3] (Randomized controlled)	16 per 1000 Difference:	11 per 1000 **5 fewer per 1000** (CI 95% 14 fewer — 48 more)	Low Due to very serious imprecision [4]	Evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment.
Serious adverse events End of follow-up 9 Critical	Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 participants in 2 studies. [5] (Randomized controlled)	200 per 1000 Difference:	128 per 1000 **72 fewer per 1000** (CI 95% 106 fewer — 26 fewer)	Moderate Due to serious risk of bias [6]	A pooled analysis of 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment.
Acute respiratory failure or ARDS Within 30 days of commencing treatment 6 Important	Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 participants in 1 studies. [7] (Randomized controlled)	117 per 1000 Difference:	55 per 1000 **62 fewer per 1000** (CI 95% 89 fewer — 7 fewer)	Low Due to very serious imprecision [8]	Evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment 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 participants in 1 studies. [9] (Randomized controlled)	25 per 1000 Difference:	10 per 1000 **15 fewer per 1000** (CI 95% 23 fewer	Very low Due to very serious imprecision and serious risk of bias [10]	Evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment compared to 10-day treatment.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir 10 days	Intervention Remdesivir 5 days	Certainty of the Evidence (Quality of evidence)	Plain language summary
			— 25 more)		
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 participants in 1 studies. [11] (Randomized controlled)	538 per 1000 Difference:	646 per 1000 **108 more per 1000** (CI 95% 11 more — 221 more)	**Low** Due to serious risk of bias and serious imprecision [12]	Evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment 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 participants in 2 studies. [13] (Randomized controlled)	662 per 1000 Difference:	616 per 1000 **46 fewer per 1000** (CI 95% 106 fewer — 20 more)	**Moderate** Due to serious risk of bias [14]	A pooled analysis of 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment.
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 participants in 2 studies. [15] (Randomized controlled)	56 per 1000 Difference:	33 per 1000 **23 fewer per 1000** (CI 95% 39 fewer — 8 more)	**Low** Due to serious risk of bias and serious imprecision [16]	A pooled analysis of 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment 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 participants in 2 studies. [17] (Randomized controlled)	638 per 1000 Difference:	676 per 1000 **38 more per 1000** (CI 95% 45 fewer — 128 more)	**Moderate** Due to serious risk of bias [18]	A pooled analysis of 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment.
		902 per 1000 Difference:	893 per 1000 **9 fewer per 1000** (CI 95% 72 fewer — 54 more)	**Low** Due to very serious imprecision [20]	Evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment.

1. Systematic review [22] with included studies: Spinner 2020, Goldman 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 [22] 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 [22] with included studies: Spinner 2020, Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **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 [22] 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: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
11. Systematic review [22] with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
13. Systematic review [22] with included studies: Goldman 2020, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
15. Systematic review [22] 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 [22] 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 [22] 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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7.5 Tocilizumab

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'.

Recommended

Offer tocilizumab to adults in hospital with COVID-19 if all 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:

- 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 October 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 plus standard care is statistically significantly more effective than standard care alone at reducing all-cause mortality at 21 to 28 days in adults in hospital with COVID-19. Tocilizumab plus standard care did not statistically significantly reduce mortality at other timepoints compared with standard care alone, although the panel noted that considerably fewer people were included at the other timepoints.

The evidence suggests that people having tocilizumab plus standard care have statistically significantly fewer serious adverse events compared with people having standard care alone. Serious adverse events reported in the studies included bacterial infection and acute respiratory distress syndrome. The panel acknowledged that the reason for this reduction is not clear but suggested it may be because of a beneficial effect of tocilizumab.

The evidence also suggests that tocilizumab plus standard care is statistically significantly more effective than standard care alone at reducing the combined outcome of death and time on organ support.

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 were published. The panel discussed that the evidence shows an additional benefit when tocilizumab is used with corticosteroids. About two-thirds of people across all studies had corticosteroids.

Long-term use of tocilizumab for non-COVID indications 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. Therefore, the risks associated with long-term use may not apply to people having tocilizumab for COVID-19. The studies had follow-up periods of between 14 and 90 days, so should have captured any adverse events of tocilizumab. The panel acknowledged the suppressive 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 its summaries of product characteristics. The panel also agreed that it would 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. This is so that they are aware of any potential long-term treatment effects.

Certainty of the Evidence

Moderate

The certainty of the evidence ranges from high to low. All-cause mortality at 21 to 28 days is of high quality. The certainty of all-cause mortality at other timepoints is moderate because of wide confidence intervals.

The serious adverse events result is of moderate quality because of a lack of blinding. The adverse events data is of low quality because of a lack of blinding and a wide confidence interval.

There is a moderate risk of bias with the combined outcome of reducing death and reducing time on organ support because of a lack of blinding.

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 is 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 and serious adverse events. It is likely that these outcomes would also be of similar importance to people with COVD-19. In addition, less serious adverse events are likely to be of particular importance to people with COVD-19. This outcome was not as commonly reported in studies.

Resources and other considerations

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 with COVID-19 to have treatment as early as possible. This may reduce the need to use more critical resources in the hospital setting. For further details, see NHS England's Interim Clinical Commissioning Policy on tocilizumab for hospitalised patients with COVID-19 pneumonia (adults).

Equity

Important issues, or potential issues not investigated

The trials identified do not provide data on tocilizumab use in pregnancy, or in children and young people. 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 when possible. The summaries of product characteristics outline special considerations for breastfeeding and conception.

The panel discussed that oxygen supplementation may not be suitable for everyone. Although this may be more of an issue in the community, the panel wanted to ensure that tocilizumab use is not reliant on having oxygen supplementation. Rather, they agreed that there should be a need 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 evidence was identified that could be used to assess the acceptability of tocilizumab use. However, in the context of the COVID-19 pandemic, it is likely that patients, and their families and clinicians, would accept tocilizumab use because the benefits of reducing death and days on organ support 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 plus standard care reduces both all-cause mortality and time on organ support compared with standard care alone. 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 the eligibility criteria for tocilizumab use are based 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 a 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

Tocilizumab decreases the risk of death in hospitalised people at 21 to 28 days. However, there is uncertainty for this outcome at other timepoints. Tocilizumab decreases the number of hospitalised people experiencing serious adverse events.

What is the evidence informing this recommendation?
Evidence comes from eleven randomised trials that compared tocilizumab with standard care or placebo in 7599 adults hospitalised with COVID-19 (Hermine 2020, Hermine 2021, RECOVERY 2021, REMAP-CAP 2021, Rosas 2021, Salama 2020, Salvarani 2020, Soin 2021, Stone 2020, Veiga 2020, Wang 2020). This is an update to the March 2021 review. During this update, we have added an extra study (Hermine 2021) and updated two studies with more recent data (REMAP-CAP 2021 and RECOVERY 2021).

The strongest evidence for prescribing tocilizumab comes from the high quality all-cause mortality data at day 21 to 28 where tocilizumab reduces mortality for hospitalised patients with COVID-19. The all-cause mortality data could not differentiate between tocilizumab and control for day 14 (n=450), day 60 (n=450), or day 90 (n=1802).

This evidence is supported by the high quality serious adverse events data, collected at the end of 9 studies, where tocilizumab has a lower number of hospitalised people experiencing serious adverse events compared to the control arms.

The REMAP-CAP study's ordinal scale combined in-hospital mortality (to day 90) and days free of organ support up to day 21, and favoured tocilizumab compared to control.

Publication status
Three studies are only available as preprints (Rosas 2021 posted to medRxiv on 12 September 2020, REMAP-CAP 2021 posted to medRxiv on 9 January 2021, and RECOVERY 2021 posted to medRxiv on 11 February 2021) 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).

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 were published which meant that corticosteroids were not routinely given across all studies.

Disease severity in trial participants

Disease severity	Number of patients	References
Moderate-Severe	4959	Wang 2020, Hermine 2020, Hermine 2021, Stone 2020, Salvarani 2020, Salama 2020, RECOVERY 2021, Soin 2021
Moderate-Critical	567	Rosas 2021, Veiga 2020
Critical	1317	REMAP-CAP 2021, RECOVERY 2021

What are the main results?
Tocilizumab decreases the risk of death in hospitalised people at 21 to 28 days (28 fewer per 100 people: RR 0.90 CI 95% 0.83 - 0.98; 6182 patients in 9 studies). However, there is uncertainty for this outcome at other timepoints (day 14, day 60, and day 90). Tocilizumab decreases the number of hospitalised people experiencing serious adverse events (37 fewer per 1000 people: RR 0.83 CI 95% 0.72 - 0.95; 3364 patients in 9 studies) but probably has little impact on adverse events (30 more per 1000 people: RR 1.06 CI 95% 0.90 - 1.24: 2012 patients in 8 studies).

Our confidence in the results
Certainty of the evidence is high for mortality at 21 to 28 days but not for the other mortality timepoints. Certainty of the evidence is high for serious adverse events. Certainly of the evidence is moderate for adverse events because it was downgraded for imprecision as the 95% confidence interval crossed the line of no effect. Certainly of the evidence was moderate for 'days free of organ support' and for the 'ordinal scale combining in-hospital mortality and days free of organ support'. This is because these two outcomes were downgraded for serious risk of bias.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care or placebo	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [All patients]	Relative risk 1.01 (CI 95% 0.46 — 2.2) Based on data from 450	**50** per 1000	**51** per 1000	**Moderate** Due to serious imprecision [2]	One study found no statistically significant difference in mortality at

Outcome Timeframe	Study results and measurements	Comparator Standard care or placebo	Intervention Tocilizumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Day 14 after commencing treatment 9 Critical	participants in 1 studies. [1] (Randomized controlled)	Difference:	**1 more per 1000** (CI 95% 27 fewer — 60 more)		14 days with tocilizumab compared with control
All-cause mortality [All patients] Day 21-28 after commencing treatment 9 Critical	Relative risk 0.9 (CI 95% 0.83 — 0.98) Based on data from 6,182 participants in 9 studies. [3] (Randomized controlled)	278 per 1000 Difference:	250 per 1000 **28 fewer per 1000** (CI 95% 47 fewer — 6 fewer)	**High**	The pooled estimate of nine studies found that tocilizumab decreased death in hospitalised patients at 21 to 28 days compared with control
All-cause mortality [All patients] Day 60 after commencing treatment 9 Critical	Relative risk 0.75 (CI 95% 0.41 — 1.36) Based on data from 450 participants in 1 studies. [4] (Randomized controlled)	102 per 1000 Difference:	77 per 1000 **25 fewer per 1000** (CI 95% 60 fewer — 37 more)	**Moderate** Due to serious imprecision [5]	One study found no statistically significant difference in mortality at 60 days with tocilizumab compared with control
All-cause mortality [All patients] Day 90 after commencing treatment 9 Critical	Relative risk 0.89 (CI 95% 0.77 — 1.04) Based on data from 1,798 participants in 2 studies. [6] (Randomized controlled)	276 per 1000 Difference:	246 per 1000 **30 fewer per 1000** (CI 95% 63 fewer — 11 more)	**Moderate** Due to serious imprecision [7]	The pooled estimate of two studies found no statistically significant difference in mortality at 90 days with tocilizumab compared with control
Serious adverse events At day 14 to day 90 9 Critical	Relative risk 0.83 (CI 95% 0.72 — 0.95) Based on data from 3,364 participants in 9 studies. [8] (Randomized controlled)	217 per 1000 Difference:	180 per 1000 **37 fewer per 1000** (CI 95% 61 fewer — 11 fewer)	**Moderate** Because of risk of bias due to lack of blinding [9]	The pooled estimate of nine studies found that there were fewer serious adverse events in the tocilizumab arm at day 14 to day 90 compared with control
Adverse events At day 14 to day 90 6 Important	Relative risk 1.06 (CI 95% 0.9 — 1.24) Based on data from 2,012 participants in 8 studies. [10] (Randomized controlled)	507 per 1000 Difference:	537 per 1000 **30 more per 1000** (CI 95% 51 fewer — 122 more)	**Low** Because of serious risk of bias due to lack of blinding, and due to serious imprecision [11]	The pooled estimate of eight studies found no statistically significant difference in adverse events at day 14 to day 90 between tocilizumab and control
Ordinal scale combining in-hospital	Based on data from: 1,352 participants in 1 studies. (Randomized	Median adjusted odds ratio 1.46 (95% CI 1.13 - 1.88)		**Moderate** Because of serious risk of bias	One study that had an ordinal scale combining in-hospital mortality at

Outcome Timeframe			Certainty of the Evidence (Quality of evidence)	Plain language summary
mortality and days free of organ support In hospital mortality at day 90 and days free of organ support at day 21 4 Important	controlled)		due to lack of blinding [12]	90 days and days free of organ support to 21 days favoured tocilizumab compared with usual care
Days free of organ support in survivors Day 21 after commencing treatment 4 Important	Based on data from: 1,352 participants in 1 studies. [13] (Randomized controlled)	Tocilizumab (median): 15 days (IQR 7.25 - 18), usual care: 13 days (IQR 4 - 17)		

1. Systematic reviewwith included studies: [96]. **Baseline/comparator:** Systematic review.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
3. Systematic review [40] with included studies: Salama 2020, Hermine 2020, Salvarini 2020, [98], Stone 2020, Veiga 2021, Rosas 2020, Soin 2021, [96]. **Baseline/comparator:** Systematic review.
4. Systematic reviewwith included studies: [96]. **Baseline/comparator:** Systematic review.
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The 95% CI crosses the line of no effect. **Publication bias: no serious.**
6. Systematic reviewwith included studies: [97], [96]. **Baseline/comparator:** Systematic review.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The 95% CI crosses the line of no effect. **Publication bias: no serious.**
8. Systematic review [40] with included studies: Stone 2020, Veiga 2021, Rosas 2020, [96], Soin 2021, Wang 2020, Hermine 2020, Salama 2020, [97]. **Baseline/comparator:** Systematic review.
9. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. Systematic review [40] with included studies: Wang 2020, Salama 2020, Veiga 2021, Hermine 2020, Rosas 2020, [41], Stone 2020, [96]. **Baseline/comparator:** Systematic review.
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The 95% CI crosses the line of no effect. **Publication bias: no serious.**
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
13. Primary study **Supporting references:** [97],
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.**

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Only in research settings

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 and other considerations

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.

7.6 Sarilumab

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'.

Conditional recommendation

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

- 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 October 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 plus standard care for both reduction in mortality and adverse events is uncertain. Sarilumab plus standard care is statistically significantly more effective than standard care alone at reducing death at 60 days in adults with COVID-19 in hospital. However, the panel noted that this result came from 1 study with a moderate risk of bias. The evidence suggests that sarilumab plus standard care has little effect on reducing death at other timepoints compared with standard care alone.

The evidence also suggests that sarilumab does not increase the risk of adverse events of any severity.

The evidence shows that sarilumab plus standard care is statistically significantly more effective than standard care alone for a combined outcome of reducing death and reducing time on organ support.

The dosage for sarilumab is covered by NHS England's Interim Clinical Commissioning Policy: Sarilumab for critically ill patients with COVID-19 pneumonia (adults).

Details of special warnings and precautions for sarilumab use are in its 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

Moderate

The certainty of the evidence for all-cause mortality is moderate because of wide confidence intervals and missing data in 1 study.

The certainty of the evidence for adverse events is low to moderate because of wide confidence intervals and a lack of blinding in 1 study.

There is a moderate risk of bias for the combined outcome of death and days free from organ support because of a lack of blinding.

Preference and values

No substantial variability expected

The panel identified critical outcomes that would be important for decision making. These included all-cause mortality and serious adverse events. It is likely that these outcomes would also be of similar importance to people with COVID-19. In addition, less serious adverse events are likely to be of particular importance to people with COVID-19. This outcome was not as commonly reported in studies.

Resources and other considerations

Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. 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 and young people. The decision about whether someone who is pregnant meets the eligibility criteria should be considered by a multidisciplinary team that includes an obstetric specialist when 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 the acceptability of sarilumab has been identified. However, in the context of the COVID-19 pandemic, it is likely that patients, and their families and clinicians would accept sarilumab use. This is because the benefits of reducing death and time on organ support seem to outweigh the risk of adverse events (if tocilizumab is unavailable for this condition or cannot be used).

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

The evidence review found that sarilumab plus standard care is statistically significantly more effective than standard care alone

at reducing death at 60 days in adults with COVID-19 in hospital. The evidence also suggests that sarilumab plus standard care has little effect on reducing death at other timepoints and has little effect on adverse events of any severity.

There is sufficient evidence to recommend either tocilizumab or sarilumab. However, the evidence for tocilizumab is more certain. This is because there are more studies and more people in the studies for tocilizumab (7,603 people) than for sarilumab plus standard care (2,053 people).

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. The panel agreed that sarilumab should be offered if tocilizumab is not available for use in COVID-19. Use the same eligibility criteria as those for tocilizumab.

Clinical Question/ PICO

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

Summary

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

What is the evidence informing this recommendation?
This is an update to the March 2021 review. During this update, we have added an extra study (Sivapalasingam 2021) and updated a study with more recent data (REMAP-CAP 2021). Evidence now comes from three randomised trials that compared sarilumab with control in 2,053 adults hospitalised with severe or critical COVID-19 (REMAP-CAP 2021, Sivapalasingam 2021, Lescure 2021) .

Publication status
Two studies are only available as preprints and therefore have not been peer reviewed: Sivapalasingam 2021 posted to medRxiv on 19 June 2021, and REMAP-CAP 2021 posted to medRxiv on 25 June 2021.

Study characteristics
One study (REMAP-CAP 2021) 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 two studies (Sivapalasingam 2021, Lescure 2021) included people with confirmed COVID-19 who were admitted to hospital with 'severe' or 'critical' disease as defined in the studies. This meant that the patient population ranged from people needing supplemental oxygen through non-invasive and invasive ventilation to treatment in intensive care.

Mean or median age ranged from 59 to 63 years and women comprised 32 to 37% of patients across the studies. There was a higher proportion of patients with diabetes (37% vs 22%) and severe cardiovascular disease (12% vs 7%) in the standard care arm compared with the sarilumab arm in one trial (REMAP-CAP 2021) but baseline characteristics were more similar across the groups in the other two trials (Sivapalasingam 2021, Lescure 2021). The majority of patients in the three studies (80%) concomitantly received corticosteroids post-randomisation. Pregnant and breastfeeding women were ineligible.

Two studies (REMAP-CAP 2021, Sivapalasingam 2021) assessed sarilumab 200 mg and 400 mg doses and the other (Lescure 2021) assessed sarilumab 400 mg.

What are the main results?
Sarilumab plus standard care is statistically significantly more effective than standard care alone at reducing death at 60 days in adults with COVID-19 in hospital (RR 0.78 95% CI 0.64 to 0.94). However, there was no statistically significant difference in mortality with sarilumab plus standard care compared with standard care at other timepoints (29 days and 90 days). There is no difference in incidence of serious adverse events (RR 0.99 95% CI 0.85 to 1.15).

There does 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 moderate for all-cause mortality at 60 days because of serious risk of bias due to omitted mortality data, and moderate for serious adverse events due to serious imprecision (wide confidence intervals).

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Sarilumab		
All-cause mortality [All patients] Within 29 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.71 — 1.1) Based on data from 924 participants in 2 studies. [1] (Randomized controlled)	311 per 1000 Difference:	274 per 1000 **37 fewer per 1000** (CI 95% 90 fewer — 31 more)	**Moderate** Due to serious imprecision [2]	
All-cause mortality [All patients] Within 60 days of commencing treatment 9 Critical	Relative risk 0.78 (CI 95% 0.64 — 0.94) Based on data from 924 participants in 2 studies. [3] (Randomized controlled)	386 per 1000 Difference:	301 per 1000 **85 fewer per 1000** (CI 95% 139 fewer — 23 fewer)	**Moderate** Because of serious risk of bias due to omitted mortality data [4]	
All-cause mortality [All patients] Within 90 days of commencing treatment 9 Critical	Relative risk 0.89 (CI 95% 0.74 — 1.06) Based on data from 889 participants in 1 studies. (Randomized controlled)	370 per 1000 Difference:	329 per 1000 **41 fewer per 1000** 96 fewer — 22 more	**Moderate** Due to serious imprecision [5]	
Serious adverse events Day 60 to day 90 6 Important	Relative risk 1.14 (CI 95% 0.75 — 1.73) Based on data from 2,053 participants in 3 studies. [6] (Randomized controlled)	184 per 1000 Difference:	210 per 1000 **26 more per 1000** (CI 95% 46 fewer — 134 more)	**Moderate** Due to serious imprecision [7]	
Adverse events Within 60 days of commencing treatment 6 Important	Relative risk 1.01 (CI 95% 0.85 — 1.2) Based on data from 416 participants in 1 studies. (Randomized controlled)	667 per 1000 Difference:	674 per 1000 **7 more per 1000** (CI 95% 100 fewer — 133 more)	**Moderate** Due to serious imprecision [8]	
	Based on data from: 887 participants in 1 studies. (Randomized controlled)	Median adjusted odds ratio 1.50 (CI 95% 1.13 - 2.00)		**Moderate** Because of serious risk of bias due to lack of blinding [10]	One study found that an ordinal scale combining 1.50 (99 favoured sarilumab compared with usual care

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Sarilumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
support to day 21 6 Important **Days free of organ support in survivors** Days free of organ support in survivors to 21 days	Based on data from: 887 participants in 1 studies. (Randomized controlled)	Sarilumab (median): 15 days (IQR 9 – 18); usual care: 13 days (IQR 4 – 17)		**Moderate** Because of serious risk of bias due to lack of blinding [11]	One study found that sarilumab had the greatest number of days free of organ support in survivors to 21 days, followed by tocilizumab, followed by usual care

1. Systematic reviewwith included studies: [127], [126]. **Baseline/comparator:** Systematic review.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Due to serious imprecision.
3. Systematic reviewwith included studies: [126], [127]. **Baseline/comparator:** Systematic review.
4. **Risk of Bias: serious.** Because of serious risk of bias due to omitted mortality data. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Due to serious imprecision.
6. Systematic reviewwith included studies: [127], [126], [97]. **Baseline/comparator:** Systematic review.
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
8. **Imprecision: serious.** Wide confidence intervals.
9. Odds ratio 1.50 (CI 95% 1.13 - 2.00)
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: no serious. Publication bias: no serious.**
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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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.

7.9 Antibiotics

Info Box

Antibiotics should not be used for preventing or treating COVID-19 unless there is clinical suspicion of additional bacterial co-infection. See the section on suspected or confirmed co-infection.

See also the recommendations on azithromycin and doxycycline in the section on therapeutics for COVID-19.

7.10 Azithromycin

Not recommended

Do not use azithromycin to treat COVID-19.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel considered that the results from studies of azithromycin for moderate to critical COVID-19 in the hospital setting and mild to moderate COVID-19 in the community setting showed no meaningful benefit in any of the critical outcomes. They were also aware of the known cardiotoxicity risks associated with macrolide antibiotics. Considering this, the panel decided that the findings could not justify the use of azithromycin to treat COVID-19. They were also concerned that using azithromycin in this way may increase antimicrobial resistance and could have important antibiotic stewardship implications.

Certainty of the Evidence

Low

For people in hospital, the certainty of the evidence for azithromycin for COVID-19 on all-cause mortality and invasive mechanical ventilation is moderate. This is because of serious imprecision with the confidence interval crossing the line of no effect. The certainty of the evidence for serious adverse events is low. This is because of serious risk of bias for some concerns around deviation from treatment protocols and serious imprecision for very few events.

The certainty of the evidence for other important outcomes for azithromycin for COVID-19 in people in hospital ranges from low to very low. This is because of serious risk of bias (for some concerns around deviation from treatment protocols) and serious imprecision (for very few events; only 1 study contributing to an outcome or the confidence interval crossing the line of no effect). The panel also considered that using hydroxychloroquine as standard care does not reflect current standard practice. Outcomes that were informed by evidence mainly from studies using hydroxychloroquine as standard care have therefore been downgraded for indirectness.

The certainty of the evidence ranges from moderate to low for the critical outcomes and very low for important outcomes for azithromycin for COVID-19 in the community setting. This is generally because of serious risk of bias (for concerns about missing data and incomplete reporting in 1 study, and lack of blinding for more subjective outcomes) and serious imprecision (for few events or only 1 study contributing to the outcome).

Preference and values

We expect few to want the intervention

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

The panel inferred that, in view of the lack of meaningful benefit for people with COVID-19, the potential for harm and the risk of causing antimicrobial resistance, most would not choose azithromycin.

Resources and other considerations

Important issues, or potential issues not investigated

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

Equity

Important issues, or potential issues not investigated

The panel were not aware of any evidence for azithromycin use in children or pregnancy. However, because the overall recommendation is not to offer azithromycin to anyone, it is not expected to cause inequity among any subgroups.

Acceptability

Intervention is likely poorly accepted

The panel were not aware of any systematically collected evidence about acceptability. However, considering the important antibiotic stewardship implications and no evidence of effectiveness to treat COVID-19, use of azithromycin would not be acceptable unless there are other licensed indications for which its use remains appropriate.

Feasibility

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about feasibility.

Azithromycin is not used for treating COVID-19 in the UK, so the recommendation supports current practice.

Rationale

The evidence suggests that azithromycin is no better than standard care at reducing risk of death in people in hospital with COVID-19. Limited evidence also suggests that azithromycin does not reduce the risk of hospitalisation or death in people with COVID-19 in the community. There is no evidence for azithromycin use for COVID-19 in children. The panel did not think there

were reasons to expect different results in this group, so agreed that the recommendation applies to all age groups. They also noted the risk of antimicrobial resistance with azithromycin.

Clinical Question/ PICO

Population: People with COVID-19 (Hospitalised)
Intervention: Azithromycin
Comparator: Standard care

Summary

Compared to standard care, azithromycin is no better at reducing risk of death in people in hospital with COVID-19.

What is the evidence informing this conclusion?
Evidence comes from 4 randomised controlled trials that compared azithromycin with standard care in almost 10,000 adults hospitalised with COVID-19. (Furtado 2020; Sekhavati 2020; Cavalcanti 2020; Horby 2020). Most data are from the RECOVERY trial (Horby 2020) which included 7763 adults hospitalised with moderate-to-critical COVID-19.

Standard care within the trials varied. There were 3 trials that included hydroxychloroquine as part of standard care (Furtado 2020; Cavalcanti 2020; Sekhavati 2020). One trial also included lopinavir/ritonavir as part of standard care as well as hydroxychloroquine (Sekhavati 2020). The largest trial, which was conducted in the UK, did not include hydroxychloroquine as part of standard care (Horby 2020). The use of corticosteroids were permitted in 3 of the trials (Horby 2020; Furtado 2020; Cavalcanti 2020).

Due to the variability in standard care, subgroup analyses were conducted for key outcomes. These subgroup analyses were for hydroxychloroquine as standard care versus no hydroxychloroquine.

Publication status
All studies have been peer-reviewed.

Study characteristics
The mean age in the studies ranges between 50 and 67 years and the proportion of women ranged between 33 and 58%. The severity of COVID-19 across the studies was moderate-to-critical. One study only included people who required no oxygen or supplemental oxygen at baseline (Cavalcanti 2020). In the largest study, 76% of people were receiving supplemental oxygen at baseline. One study had 42% of people receiving oxygen at baseline and 49% people receiving mechanical ventilation at baseline.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 5 and 10 days. All studies used the oral route of administration for azithromycin. Two studies also used the IV route of administration (Furtado 2020 and Horby 2020) and 1 study used a nasogastric route as an option (Furtado 2020).

Children and pregnant women were excluded from the trials.

What are the main results?

Critical outcomes
All-cause mortality
Moderate quality evidence from 3 studies found no significant difference for all-cause mortality at 28-30 days with azithromycin compared with standard care for people who were hospitalised (5 fewer deaths per 1000 people [RR 0.98 95% CI 0.90 to 1.06; 8271 people in 3 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine was no different from the overall results.

Low quality evidence from 2 studies found no significant difference for all-cause mortality at 15 days with azithromycin compared with standard care for people who were hospitalised (0 fewer deaths per 1000 people [RR 1.00 95% CI 0.75 to 1.34; 728 people in 2 studies]).

Invasive mechanical ventilation
Moderate quality evidence from 1 study found no significant difference for requirement of IMV at 28-30 days with azithromycin compared with standard care for people who were hospitalised (8 fewer events per 1000 people [RR 0.92 95% CI 0.79 to 1.07; 7311 people in 1 study]).

Very low-quality evidence from 1 study found no significant difference for requirement of IMV at 15 days with azithromycin compared with standard care for people who were hospitalised (35 more events per 1000 people [RR 1.46 95% CI 0.73 to 2.92; 331 people in 1 study]).

Serious adverse events
Low quality evidence from 3 studies found no significant difference for serious adverse events with azithromycin compared with standard care for people who were hospitalised (2 more events per 1000 people [RR 1.14 95% CI 0.91 – 1.43; 8640 people in 3 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine were no different from the overall results.

Important outcomes
Discharge from hospital
Low quality evidence from 2 studies found no significant difference for discharge from hospital at 29 days with azithromycin compared with standard care for people who were hospitalised (54 fewer events per 1000 people [RR 0.92 95% CI 0.71 to 1.19; 8161 people in 2 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine remained non-significant. However, there were differences in direction of effect (with hydroxychloroquine RR 0.78 95% CI 0.6 to 1.01; 397 people in 1 study; without hydroxychloroquine RR 1.02 95% CI 0.99 to 1.05; 7764 people in 1 study).

Very low-quality evidence from 2 studies found no significant difference for discharge from hospital at 15 days with azithromycin compared with standard care for people who were hospitalised (42 fewer events per 1000 people [RR 0.92 95% CI 0.82 to 1.02; 728 people in 2 studies]).

ICU admission
Low quality evidence from 1 study found no significant difference for ICU admission with azithromycin compared with standard care for people who were hospitalised (91 fewer events per 1000 people [RR 0.28 95% CI 0.06 to 1.29; 111 people in 1 study]).

Duration of hospital stay
Very low-quality evidence from 2 studies found no significant difference for duration of hospital stay with azithromycin compared with standard care for people who were hospitalised (MD -0.41 days 95% CI -2.42 to 1.59; 442 people in 2 studies).

Adverse events
Very low-quality evidence from 1 study found no significant difference for adverse events with azithromycin compared with standard care for people who were hospitalised (57 more events per 1000 people [RR 1.17 95% CI 0.91 to 1.50; 438 people in 1 study]).

Our confidence in the results
There were few concerns around risk of bias of studies. Although all studies were open label, it was not considered high risk of bias for the outcomes reported. This is because the objective outcomes such as all-cause mortality will not likely be affected by knowledge of intervention allocation. Other outcomes such as discharge from hospital could be affected by knowledge of intervention, but is probably unlikely in the pandemic situation. One study reported minor deviation from intervention protocols where some patients in the standard care arms also received azithromycin (Cavalcanti 2020). Outcomes that included this study were downgraded for risk of bias (serious adverse events, adverse events, duration of hospital stay and discharge from hospital).

The outcome discharge from hospital was downgraded for serious inconsistency due to statistical heterogeneity of I^2 of more than 50%.

Where an outcome was informed only by studies that had hydroxychloroquine as standard care, the outcome was downgraded due to serious indirectness. This is because hydroxychloroquine is not the current standard of care in the UK. This included 15-day all-cause mortality, 15-day invasive mechanical ventilation, 15-day discharge from hospital, ICU admission, duration of hospital stay and adverse events outcomes.

All outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect or if only 1 study informed the outcome.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality Within 28-30 days of starting treatment 9 Critical	Relative risk 0.98 (CI 95% 0.9 — 1.06) Based on data from 8,271 participants in 3 studies. [1] (Randomized controlled)	228 per 1000 Difference:	223 per 1000 **5 fewer per 1000** (CI 95% 23 fewer — 14 more)	**Moderate** Due to serious imprecision [2]	A pooled analysis of 3 studies found no significant difference for all-cause mortality at 28-30 days with azithromycin compared with standard care for people who were hospitalised.
All-cause mortality Within 15 days of starting treatment 9 Critical	Relative risk 1 (CI 95% 0.75 — 1.34) Based on data from 728 participants in 2 studies. [3] (Randomized controlled)	175 per 1000 Difference:	175 per 1000 **0 fewer per 1000** (CI 95% 44 fewer — 60 more)	**Low** Due to serious indirectness and due to serious imprecision [4]	A pooled analysis of 2 studies found no significant difference for all-cause mortality at 15 days with azithromycin compared with standard care for people who were hospitalised
Invasive mechanical ventilation Within 28-30 days of starting treatment 9 Critical	Relative risk 0.92 (CI 95% 0.79 — 1.07) Based on data from 7,311 participants in 1 studies. [5] (Randomized controlled)	94 per 1000 Difference:	86 per 1000 **8 fewer per 1000** (CI 95% 20 fewer — 7 more)	**Moderate** Due to serious imprecision [6]	Evidence from 1 study found no significant difference for requirement of IMV at 28-30 days with azithromycin compared with standard care for people who were hospitalised
Invasive mechanical ventilation Within 15 days of starting treatment 9 Critical	Relative risk 1.46 (CI 95% 0.73 — 2.92) Based on data from 331 participants in 1 studies. [7] (Randomized controlled)	75 per 1000 Difference:	110 per 1000 **35 more per 1000** (CI 95% 20 fewer — 144 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [8]	Evidence from 1 study found no significant difference for requirement of IMV at 15 days with azithromycin compared with standard care for people who were hospitalised
Serious adverse events During treatment 9 Critical	Relative risk 1.14 (CI 95% 0.91 — 1.43) Based on data from 8,640 participants in 3 studies. [9] (Randomized controlled)	14 per 1000 Difference:	16 per 1000 **2 more per 1000** (CI 95% 1 fewer — 6 more)	**Low** Due to serious risk of bias and serious imprecision [10]	A pooled analysis of 3 studies found no significant difference for serious adverse events with azithromycin compared with standard care for people who were hospitalised
Discharge from hospital Within 29 days of starting treatment 6 Important	Relative risk 0.92 (CI 95% 0.71 — 1.19) Based on data from 8,161 participants in 2 studies. [11] (Randomized controlled)	671 per 1000 Difference:	617 per 1000 **54 fewer per 1000** (CI 95% 195 fewer — 127 more)	**Low** Due to serious inconsistency, Due to serious imprecision [12]	A pooled analysis of 2 studies found no significant difference for discharge from hospital at 29 days with azithromycin compared with standard care for people who were hospitalised

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
Discharge from hospital Within 15 days of starting treatment 6 Important	Relative risk 0.92 (CI 95% 0.82 — 1.02) Based on data from 728 participants in 2 studies. [13] (Randomized controlled)	520 per 1000 Difference:	478 per 1000 **42 fewer per 1000** (CI 95% 94 fewer — 10 more)	Very low Due to serious inconsistency, serious risk of bias, serious indirectness and to serious imprecision [14]	A pooled analysis of 2 studies found no significant difference for discharge from hospital at 15 days with azithromycin compared with standard care for people who were hospitalised
ICU admission During treatment 6 Important	Relative risk 0.28 (CI 95% 0.06 — 1.29) Based on data from 111 participants in 1 studies. [15] (Randomized controlled)	127 per 1000 Difference:	36 per 1000 **91 fewer per 1000** (CI 95% 119 fewer — 37 more)	Low Due to serious imprecision and serious indirectness [16]	Evidence from 1 study found no significant difference for ICU admission with azithromycin compared with standard care for people who were hospitalised
Adverse events During treatment 6 Important	Relative risk 1.17 (CI 95% 0.91 — 1.5) Based on data from 438 participants in 1 studies. [17] (Randomized controlled)	337 per 1000 Difference:	394 per 1000 **57 more per 1000** (CI 95% 30 fewer — 169 more)	Very low Due to serious risk of bias, serious indirectness and serious imprecision [18]	Evidence from 1 study found no significant difference for adverse events with azithromycin compared with standard care for people who were hospitalised
		Difference:	**MD 0.41 lower** (CI 95% 2.42 lower — 1.59 higher)	Very low Due to serious risk of bias, serious indirectness and serious imprecision [20]	A pooled analysis of 2 studies found no significant difference for duration of hospital stay with azithromycin compared with standard care for people who were hospitalised

1. Systematic review [1] with included studies: Furtado 2020 (COALITION II), Horby 2020 (RECOVERY), Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
3. Systematic review [1] with included studies: Furtado 2020 (COALITION II), Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** due to 95% CI crosses the line of no effect, Only data from one study. **Publication bias: no serious.**
5. Systematic review [1] with included studies: Horby 2020 (RECOVERY). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
7. Systematic review [1] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** due to minor deviation from intervention. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
9. Systematic review [1] with included studies: Cavalcanti 2020, Horby 2020 (RECOVERY), Furtado 2020 (COALITION II). **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** due to minor deviations from intervention. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** due to few events. **Publication bias: no serious.**

11. Systematic review [1] with included studies: Horby 2020 (RECOVERY), Furtado 2020 (COALITION II). **Baseline/ comparator:** Control arm of reference used for intervention.
12. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 77 %.. **Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
13. Systematic review [1] with included studies: Cavalcanti 2020, Furtado 2020 (COALITION II). **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** due to minor deviations from intervention. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** 95% CI crosses line of no effect, due to [reason]. **Publication bias: no serious.**
15. Systematic review [1] with included studies: Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
17. Systematic review [1] with included studies: Cavalcanti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** due to minor deviation from intervention. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care.. **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
19. Systematic review [1] with included studies: Cavalcanti 2020, Sekhavati 2020. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: serious.** due to minor deviation from intervention. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was high, with I^2 77%.. **Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** 95%CI crosses line of no effect. **Publication bias: no serious.**

References

1. Azithromycin for COVID-19 internal meta-analysis.

2. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A., et al. : Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med 2020; Journal

3. Furtado RHM, Berwanger O., Fonseca HA, Corr?a TD, Ferraz LR, Lapa MG, et al. : Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet 2020;396(10256):959-967 Journal

4. Sekhavati E., Jafari F., SeyedAlinaghi S., Jamalimoghadamsiahkali S., Sadr S., Tabarestani M., et al. : Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial. Int J Antimicrob Agents 2020;56(4):106143 Journal

5. Horby : Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021; Journal

Clinical Question/ PICO

Population: People with COVID-19 (Outpatients)
Intervention: Azithromycin
Comparator: Standard care

Summary

Compared to standard care, azithromycin probably does not reduce the risk of hospitalisation or death in people with COVID-19 managed in the community.

What is the evidence informing this conclusion?
Evidence comes from 3 randomised controlled trials that compared azithromycin with standard care in over 2000 adults with COVID-19 managed as outpatients or in the community (Omrani 2020; Butler 2021; Hinks 2021). Of these trials, 2 were conducted in the UK (Butler 2021; Hinks 2021).

Standard care within the trials varied. There was 1 trial that included hydroxychloroquine as part of standard care (Omrani 2020). The 2 trials conducted in the UK did not include hydroxychloroquine as part of standard care (Butler 2021; Hinks 2021). Concomitant corticosteroids use was reported in 1 trial (Hinks 2021).

Due to the variability in standard care, subgroup analyses were conducted for key outcomes. These subgroup analyses were for hydroxychloroquine as standard care versus no hydroxychloroquine.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 3 and 14 days. All studies used the oral route of administration for azithromycin.

There was 1 trial that was stopped early due to meeting its prespecified futility criterion (Butler 2021).

Publication status
There was 1 study which is currently only available as a pre-print which means it has not yet been peer-reviewed (Hinks 2021).

Study characteristics
The mean age in the studies ranges between 40 and 60 years and the proportion of women ranged between 48 and 57%. The PRINCIPLE trial recruited people who were 65 years or older or 50 years older with at least 1 comorbidity (Butler 2021). Whilst the Q-PROTECT trial planned to recruit women, over 98% were males (Omrani 2020). This was due female quarantine areas in Qatar often being inaccessible to male study physicians.

The severity of COVID-19 across the studies was mild to moderate but without the need for hospital admission.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 3 and 14 days.

Children and pregnant women were excluded from the trials.

What are the main results?

Critical outcomes
All-cause mortality
Low quality evidence from 3 studies found no significant difference for all-cause mortality with azithromycin compared with standard care for people who were managed as outpatients (0 fewer deaths per 1000 people [RR 1.01 95% CI 0.06 to 16.05; 1919 people in 3 studies]). There were no deaths reported in 2 of these studies (Omrani 2020 and Butler 2020). This meant that subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine was not possible.

Hospitalisation or death (composite)
Low quality evidence from 2 studies found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 people [RR 0.92 95% CI 0.59 to 1.43; 1615 people in 2 studies]).

Low quality evidence from 1 study found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients (13 fewer events per 1000 people [RR 0.82 95% CI 0.39 to 1.71; 422 people in 1 study]).

NIV/IMV or death (composite)
Moderate quality evidence from 1 study found no significant difference for NIV/IMV or death for azithromycin compared with standard care for people who were managed as outpatients (0 fewer events per 1000 [RR 1.01 95% CI 0.14 to 7.10; 292 people in 1 study]).

Invasive mechanical ventilation or ECMO
Low quality evidence from 1 study found no significant difference for IMV or ECMO for azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 [RR 0.50 95% CI 0.10 to 2.59; 1121 people in 1 study]).

Important outcomes
Virologic clearance
Low quality evidence from 1 study found no significant difference for virologic clearance at day 6 for azithromycin compared with standard care for people who were managed as outpatients (22 fewer events per 1000 [RR 0.83 95% CI 0.44 to 1.54; 301 people in 1 study]).

Low quality evidence from 1 study found no significant difference for virologic clearance at day 14 for azithromycin

compared with standard care for people who were managed as outpatients (86 fewer per 1000 [RR 0.70 95% CI 0.46 to 1.05; 295 people in 1 study]).

Patient-reported clinical recovery
Patient reported recovery was defined as the first instance that a participant reported feeling recovered (Butler 2021).

Very low-quality evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients (38 more events per 1000 [RR 1.05 95% CI 0.99 to 1.11; 1323 people in 1 study]).
Very low-quality evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients (41 more events per 1000 people [RR 1.06 95% CI 0.94 to 1.20; 422 people in 1 study]).

Sustained clinical recovery
Sustained clinical recovery was defined as a participant who reported feeling recovered and subsequently remained well until 28 days after random assignment (Butler 2021).

Very low-quality evidence from 1 study found no significant difference for sustained clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients (26 fewer events per 1000 people [RR 0.96 95% CI 0.88 to 1.05; 1129 people in 1 study]).

ICU admission
Very low-quality evidence from 1 study found no significant difference for ICU admission at 28 days for azithromycin compared with standard care for people who were managed as outpatients (2 fewer ICU admissions per 1000 people [RR 0.76 95% CI 0.18 to 3.15; 1120 people in 1 study]).

Supplemental oxygen
Very low-quality evidence from 1 study found no significant difference for need for supplemental oxygen at 28 days for azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 people [RR 0.84 95% CI 0.38 to 1.85; 1122 people from 1 study]).

Our confidence in the results
Although all studies were open label, it was not considered high risk of bias for the mortality and invasive mechanical ventilation outcomes reported. However, outcomes which were considered more subjective were downgraded for risk of bias due to lack of blinding (patient-reported clinical recovery, sustained clinical recovery, ICU admission and supplemental oxygen). 1 study was unclear in how it accounted for missing data. Outcomes that included this study were downgraded for risk of bias (all-cause mortality, hospitalisation or death, invasive mechanical ventilation, patient-reported recovery, sustained clinical recovery, ICU admission and supplemental oxygen).

All outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect or if only 1 study informed the outcome.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of starting treatment 9 Critical	Relative risk 1.01 (CI 95% 0.06 — 16.05) Based on data from 1,919 participants in 3 studies. [1] (Randomized controlled)	1 per 1000 Difference:	1 per 1000 **0 fewer per 1000** (CI 95% 1 fewer — 15 more)	**Low** Due to serious risk of bias and serious imprecision [2]	A pooled analysis of 3 studies found no significant difference for all-cause mortality with azithromycin compared with standard care for people who were managed as outpatients.
Hospitalisation or death (composite) - All	Relative risk 0.92 (CI 95% 0.59 — 1.43) Based on data from 1,615 participants in 2	46 per 1000	42 per 1000	**Low** Due to serious risk of bias and	A pooled analysis of 2 studies found no significant difference for hospitalisation or death

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin		Plain language summary
patients [3] Within 28 days of starting treatment 9 Critical	studies. [4] (Randomized controlled)	Difference:	**4 fewer per 1000** (CI 95% 19 fewer — 20 more)	serious imprecision [5]	with azithromycin compared with standard care for people who were managed as outpatients
	Relative risk 0.82 (CI 95% 0.39 — 1.71) Based on data from 422 participants in 1 studies. [7] (Randomized controlled)	72 per 1000 Difference:	59 per 1000 **13 fewer per 1000** (CI 95% 44 fewer — 51 more)	**Low** Due to serious risk of bias and serious imprecision [8]	Evidence from 1 study found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients.
NIV/IMV or death (composite) Within 28 days of starting treatment 9 Critical	Relative risk 1.01 (CI 95% 0.14 — 7.1) Based on data from 292 participants in 1 studies. [9] (Randomized controlled)	14 per 1000 Difference:	14 per 1000 **0 fewer per 1000** (CI 95% 12 fewer — 85 more)	**Moderate** Due to serious imprecision [10]	Evidence from 1 study found no significant difference for NIV/IMV or death for azithromycin compared with standard care for people who were managed as outpatients.
Invasive mechanical ventilation or ECMO Within 28 days of starting treatment 9 Critical	Relative risk 0.5 (CI 95% 0.1 — 2.59) Based on data from 1,121 participants in 1 studies. [11] (Randomized controlled)	8 per 1000 Difference:	4 per 1000 **4 fewer per 1000** (CI 95% 7 fewer — 13 more)	**Low** Due to serious risk of bias and serious imprecision [12]	Evidence from 1 study found no significant difference for IMV or ECMO for azithromycin compared with standard care for people who were managed as outpatients.
Virologic clearance 6 days 6 Important	Relative risk 0.83 (CI 95% 0.44 — 1.54) Based on data from 301 participants in 1 studies. [13] (Randomized controlled)	128 per 1000 Difference:	106 per 1000 **22 fewer per 1000** (CI 95% 72 fewer — 69 more)	**Low** Due to serious indirectness and serious imprecision [14]	Evidence from 1 study found no significant difference for virologic clearance at day 6 for azithromycin compared with standard care for people who were managed as outpatients.
Virologic clearance 14 days 6 Important	Relative risk 0.7 (CI 95% 0.46 — 1.05) Based on data from 295 participants in 1 studies. [15] (Randomized controlled)	288 per 1000 Difference:	202 per 1000 **86 fewer per 1000** (CI 95% 156 fewer — 14 more)	**Low** Due to serious indirectness and serious imprecision [16]	Evidence from 1 study found no significant difference for virologic clearance at day 14 for azithromycin compared with standard care for people who were managed as outpatients.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Azithromycin	Certainty of the Evidence (Quality of evidence)	Plain language summary
Patient reported clinical recovery - All patients Within 28 days of starting treatment 6 Important	Relative risk 1.05 (CI 95% 0.99 — 1.11) Based on data from 1,323 participants in 1 studies. [17] (Randomized controlled)	767 per 1000 Difference:	805 per 1000 **38 more per 1000** (CI 95% 8 fewer — 84 more)	**Very low** Due to very serious risk of bias and serious imprecision [18]	Evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients.
Patient reported clinical recovery - SARS-CoV-2 positive popualtion Within 28 days of starting treatment 6 Important	Relative risk 1.06 (CI 95% 0.94 — 1.2) Based on data from 422 participants in 1 studies. [19] (Randomized controlled)	691 per 1000 Difference:	732 per 1000 **41 more per 1000** (CI 95% 41 fewer — 138 more)	**Very low** Due to very serious risk of bias and serious imprecision [20]	Evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients.
Sustained clinical recovery Within 28 days of starting treatment 6 Important	Relative risk 0.96 (CI 95% 0.88 — 1.05) Based on data from 1,129 participants in 1 studies. [21] (Randomized controlled)	658 per 1000 Difference:	632 per 1000 **26 fewer per 1000** (CI 95% 79 fewer — 33 more)	**Very low** Due to very serious risk of bias and serious imprecision [22]	Evidence from 1 study found no significant difference for sustained clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients.
ICU admission Within 28 days of starting treatment 6 Important	Relative risk 0.76 (CI 95% 0.18 — 3.15) Based on data from 1,120 participants in 1 studies. [23] (Randomized controlled)	8 per 1000 Difference:	6 per 1000 **2 fewer per 1000** (CI 95% 7 fewer — 17 more)	**Very low** Due to very serious risk of bias and serious imprecision [24]	Evidence from 1 study found no significant difference for ICU admission at 28 days for azithromycin compared with standard care for people who were managed as outpatients.
		24 per 1000 Difference:	20 per 1000 **4 fewer per 1000** (CI 95% 15 fewer — 20 more)	**Very low** Due to very serious risk of bias and serious imprecision [26]	Evidence from 1 study found no significant difference for need for supplemental oxygen at 28 days for azithromycin compared with standard care for people who were managed as outpatients

1. Systematic review [1] with included studies: Omrani 2020, Hinks 2021, Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Very few events. **Publication bias: no serious.**
3. Population includes people who tested negative for SARS-CoV-19 during treatment
4. Systematic review [1] with included studies: Hinks 2021, Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.

5. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
6. Subpopulation who testing positive for SARS-CoV-19
7. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**
9. Systematic review [1] with included studies: Hinks 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
11. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
13. Systematic review [1] with included studies: Omrani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
15. Systematic review [1] with included studies: Omrani 2020. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. . **Imprecision: serious.** due to [reason]. **Publication bias: no serious.**
17. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: very serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
19. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
21. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
23. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
25. Systematic review [1] with included studies: Butler 2021 (PRINCIPLE). **Baseline/comparator:** Control arm of reference used for intervention.
26. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**

References

1. Azithromycin for COVID-19 internal meta-analysis.

6. Omrani AS, Pathan SA, Thomas SA, Harris TRE, Coyle PV, Thomas CE, et al. : Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. EClinicalMedicine 2020;29 100645 Journal

7. Butler : Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet (London, England) 397(10279):1063-1074 Journal

8. Hinks TS CLKRE : A randomised clinical trial of azithromycin versus standard care in ambulatory COVID-19 ? the ATOMIC2 trial. medRxiv 2021;

7.11 Budesonide (inhaled)

Only in research settings

Only use budesonide to treat COVID-19 as part of a clinical trial.

People already on budesonide for conditions other than COVID-19 should continue treatment if they test positive for COVID-19.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel considered that the clinical evidence suggests there is no statistically significant difference for the outcomes of hospitalisation and death, or need for mechanical ventilation in people having inhaled budesonide and usual care compared with usual care alone. They considered that inhaled budesonide statistically significantly reduces the need for oxygen administration compared with usual care. The panel acknowledged that the event rates for these outcomes were low. This may be explained in part by the fact that the population had mild COVID-19 that was managed in the community. The panel noted that the thresholds for starting oxygen therapy were not reported in the trials.

Time to first reported recovery (patient reported) and time to sustained recovery was statistically significantly reduced with inhaled budesonide compared with usual care. However, the panel acknowledged that corticosteroids can potentially affect wellbeing without affecting the COVID-19 disease process. There was a statistically significant reduction in the number of people who had COVID-19-related urgent care visits. There was no statistically significant difference in serious adverse events for budesonide compared with usual care. The panel also discussed that non-serious adverse events were not reported in the studies. However, they acknowledged that the side-effect profile of budesonide is well known.

Certainty of the Evidence

Moderate

Most of the evidence was rated as low to moderate in quality. Outcomes that were self-reported were downgraded because of high risk of bias. When 95% confidence intervals crossed the line of no effect, the outcome was downgraded for imprecision. The outcome for COVID-19-related urgent-care visits was downgraded because of indirectness. It was not possible to determine from the data what the nature of the visits were because it included hospitalisations as well as emergency department attendance. These can lead to different outcomes for people with COVID-19.

The panel discussed the limitations of the trials and noted that the STOIC trial was a small study with very few events. They also noted the trial was stopped early as a result of an independent statistical review

Risk of bias was rated as ‘low’ or ‘some concerns’ for all outcomes in the studies. Both trials included were open-label studies. So, the lack of blinding could have introduced bias to the more subjective outcomes such as self-reported recovery, resolution of symptoms or sustained recovery. This is because people in the trials would have been aware of the treatment they were having.

The panel discussed that the PRINCIPLE trial had a restricted population of mainly older adults and had concerns about the

applicability of the trial to younger people with COVID-19. The panel noted that inhalers can be difficult to use for people unfamiliar with the devices, and so the amount of budesonide inhaled may be variable, potentially affecting the results.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences and values, but they identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation, time to recovery 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 and longer-term outcomes such as functional independence, are likely to be of particular importance to patients. These outcomes were not reported in studies.

Resources and other considerations

Important issues, or potential issues not investigated

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

Equity

Important issues, or potential issues not investigated

The panel discussed that not everyone will be able to use an inhaler, which could cause equity issues should inhaled budesonide be recommended for treating COVID-19 in the future.

Acceptability

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

Inhaled budesonide is not routinely used for treating COVID-19 in the UK, so the recommendation supports current practice.

Rationale

Trial evidence suggests some benefit with inhaled budesonide in reducing how long it takes to recover from COVID-19. However, this evidence is limited because it comes from only 2 trials, 1 of which was very small and stopped early. Also, the population in the trials was mainly older people, which limits its generalisability to other age groups. The panel concluded that more research is needed to address these issues, and that inhaled budesonide should therefore only be used as part of a clinical trial.

Clinical Question/ PICO

Population: Non-hospitalised adults with COVID-19
Intervention: Inhaled budesonide
Comparator: Standard care, standard care plus placebo, or placebo

Summary

What is the evidence informing this recommendation?

The evidence review has been developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

Two studies identified from the search are included in this evidence review. The 2 randomised trials compared inhaled budesonide with usual care in 3217 non-hospitalised people with mild COVID-19 (Ramakrishnan 2021 [STOIC trial] and Yu 2021 [PRINCIPLE trial]).

Study characteristics

Both studies used a dosage of 800 micrograms twice daily (1600 micrograms total daily dose) of inhaled budesonide. The included studies compared inhaled budesonide to usual care which was based on advice from the UK National Health Service (NHS). The mean ages in the STOIC trial were 44 (range 19-71) years in the budesonide group and 46 (19-79) years in the usual care group. The PRINCIPLE trial restricted enrolment to a higher risk population with 39% of the participants aged between 50 and 64 years and 61% were aged over 64 years. The proportion of women ranged from 52% to 58%. Both studies were conducted in a non-hospital setting.

What are the main results?

Efficacy

In non-hospitalised adults with COVID-19-, there were no statistically significant differences for reduction of hospitalisation or death, need for mechanical ventilation, ICU admission, symptom-related outcomes or hospital assessment without admission (Yu 2021) but there was a statistically significant difference favouring inhaled budesonide for reducing need for oxygen administration, time to first reported recovery, sustained recovery (Yu 2021) and the number of COVID-19-related urgent care visits, including emergency department assessment or hospitalisation (Ramakrishnan 2021).

Safety

There was no statistically significant difference in serious adverse events (Yu 2021).

Subgroup analysis

There was insufficient detail to accurately assess subgroups of interest.

Limitations of the evidence

There were some differences in how the included studies were designed which meant that meta-analysis was not appropriate. The population inclusion criteria of the STOIC trial (Ramakrishnan 2021) was broad (symptomatic adults aged ≥ 18 years) whereas the PRINCIPLE trial (Yu 2021 Academic in confidence) was restricted to adults that were at higher risk of complications with COVID-19 (≥65 years or ≥50 years with comorbidities). This restricted population in the PRINCIPLE trial will mean that the data may not be generalisable to younger adults with or without comorbidities.

The STOIC trial was terminated early after independent statistical review. This was because recruitment was reduced after a second national lockdown came into effect in England and implementation of the COVID-19 vaccine had started. Although the STOIC trial was terminated early and did not reach its target sample size, independent statistical review concluded that the addition of more participants would not have changed the result. However, this means that it was a very small trial with few events which may limit impact on decision-making.

Risk of bias for all outcomes was rated as 'low' or 'some concerns'. Both studies were open-label studies whereby lack of blinding could introduce bias to the more subjective outcomes. Lack of blinding is less likely to introduce bias to objective outcomes such as hospitalisation or death.

All included studies were in adults, so it is not possible to say what the efficacy or safety of inhaled budesonide for treating COVID-19 is in children or young people.

Our confidence in the results

The majority of the evidence was rated as low to moderate quality. Outcomes that were self-reported were downgraded due to high risk of bias. Where 95% confidence intervals crossed the line of no effect, the outcome was downgraded for imprecision. The outcome for COVID-19 related urgent-care visits was downgraded due to indirectness as it was not possible to determine from the data what the nature of the visits were as it included hospitalisations as well as emergency department attendance which can lead to different outcomes for patients.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Inhaled budesonide	Certainty of the Evidence (Quality of evidence)	Plain language summary
Hospitalisation or death related to COVID-19 [SARS-CoV-2 positive only] Within 28 days of starting treatment 9 Critical	Odds Ratio 0.75 (CI 95% 0.55 — 1.03) Based on data from 1,856 participants in 1 studies. (Randomized controlled)			**Moderate** Due to serious imprecision [1]	1 study found a non-statistically significant reduction in hospitalisation or death with inhaled budesonide compared with usual care.
Hospitalisation or death related to COVID-19 [whole study population] Within 28 days of starting treatment 9 Critical	Odds Ratio 0.78 (CI 95% 0.57 — 1.04) Based on data from 2,848 participants in 1 studies. (Randomized controlled)			**Moderate** Due to serious imprecision [2]	1 study found a non-statistically significant reduction in hospitalisation or death with inhaled budesonide compared with usual care.
Mechanical ventilation [SARS-CoV-2 positive only] Within 28 days of starting treatment 9 Critical	Relative risk 0.94 (CI 95% 0.44 — 1.98) Based on data from 1,560 participants in 1 studies. [3]	18 per 1000 Difference:	17 per 1000 **1 fewer per 1000** (CI 95% 10 fewer — 18 more)	**Moderate** Due to serious imprecision [4]	1 study found no statistically significant difference in mechanical ventilation with inhaled budesonide compared with usual care
Serious adverse events Within 28 days of starting treatment 9 Critical	Relative risk 1.36 (CI 95% 0.27 — 6.71) Based on data from 1,856 participants in 1 studies. [5] (Randomized controlled)	3 per 1000 Difference:	4 per 1000 **1 more per 1000** (CI 95% 2 fewer — 17 more)	**Low** Due to very serious imprecision [6]	1 study found no statistically significant difference in serious adverse events with inhaled budesonide compared with usual care
Time to first reported recovery [SARS-CoV-2 positive only] 9 Critical	Hazard Ratio 1.21 (CI 95% 1.08 — 1.36) Based on data from 1,856 participants in 1 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [7]	1 study found a statistically significant decrease in time to first reported recovery with inhaled budesonide compared with usual care.
Time to first reported recovery [whole study population]	Hazard Ratio 1.18 (CI 95% 1.07 — 1.3) Based on data from 2,848 participants in 1 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [8]	1 study found a statistically significant decrease in time to first reported recovery with inhaled budesonide compared with usual

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care, standard care plus placebo, or placebo	**Intervention** Inhaled budesonide	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical					care.
	Relative risk 0.18 (CI 95% 0.04 — 0.79) Based on data from 146 participants in 1 studies. [9] (Randomized controlled)	151 per 1000 Difference:	27 per 1000 **124 fewer per 1000** (CI 95% 145 fewer — 32 fewer)	Moderate Due to serious indirectness [10]	
	Relative risk 0.12 (CI 95% 0.02 — 0.96) Based on data from 131 participants in 1 studies. [11] (Randomized controlled)	123 per 1000 Difference:	15 per 1000 **108 fewer per 1000** (CI 95% 121 fewer — 5 fewer)	Moderate Due to serious indirectness [12]	
Hospital assessment without admission [SARS-CoV-2 positive only] Within 28 days of starting treatment 9 Critical	Relative risk 1.01 (CI 95% 0.57 — 1.82) Based on data from 1,583 participants in 1 studies. [13] (Randomized controlled)	28 per 1000 Difference:	28 per 1000 **0 fewer per 1000** (CI 95% 12 fewer — 23 more)	Low Due to serious imprecision, Due to serious risk of bias [14]	1 study found no statistically significant difference in hospital assessment without admission with inhaled budesonide compared with usual care.
ICU admission [SARS-CoV-2 positive only] Within 28 days of starting treatment 6 Important	Relative risk 0.48 (CI 95% 0.23 — 1.01) Based on data from 1,550 participants in 1 studies. [15] (Randomized controlled)	27 per 1000 Difference:	13 per 1000 **14 fewer per 1000** (CI 95% 21 fewer — 0 fewer)	Moderate Due to serious imprecision [16]	1 study found a non-statistically significant reduction in ICU admission with inhaled budesonide compared with usual care.

	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Inhaled budesonide		
		93 per 1000 Difference:	64 per 1000 **29 fewer per 1000** (CI 95% 47 fewer — 2 fewer)	High	1 study found a statistically significant reduction in oxygen administration with inhaled budesonide compared with usual care
Sustained recovery [SARS-CoV-2 positive only] Within 28 days of starting treatment 6 Important		488 per 1000 Difference:	586 per 1000 **98 more per 1000** (CI 95% 49 more — 156 more)	Moderate Due to serious risk of bias [19]	1 study found a statistically significant improvement in sustained recovery with inhaled budesonide compared with usual care.
Time to sustained recovery [SARS-CoV-2 positive only] 4 Important				Moderate Due to serious risk of bias [20]	1 study found a statistically significant decrease in time to sustained recovery with inhaled budesonide compared with usual care.
Initial reduction of severity of symptoms [SARS-CoV-2 positive only] Within 28 days of starting treatment 6 Important		816 per 1000 Difference:	840 per 1000 **24 more per 1000** (CI 95% 8 fewer — 65 more)	Low Due to serious risk of bias, Due to serious imprecision [22]	1 study found no statistically significant difference in initial severity of symptoms with inhaled budesonide compared with usual care.
Time to initial reduction of severity of symptoms [SARS-CoV-2 positive only] 6 Important				Moderate Due to serious risk of bias [23]	1 study found a statistically significant decrease in time to initial reduction of severity of symptoms with inhaled budesonide compared with usual care.
		681 per 1000 Difference:	783 per 1000 **102 more per 1000**	Low Due to serious risk of bias, Due to serious imprecision [25]	1 study found no statistically significant difference in symptom resolution with inhaled budesonide compared with usual care.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Inhaled budesonide	Certainty of the Evidence (Quality of evidence)	Plain language summary
6 Important			(CI 95% 34 fewer — 279 more)		
Alleviation of all of symptoms [SARS-CoV-2 positive only] Within 28 days of starting treatment 6 Important	Relative risk 0.99 (CI 95% 0.96 — 1.02) Based on data from 1,433 participants in 1 studies. [26] (Randomized controlled)	910 per 1000 Difference:	901 per 1000 **9 fewer per 1000** (CI 95% 36 fewer — 18 more)	**Low** Due to serious risk of bias, Due to serious imprecision [27]	1 study found no statistically significant difference in alleviation of all symptoms with inhaled budesonide compared with usual care.
Time to alleviation of all symptoms [SARS-CoV-2 positive only] 6 Important	Hazard Ratio 1.07 (CI 95% 0.96 — 1.19) Based on data from 1,433 participants in 1 studies. (Randomized controlled)	Difference:	**MD 4 lower** (CI 95% 6.22 lower — 1.78 lower)	**Low** Due to serious risk of bias, Due to serious imprecision [28]	1 study found no statistically significant difference in time to alleviation of all symptoms with inhaled budesonide compared with usual care.

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
3. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
5. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** 95% CI crosses the line of no effect and very few events. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
8. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
9. Systematic review [92] with included studies: STOIC 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important). **Imprecision: no serious. Publication bias: no serious.**
11. Systematic review [92] with included studies: STOIC 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: no serious. Indirectness: serious.** Differences between the outcomes of interest and those reported (e.g

short-term/surrogate,not patient-important). **Imprecision: no serious. Publication bias: no serious.**
13. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
15. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
17. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
19. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
20. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
21. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
23. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
24. Systematic review [92] with included studies: STOIC 2021. **Baseline/comparator:** Control arm of reference used for intervention.
25. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
26. Systematic review [92] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
27. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
28. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
29. Systematic review [92] with included studies: STOIC 2021. **Baseline/comparator:** Control arm of reference used for intervention.
30. **Risk of Bias: serious.** Open label study which may have influenced a subjective outcome.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

References

92. Inhaled budesonide for COVID-19.

94. Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. : Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. The Lancet. Respiratory medicine 2021;9(7):763-772 Pubmed Journal

95. Yu L-M, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. : Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet (London, England) 2021;398(10303):843-855 Pubmed Journal

7.12 Colchicine

Not recommended

Do not use colchicine to treat COVID-19.

Evidence To Decision

Benefits and harms

Important harms

Hospital settings

The panel considered that the results from studies of colchicine for COVID-19 in hospitals showed no benefit of effect on all-cause mortality, mechanical ventilation, discontinuation due to adverse events, clinical progression, ICU admission, or discharge from hospital within 28 days.

The evidence shows that people having colchicine plus standard care have statistically significantly more adverse events compared with people having standard care alone. Known adverse effects such as diarrhoea appear to have been under-reported in the identified evidence in hospital settings. The panel noted that colchicine commonly causes diarrhoea, which can lead to potassium deficiency (hypokalaemia). They advised that, because of the adverse events, colchicine tends to be used (for the treatment of gout) only for 3 to 4 days.

Although one study suggests that colchicine plus standard care reduces duration of hospital stay at a mean follow-up of 21 days compared with placebo plus standard care, this reduction of hospital stay is not statistically significant (a mean difference of 1.84 days (95% CI 0.78 to 2.90)).

Community settings

The panel considered that the results from studies of colchicine for COVID-19 in the community showed no benefit on hospitalisation for COVID-19, all-cause mortality, all-cause mortality or hospitalisation, mechanical ventilation, number of participants who experienced alleviation of all symptoms, or reported recovery time.

The evidence shows that people having colchicine plus standard care have a statistically significant reduction in serious adverse events compared with standard care alone or with placebo. This is possibly because pneumonia was reported less frequently in patients of the colchicine group compared with those in the placebo group. However, people having colchicine plus standard care have a statistically significant increase in adverse events compared with standard care plus placebo. The adverse event diarrhoea was higher with colchicine than with placebo in Tardif 2021.

Certainty of the Evidence

Very low

The panel agreed that the certainty of evidence on colchicine for people with COVID-19 in hospital and in the community ranges from high to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with most studies having some degree of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care in hospitals not including corticosteroids); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Two studies were only available as preprints.

Preference and values

We expect few to want the intervention

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

The panel thought that people would not want to take a treatment with no known benefits but well-established side effects such as diarrhoea.

Resources and other considerations

Important issues, or potential issues not investigated

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

Colchicine costs from £2.54 for 28 tablets (BNF, November 2021). The panel therefore expected a negligible effect on resources.

Equity

No important issues with the recommended alternative

Colchicine should not be used in pregnancy and no studies in children were identified. However, because the overall recommendation is not to offer colchicine to anyone, it is not expected to cause inequity among any subgroups.

Acceptability

Intervention is likely poorly accepted

The panel were not aware of any systematically collected evidence about acceptability.

Colchicine is not licensed in the UK for treating COVID-19. The panel noted that its side effects are unlikely to be acceptable to patients or prescribers, especially diarrhoea and hypokalaemia. The panel noted that diarrhoea is particularly concerning in older people because frequent toilet visits and dehydration could be a risk factor for falls. They also noted that avoidable diarrhoea would not be acceptable in the intensive care setting.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

Colchicine is not used for treating COVID-19 in the UK, so the recommendation supports current practice.

Rationale

The evidence from trials of colchicine to treat COVID-19 in adults, both in hospital and community settings, shows no beneficial effect on all-cause mortality or need for mechanical ventilation compared with standard care. It also shows no effect on duration of hospital stay or hospitalisation. The evidence also shows that colchicine causes statistically significantly more adverse events than standard care within 21 days of starting treatment in hospital or 30 days in the community. There is no evidence for children or young people. Therefore, colchicine should not be used to treat COVID-19 in people of any age.

Clinical Question/ PICO

Population: People with COVID-19 in hospital
Intervention: Colchicine
Comparator: Placebo or standard care

Summary

There is no evidence that colchicine is more effective than placebo or standard care in treating hospitalised patients with COVID-19.

What is the evidence informing this conclusion?
This is a November 2021 update of the evidence review from May 2021 and includes 1 new study (RECOVERY 2021). Evidence comes from 4 randomised trials that compared colchicine with placebo or standard care in 11620 adults admitted to hospital with COVID-19 (Deftereos 2020, Lopes 2021, Salehzadeh 2020, RECOVERY 2021).

The colchicine arm of the RECOVERY trial stopped recruitment because of futility of the intervention – that is, no effect on mortality was seen for existing participants and recruitment of further participants was not expected to change this finding.

Publication status
Salehzadeh 2020 was only available as a preprint and has therefore not been peer reviewed.

Study characteristics
The median age ranged from 55 to 64 years and the proportion of women ranged from 42% to 59%. The severity of COVID-19 was not clearly reported across studies. In Deftereos 2020, an arterial oxygen partial pressure of lower than 95 mmHg on room air was a key inclusion criterion. Lopes 2021 specified moderate to severe COVID-19 as an inclusion criterion but did not report how many patients of each category of severity were recruited. Salehzadeh 2020 did not define disease severity other than specifying COVID-19 with confirmed lung involvement. In RECOVERY 2021, 15% of participants had no oxygen support or simple oxygen, 31-33% had non-invasive ventilation, and 45-46% had invasive mechanical ventilation.

The dosage of colchicine differed across the studies. Deftereos 2020, RECOVERY 2021, and Lopes 2021 used a higher initial dose (from 1,000 micrograms daily to 2,000 micrograms daily) for between 1 and 5 days before switching to a lower maintenance dose. The daily dose in the maintenance phase was 1,000 micrograms (Deftereos 2020, RECOVERY 2021, Lopes 2021, Salehzadeh 2020). Duration of treatment ranged from 6 days to 3 weeks across the studies.

Participants in 3 studies received hydroxychloroquine (or chloroquine) and azithromycin as part of standard care (Deftereos 2020, Lopes 2021, Salehzadeh 2020). Deftereos 2020 compared colchicine with standard care which included using hydroxychloroquine (or chloroquine) in 98% of participants and azithromycin in 92% of participants. RECOVERY 2021 compared colchicine with standard care which included using corticosteroids in 93% of participants and remdesivir in 22% of participants.

Follow-up ranged from 2 to 3 weeks; however Lopes 2021 did not clearly report the duration of follow-up.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

For further details see the evidence review.

What are the main results?
Critical outcomes

There was no statistically significant effect on mortality or need for mechanical ventilation within 21 to 28 days of starting colchicine treatment compared with placebo or standard care.

Important outcomes

There was a statistically significant increase in adverse events with colchicine compared with standard care.

No statistically significant differences were seen with colchicine compared with control for the other important outcomes reviewed. This includes duration of hospital stay.

Our confidence in the results
The certainty of evidence is moderate to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with all studies having some degree of risk of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care not including corticosteroids); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). One study was only available as a preprint.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard care	**Intervention** Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality within 21-28 days of starting treatment 9 Critical	Relative risk 0.66 (CI 95% 0.24 — 1.85) Based on data from 11,517 participants in 3 studies. [1]	206 per 1000 Difference:	136 per 1000 **70 fewer per 1000** (CI 95% 157 fewer — 175	**Moderate** Due to serious imprecision [2]	The pooled estimate of three studies found no statistically significant difference in all-cause mortality at 21 to 28 days, and at an unspecified timepoint with colchicine

Outcome Timeframe	Study results and measurements	Comparator Placebo or standard care	Intervention Colchicine	Certainty of the Evidence (Quality of evidence)	Plain language summary
			more)		compared with control
Mechanical ventilation within 21-28 days of starting treatment 9 Critical	Relative risk 0.53 (CI 95% 0.09 — 3.15) Based on data from 10,916 participants in 2 studies. [3]	244 per 1000 Difference:	129 per 1000 **115 fewer per 1000** (CI 95% 222 fewer — 525 more)	Very low Because of serious risk of bias due to lack of blinding, and due to serious imprecision, serious inconsistency, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen [4]	The pooled estimate of two studies found no statistically significant difference in mechanical ventilation at 21 to 28 days with colchicine compared with control
Serious adverse events within 21 days of starting treatment 6 Important	Relative risk Based on data from 105 participants in 1 studies.	0 per 1000	CI 95%	Moderate Because of serious risk of bias due to lack of blinding, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen [5]	One study found there were no serious adverse events at 3 weeks for either colchicine or standard care
Adverse events within 21 days of starting treatment 6 Important	Relative risk 2.61 (CI 95% 1.67 — 4.07) Based on data from 105 participants in 1 studies. [6]	300 per 1000 Difference:	783 per 1000 **483 more per 1000** (CI 95% 201 more — 921 more)	Low Because of serious risk of bias due to lack of blinding, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen [7]	One study found that there was a statistically significant increase in adverse events with colchicine compared with standard care within 21 days of starting treatment
		0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	Very low Because of serious bias due to lack of blinding, and due to very serious imprecision with fewer than 300 participants, and due to indirectness	The pooled estimate of two studies found no statistically significant difference in discontinuation due to adverse events with colchicine compared with standard care

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard care	**Intervention** Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
				because standard care did not include dexamethasone for hospitalised patients on oxygen [9]	
Clinical progression (scale) within 21 days of starting treatment. Increase of 2 grades on 7-grade scale 6 Important	Relative risk 0.13 (CI 95% 0.02 — 1.02) Based on data from 105 participants in 1 studies. [10]	140 per 1000 Difference:	18 per 1000 **122 fewer per 1000** (CI 95% 137 fewer — 3 more)	**Very low** Because of serious bias due to lack of blinding, and due to very serious imprecision with fewer than 300 participants, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen [11]	One study found a non-statistically significant reduction in clinical progression with colchicine compared with standard care
ICU admission follow-up timepoint was not provided 6 Important	Relative risk 0.33 (CI 95% 0.04 — 3.06) Based on data from 72 participants in 1 studies. [12]	83 per 1000 Difference:	27 per 1000 **56 fewer per 1000** (CI 95% 80 fewer — 171 more)	**Very low** Because of serious bias due to lack of specified follow-up timepoints, and due to very serious imprecision with fewer than 300 participants [13]	One study found no statistically significant difference in ICU admission with colchicine compared with placebo
Discharge from hospital by day 10 6 Important	Relative risk 1.5 (CI 95% 1.14 — 1.98) Based on data from 72 participants in 1 studies. [14]	611 per 1000 Difference:	917 per 1000 **306 more per 1000** (CI 95% 86 more — 599 more)	**Moderate** Because of serious bias due to lack of specified follow-up timepoints [15]	One study found that more people were discharged from hospital by day 10 in the colchicine arm compared with placebo
Discharge from hospital within 28 days 6 Important	Relative risk 0.99 (CI 95% 0.96 — 1.01) Based on data from 11,340 participants in 1 studies. [16] (Randomized controlled)	704 per 1000 Difference:	697 per 1000 **7 fewer per 1000** (CI 95% 28 fewer — 7 more)	**Low** Because of serious bias due to lack of blinding, and due to serious imprecision [17]	One study found no statistically significant difference in discharge from hospital within 28 days with colchicine compared with standard care
Duration of hospital stay at a mean follow-	Based on data from: 100	Difference:	**MD 1.84 lower** (CI 95% 2.9 lower — 0.78 lower)	**Very low** Because of very serious bias due	One study found that the duration of hospital stay was less with

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard care	**Intervention** Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
up of 21 days (mean difference) 6 Important	participants in 1 studies. [18]			to randomisation method not being provided, lack of blinding, and due to selective reporting of outcomes, and due to indirectness because standard care did not include corticosteroids for hospitalised patients on oxygen [19]	colchicine compared with standard care at a mean follow-up of 21 days

1. Systematic review [142] with included studies: Lopes 2021, GRECCO-19 2020, RECOVERY 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [47], [146], [46],
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
3. Systematic review [142] with included studies: RECOVERY 2021, GRECCO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:... %.. **Indirectness: serious.** Standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**
6. Systematic review [142] with included studies: GRECCO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**
8. Systematic review [142] with included studies: Lopes 2021, GRECCO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: very serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**
10. Systematic review [142] with included studies: GRECCO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention.
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.
12. Systematic review [142] with included studies: Lopes 2021. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Risk of Bias: serious.** Because of serious bias due to lack of specified follow-up timepoints. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**

14. Systematic review [142] with included studies: Lopes 2021. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Risk of Bias: serious.** Lack of specified follow-up timepoints. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
16. Systematic review [142] with included studies: RECOVERY 2021. **Baseline/comparator:** Control arm of reference used for intervention.
17. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
18. Systematic review [142] with included studies: Salehzadeh 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [48],
19. **Risk of Bias: very serious.** Due to randomisation method not being provided, lack of blinding, and due to selective reporting of outcomes. **Inconsistency: no serious. Indirectness: serious.** Because standard care did not include corticosteroids for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**

References

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Clinical Question/ PICO

Population:	People with COVID-19 in the community
Intervention:	Colchicine
Comparator:	Placebo

Summary

There is no evidence that colchicine is more effective than placebo or standard care in treating patients in the community with COVID-19.

What is the evidence informing this conclusion?
This is a November 2021 update of an evidence review from May 2021 and includes 1 new study (PRINCIPLE 2021). Evidence comes from 2 randomised trials that compared colchicine with placebo or standard care in 4764 adults in the community with COVID-19 (Tardiff 2021 (COLCORONA trial), PRINCIPLE 2021).

Publication status
PRINCIPLE 2021 was only available as a preprint and has therefore not been peer reviewed.

Study characteristics
The age of participants ranged from 18 to over 65 years and the proportion of women ranged from 49 to 59%. The studies did not clearly define the severity of COVID-19.

For Tardif 2021, the dosage of colchicine was 500 micrograms twice daily for the first 3 days then once daily for 27 days. For PRINCIPLE 2021, participants received colchicine 500 micrograms daily for 14 days.

As standard care in PRINCIPLE 2021, participants received medications focused on managing symptoms with antipyretics. In Tardif 2021, small percentages of participants were given hydroxychloroquine, oral anticoagulants, aspirin, and/or other platelet agents.

Follow-up after starting treatment was 28 days for PRINCIPLE 2021 and 30 days for Tardif 2021.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

For further details see the evidence review.

What are the main results?
Critical outcomes

For the critical outcomes of hospitalisation for COVID-19, all-cause mortality, and need for mechanical ventilation, there was no statistically significant effect 28-30 days after starting colchicine treatment compared with control.

Important outcomes

There was a statistically significant increase in adverse events with colchicine compared with standard care. There was a statistically significant increase in serious adverse events with standard care compared with colchicine. This was potentially due to a greater number of cases of pneumonia in the standard care arm.

No statistically significant differences were seen with colchicine compared with control for the other important outcomes reviewed. This includes time to reported recovery.

Our confidence in the results
The certainty of evidence is high to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with one study having some degree of risk of bias); inconsistency (for example, when point estimates varied widely between studies); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect). One study was only available as a preprint.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation for COVID-19 within 30 days of starting treatment 9 Critical	Relative risk 0.8 (CI 95% 0.62 — 1.03) Based on data from 4,488 participants in 1 studies. [1] (Randomized controlled)	57 per 1000 Difference:	46 per 1000 **11 fewer per 1000** (CI 95% 22 fewer — 2 more)	**Moderate** Due to serious imprecision [2]	One study found no statistically significant difference in hospitalisation for COVID-19 at 30 days with colchicine compared with placebo
All-cause mortality within 30 days of starting treatment 9 Critical	Relative risk 0.56 (CI 95% 0.19 — 1.67) Based on data from 4,488 participants in 1 studies. [3]	4 per 1000 Difference:	2 per 1000 **2 fewer per 1000** (CI 95% 3 fewer — 3 more)	**Moderate** Due to serious imprecision [4]	One study found no statistically significant difference in mortality at 30 days with colchicine compared with placebo
All-cause mortality or hospitalisation (28 or 30 days)	Relative risk 0.83 (CI 95% 0.65 — 1.06) Based on data from 4,764 participants in 2 studies. [5]	56 per 1000 Difference:	46 per 1000 **10 fewer per 1000**	**Moderate** Due to serious imprecision [6]	Two studies found a non-significant reduction in all-cause mortality or hospitalisation at 28 to 30 days with colchicine compared with control

Outcome Timeframe	Study results and measurements	Comparator Placebo			Plain language summary
9 Critical			(CI 95% 20 fewer — 3 more)		
Mechanical ventilation within 28-30 days of starting treatment 6 Important	Relative risk 0.53 (CI 95% 0.26 — 1.09) Based on data from 4,763 participants in 2 studies. [7]	9 per 1000 Difference:	5 per 1000 **4 fewer per 1000** (CI 95% 7 fewer — 1 more)	**Moderate** Due to serious imprecision [8]	The pooled estimate of two studies found a non-statistically significant reduction in mechanical ventilation at 28 to 30 days with colchicine compared with control
Serious adverse events within 28-30 days of starting treatment 6 Important	Relative risk 0.78 (CI 95% 0.61 — 0.99) Based on data from 4,688 participants in 2 studies. [9]	60 per 1000 Difference:	47 per 1000 **13 fewer per 1000** (CI 95% 23 fewer — 1 fewer)	**High**	The pooled estimate of two studies found a statistically significant reduction in serious adverse events in the colchicine arm at day 28 or day 30 compared with control
Adverse events within 30 days of starting treatment 6 Important	Relative risk 1.56 (CI 95% 1.38 — 1.76) Based on data from 4,412 participants in 1 studies. [10]	155 per 1000 Difference:	242 per 1000 **87 more per 1000** (CI 95% 59 more — 118 more)	**High**	One study found a statistically significant increase in adverse events in the colchicine arm at day 30 compared with placebo
Participants who experienced alleviation of all symptoms within 28 days of starting treatment 6 Important	Relative risk 1 (CI 95% 0.92 — 1.1) Based on data from 252 participants in 1 studies. [11]	883 per 1000 Difference:	883 per 1000 **0 fewer per 1000** (CI 95% 71 fewer — 88 more)	**Very low** Because of serious risk of bias due to a high dropout rate, concerns with randomisation, and lack of blinding, and due to serious imprecision [12]	One study found no statistically significant difference in the number of participants who experienced alleviation of all symptoms within 28 days of starting treatment with colchicine and standard care compared with standard care
Reported recovery (days) within 28 days of starting treatment 6 Important	Odds Ratio 0.92 (CI 95% 0.72 — 1.17) Based on data from 276 participants in 1 studies. (Randomized controlled)		CI 95%	**Very low** Because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding, and due to serious imprecision [13]	One study found no statistically significant difference in reported recovery with colchicine plus standard care compared with standard care alone
Time to alleviation of all symptoms estimated	Based on data from: 252 participants in 1 studies.	Difference:	**MD 0.94 higher** (CI 95% 0.68 higher — 1.2 higher)	**Low** Because of serious risk of bias due to a high	One study found that alleviation of all symptoms happened sooner with colchicine

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Colchicine	Certainty of the Evidence (Quality of evidence)	Plain language summary
treatment effect (median days) within 28 days of starting treatment, mean difference 6 Important	[14] (Randomized controlled)			dropout rate, concerns with randomisation, and lack of blinding [15]	and standard care compared with standard care
Time to reported recovery, median difference in days within 28 days of starting treatment, median difference 6 Important	Based on data from: 276 participants in 1 studies. (Randomized controlled)	Median difference: 1.14 (95 CI -1.86 to 5.21). A positive value in estimated median difference in time to recovery corresponds to an increase in time to recovery in days in colchicine compared with standard care		**Very low** Because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding, and due to serious imprecision [16]	One study found no statistically significant difference in time to reported recovery with colchicine plus standard care compared with standard care alone

1. Systematic review [143] with included studies: COLCORONA 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [49],
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
3. Systematic review [143] with included studies: COLCORONA 2021. **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 [143] with included studies: COLCORONA 2021, PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [147], [49],
6. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.** Due to serious imprecision. **Publication bias: no serious.**
7. Systematic review [143] with included studies: COLCORONA 2021, PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
9. Systematic review [143] with included studies: COLCORONA 2021, PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. Systematic review [143] with included studies: COLCORONA 2021. **Baseline/comparator:** Control arm of reference used for intervention.
11. Systematic review [143] with included studies: PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** due to a high dropout rate, concerns with randomisation, and lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
13. **Risk of Bias: very serious.** Because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
14. Systematic review [143] with included studies: PRINCIPLE 2021. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Risk of Bias: very serious.** Due to a high dropout rate, concerns with randomisation, and lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

16. **Risk of Bias: very serious.** because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**

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7.13 Doxycycline

Not recommended

Do not use doxycycline to treat COVID-19 in the community.

Evidence To Decision

Benefits and harms

Important harms

The panel discussed evidence from a trial comparing doxycycline plus standard care with standard care alone to treat COVID-19 in the community in people 65 years and over or people 50 and over if they have comorbidities. They agreed that the evidence suggests that, in these groups, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission into intensive care, the need for mechanical ventilation or oxygen, or significant adverse events. They also agreed that the evidence suggests doxycycline does not improve symptoms or recovery. The panel noted the lack of statistically significant benefits with doxycycline in both the main analysis population and the analysis in people with laboratory-confirmed positive COVID-19. The panel were aware that randomisation to doxycycline in the trial was stopped because of futility in December 2020. No evidence was identified for other groups or settings.

The panel noted that doxycycline may cause side effects such as gastrointestinal disturbances and photosensitivity. They were also concerned that using doxycycline to treat COVID-19 in the community may increase risk of antimicrobial resistance, which could have important antibiotic stewardship implications.

Certainty of the Evidence

Moderate

The certainty of evidence was rated as moderate because of serious imprecision (apart from 1 outcome that was rated as high). The panel were aware of imprecision issues, including there being only 1 study, the confidence intervals crossing the line of no effect and few events for some outcomes.

The panel were unclear on which symptoms were included in the measures of symptom alleviation and recovery.

The panel also discussed the relatively low proportion of people in the trial with laboratory-confirmed COVID-19. They thought this reflected the pragmatic treatment of COVID-19 in the community in the early stages of the pandemic, which was based on the presence of symptoms and limited testing capacity. However, they noted that testing is now more widely available in the community.

Because there are potential harms from doxycycline use (side effects and risk of antimicrobial resistance), the panel made a

strong recommendation against use in the community.

Preference and values

We expect few to want the intervention

The panel were not aware of any systematically collected data on peoples' preferences and values. They noted the importance to people with COVID-19 in the community of avoiding hospital admission. However, the included trial only reported a composite outcome of hospitalisation and death, and reported hospital assessment without admission but not hospitalisation. Avoiding admission into intensive care was also considered an important outcome by the panel. They inferred that most people would not choose doxycycline because of the lack of meaningful benefit in treating COVID-19, the potential for side effects and the risk of antimicrobial resistance.

Resources and other considerations

Important issues, or potential issues not investigated

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

Equity

No important issues with the recommended alternative

No evidence was found in people under 65 years, people under 50 years with comorbidities or pregnant women. However, because the overall recommendation is not to offer doxycycline to anyone in the community, it is not expected to cause inequity among any groups.

Acceptability

Intervention is likely poorly accepted

The panel were not aware of any systematically collected evidence about acceptability. However, the evidence does not suggest benefits with doxycycline and there are potential harms (from side effects and a risk of promoting antimicrobial resistance). So, its use in the community is not likely to be acceptable unless there are other licensed indications for which its use remains appropriate.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility.

Rationale

There is evidence from 1 trial in the community of doxycycline for COVID-19 in people 65 years and over and in people 50 years and over with comorbidities. The results suggest that, compared with standard care alone, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission to intensive care, the need for mechanical ventilation or oxygen, or significant adverse events in these groups. The results also suggest that it does not improve symptoms or recovery.

There is no evidence for doxycycline use in the community for COVID-19 in people under 65 years or people under 50 years with comorbidities. But, it is unlikely that the results in these groups will differ, so the panel agreed that the recommendation applies to all age groups in the community. They also noted the risks of side effects and antimicrobial resistance with doxycycline. There was no evidence found for doxycycline use in hospital settings.

Clinical Question/ PICO

Population: People with COVID-19 (Community)
Intervention: Doxycycline plus standard care
Comparator: Standard care

Summary

The evidence suggests that doxycycline plus standard care does not give statistically significant improvements in hospitalisation/death, mechanical ventilation, oxygen administration, ICU admission, measures of symptom alleviation and recovery, or significant adverse events in people with COVID-19 in the community.

What is the evidence informing this conclusion?

These findings are based on 1 RCT (PRINCIPLE) (Butler 2021). This UK study recruited participants from the community with ongoing symptoms (starting within the last 14 days) from PCR-confirmed or suspected COVID-19. Participants were aged 65 years and above or aged 50 years and above with comorbidities.

The RCT compared doxycycline plus standard care (N=780) with standard care (N=948) in adults with COVID-19. In December 2020 randomisation to doxycycline was stopped as pre-specified futility criteria were met.

Publication status

All studies have been peer-reviewed.

Study characteristics

Participants were recruited from the community (from general practices, online, or by telephone). Eligible participants had ongoing symptoms from PCR-confirmed or suspected COVID-19 (that must have started within the last 14 days) (in accordance with the United Kingdom [UK] National Health Service [NHS] definition of high temperature and/or new, continuous cough and/or change in sense of smell/taste). Eligible participants were aged 65 years and older, or 50 years and older if they had comorbidities (weakened immune system; heart disease; hypertension; asthma or lung disease; diabetes; hepatic impairment; stroke or neurological problem; and self-reported obesity or body mass index ≥35 kg/m^2.) People who were already taking acute antibiotics were excluded.

The intervention was doxycycline 200mg on day one, followed by 100mg daily for six days. Standard care for suspected uncomplicated COVID-19 in the community in the UK NHS is largely supportive (antibiotics only being recommended for suspected COVID-19 pneumonia if bacterial aetiology is suspected or the patient is at high risk, in which instance guidelines recommend doxycycline).

The proportion of people with a positive swab result varied from 35.1% (standard care group) to 55.4% (doxycycline group). Participants had a mean (standard deviation [SD]) age of 61.1 (7.9) years; over half (55.7%) were female and the majority (87.2%) had comorbidities. The median (interquartile range [IQR]) duration of illness prior to randomisation was 6 (4–9) days.

What are the main results?

Hospitalisation/death within 28 days (critical outcome)

One RCT (Butler 2021) found no statistically significant difference in hospitalisation/death within 28 days with doxycycline plus standard care compared with standard care (7 more per 1000 patients; RR 1.13 [95% CI 0.73 — 1.74]) in people with COVID-19 in the community

Mechanical ventilation (critical outcome)

One RCT (Butler 2021) reported no statistically significant difference in mechanical ventilation within 28 days with doxycycline plus standard care compared with standard care (4 fewer per 1000 patients; RR 0.49 [95% CI 0.12 — 2.05]) in people with COVID-19 in the community.

Significant adverse events (critical outcome)

One RCT (Butler 2021) showed no statistically significant difference in significant adverse events with doxycycline plus standard care compared with standard care (5 fewer per 1000; RR 0.11 [95% CI 0.01 — 1.99]) in people with COVID-19 in the community.

Oxygen administration (important outcome)

One RCT (Butler 2021) reported no statistically significant difference in oxygen administration within 28 days with doxycycline plus standard care compared with standard care (1 fewer per 1000 patients; RR 0.98 [95% CI 0.55 — 1.76]) in people with COVID-19 in the community

ICU admission (important outcome)

One RCT (Butler 2021) found no statistically significant difference in ICU admission within 28 days with doxycycline plus standard care compared with standard care (5 fewer per 1000; RR 0.55 [95% CI 0.16 — 1.93]) in people with COVID-19 in the community.

Alleviation of all symptoms within 28 days (important outcome)

One RCT (Butler 2021) found a non statistically significant improvement in alleviation of symptoms within 28 days with doxycycline plus standard care compared with standard care (28 fewer per 1000; RR 0.97 [95% CI 0.94 — 1.00]) in people with COVID-19 in the community.

Initial reduction of severity of symptoms within 28 days (important outcome)

One RCT (Butler 2021) found no statistically significant difference of initial reduction of severity of symptoms within 28 days with doxycycline plus standard care compared with standard care (11 more per 1000; RR 1.01 [95% CI 0.98 — 1.05]) in people with COVID-19 in the community.

Sustained alleviation of all symptoms within 28 days (important outcome)

One RCT (Butler 2021) found no statistically significant difference in alleviation of all symptoms within 28 days with doxycycline plus standard care compared with standard care (5 more per 1000; RR 1.01 [95% CI 0.96 — 1.06]) in people with COVID-19 in the community.

Sustained recovery (important outcome)

One RCT (Butler 2021) found no statistically significant difference in sustained recovery within 28 days with doxycycline plus standard care compared with standard care (29 more per 1000; RR 1.05 [95% CI 0.97— 1.13]) in people with COVID-19 in the community.

Time to initial reduction of severity of symptoms (important outcome)

One RCT (Butler 2021) reported no statistically significant difference in time to initial reduction of severity of symptoms with doxycycline plus standard care (HR 0.99 [95% CI 0.88 — 1.11]) compared with standard care in people with COVID-19 in the community.

Time to alleviation of all symptoms (important outcome)

There was no statistically significant difference in time to alleviation of all symptoms with doxycycline plus standard care compared with standard care (HR 0.96 [95% CI 0.86 — 1.09]) in 1 RCT (Butler 2021) in people with COVID-19 in the community.

Time to sustained alleviation of all symptoms (important outcome)

There was no statistically significant difference in 1 RCT (Butler 2021) for time to initial reduction of severity of symptoms with doxycycline plus standard care compared with standard care (HR 1.03 95% CI 0.90 — 1.17]) in people with COVID-19 in the community.

Time to first reported recovery (important outcome)

One RCT (Butler 2021) showed no statistically significant difference in time to first reported recovery with doxycycline plus standard care compared with standard care (HR 1.04 [95% CI 0.93 — 1.17]) in people with COVID-19 in the community.

Time to sustained recovery (important outcome)

One RCT (Butler 2021) found no statistically significant difference in time to sustained recovery with doxycycline plus standard care compared with standard care (HR 1.00 95 CI 0.88 — 1.14]) in people with COVID-19 in the community.

Our confidence in the results

The certainty of evidence for the critical outcomes of hospitalisation/death, mechanical ventilation and significant adverse events was rated as moderate (due to serious imprecision).

The certainty of evidence for the important outcome of alleviation of all symptoms at 28 days was considered to be high. However, the certainty of evidence for all remaining important outcomes was rated as moderate due to serious imprecision.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Doxycycline plus standard care	Certainty of the Evidence (Quality of evidence)	Plain language summary
Hospitalisation/ death Within 28 days 9 Critical	Relative risk 1.13 (CI 95% 0.73 — 1.74) Based on data from 1,728 participants in 1 studies. [1] (Randomized controlled)	45 per 1000 Difference:	52 per 1000 **7 more per 1000** (CI 95% 11 fewer — 34 more)	**Moderate** Due to serious imprecision [2]	One study found no statistically significant difference in hospitalisation/death within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Mechanical ventilation Within 28 days 9 Critical	Relative risk 0.49 (CI 95% 0.12 — 2.05) Based on data from 1,378 participants in 1 studies. [3] (Randomized controlled)	8 per 1000 Difference:	4 per 1000 **4 fewer per 1000** (CI 95% 7 fewer — 8 more)	**Moderate** Due to serious imprecision [4]	One study found no statistically significant difference in mechanical ventilation within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Significant adverse events 9 Critical	Relative risk 0.11 (CI 95% 0.01 — 1.99) Based on data from 1,728 participants in 1 studies. [5] (Randomized controlled)	5 per 1000 Difference:	0 per 1000 **5 fewer per 1000** (CI 95% 5 fewer — 5 more)	**Moderate** Due to serious imprecision [6]	One study found no statistically significant difference in significant adverse events with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Oxygen administration Within 28 days 6 Important	Relative risk 0.98 (CI 95% 0.55 — 1.76) Based on data from 1,378 participants in 1 studies. [7] (Randomized controlled)	32 per 1000 Difference:	31 per 1000 **1 fewer per 1000** (CI 95% 14 fewer — 24 more)	**Moderate** Due to serious imprecision [8]	One study found no statistically significant difference in oxygen administration within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
ICU admission Within 28 days 6 Important	Relative risk 0.55 (CI 95% 0.16 — 1.93) Based on data from 1,375 participants in 1 studies. [9] (Randomized controlled)	10 per 1000 Difference:	5 per 1000 **5 fewer per 1000** (CI 95% 8 fewer — 9 more)	**Moderate** Due to serious imprecision [10]	One study found no statistically significant difference in ICU admission within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Alleviation of all symptoms Within 28 days	Relative risk 0.97 (CI 95% 0.94 — 1) Based on data from 1,222 participants in 1 studies. [11] (Randomized	947 per 1000 Difference:	921 per 1000 **28 fewer per 1000**	**High** 12	One study found a non-statistically significant improvement in alleviation of all symptoms within 28

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Doxycycline plus standard care		
6 Important	controlled)		(CI 95% 57 fewer — 75 more)		days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Initial reduction of severity of symptoms Within 28 days 6 Important	Relative risk 1.01 (CI 95% 0.98 — 1.05) Based on data from 1,424 participants in 1 studies. [13] (Randomized controlled)	888 per 1000 Difference:	899 per 1000 **11 more per 1000** (CI 95% 18 fewer — 44 more)	**Moderate** Due to serious imprecision [14]	One study found no statistically significant difference in initial reduction of severity of symptoms within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.
Sustained alleviation of all symptoms Within 28 days 6 Important	Relative risk 1.01 (CI 95% 0.96 — 1.06) Based on data from 1,163 participants in 1 studies. [15] (Randomized controlled)	831 per 1000 Difference:	836 per 1000 **5 more per 1000** (CI 95% 33 fewer — 50 more)	**Moderate** Due to serious imprecision [16]	One study found no statistically significant difference in sustained alleviation of all symptoms within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
Sustained recovery Within 28 days 6 Important	Relative risk 1.05 (CI 95% 0.97 — 1.13) Based on data from 1,424 participants in 1 studies. [17] (Randomized controlled)	615 per 1000 Difference:	644 per 1000 **29 more per 1000** (CI 95% 18 fewer — 80 more)	**Moderate** Due to serious imprecision [18]	One study found no statistically significant difference in sustained recovery within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
Time to initial reduction of severity of symptoms 6 Important	Hazard Ratio 0.99 (CI 95% 0.88 — 1.11) Based on data from 1,424 participants in 1 studies. (Randomized controlled)			**Moderate** Due to serious imprecision [19]	One study found no statistically significant difference in time to initial reduction of severity of symptoms with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
Time to alleviation of all symptoms 6 Important	Hazard Ratio 0.96 (CI 95% 0.86 — 1.09) Based on data from 1,222 participants in 1 studies. (Randomized controlled)			**Moderate** Due to serious imprecision [20]	One study found no statistically significant difference in time to alleviation of all symptoms with doxycycline plus standard care compared

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Doxycycline plus standard care	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					with standard care in people with COVID-19 in the community
Time to sustained alleviation of all symptoms 6 Important	Hazard Ratio 1.03 (CI 95% 0.9 — 1.17) Based on data from 1,163 participants in 1 studies. (Randomized controlled)			**Moderate** Due to serious imprecision [21]	One study found no statistically significant difference in time to sustained alleviation of all symptoms with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
Time to first reported recovery 6 Important	Hazard Ratio 1.04 (CI 95% 0.93 — 1.17) Based on data from 1,728 participants in 1 studies. (Randomized controlled)			**Moderate** Due to serious imprecision [22]	One study found no statistically significant difference in time to first reported recovery with doxycycline plus standard care compared with standard care in people with COVID-19 in the community
				Moderate Due to serious imprecision [23]	One study found no statistically significant difference in time to sustained recovery with doxycycline plus standard care compared with standard care in people with COVID-19 in the community

1. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
3. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to confidence intervals crossing line of no effect.
5. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study.
7. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
9. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to confidence intervals crossing line of no effect.
11. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for

intervention.
12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Only data from one study.
13. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
15. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
17. Systematic review [77] with included studies: Butler 2021. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
19. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
21. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
22. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
23. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.

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74. Butler CC, Yu L-M, Dorward J, Gbinigie O, Hayward G, Saville BR, et al. : Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. The Lancet. Respiratory medicine 2021; Pubmed Journal

77. Doxycycline for suspected or confirmed COVID-19.

7.14 Ivermectin

Only in research settings

Do not use ivermectin to treat COVID-19 except as part of a clinical trial.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Hospital settings

The panel stated that mortality is an important outcome. They noted that the evidence does not show a statistically significant difference in mortality for people in hospital with COVID-19 having ivermectin compared with people having standard care. They also considered that the certainty of evidence for this outcome is very low.

Although the evidence suggests a statistically significant reduction in duration of hospitalisation for people with COVID-19 who have ivermectin, the panel had concerns with the results. They noted that the certainty of evidence is very low for that

outcome. They also agreed that there are issues with the applicability of the evidence in the hospital setting. This was because most people in the studies had less severe COVID-19 than people who would be hospitalised in the UK.

The panel agreed that the evidence shows no difference between ivermectin and control for the other critical outcomes of admission to intensive care, need for invasive mechanical ventilation, discharge from hospital and adverse events.

The panel discussed the evidence suggesting statistically significant benefits with ivermectin for COVID-19 in people in hospital for viral clearance (at 7 to 12 days), duration to viral clearance and duration of symptoms. However, they agreed that the evidence supporting these benefits is of low to very low certainty. The panel suggested that the value of any benefits in viral clearance might lead to reduced infectivity or viral shedding but considered that this is uncertain. They also agreed that the evidence shows no statistically significant benefits for the other important outcomes of number of people needing oxygen, clinical improvement, clinical worsening, time to recovery and viral clearance (at 1 to 7 days).

Community settings

The panel discussed the evidence on ivermectin use for people with COVID-19 in the community. They agreed the evidence shows no statistically significant differences for ivermectin in: mortality; need for invasive mechanical ventilation; adverse events; need for hospitalisation; number of people needing oxygen; clinical progression; clinical recovery; presence of symptoms at day 7; viral clearance (at 7 to 12 days); virological clearance (within 14 days); or recovery. The panel noted that the certainty of evidence is low to very low for all outcomes.

The panel also noted that evidence suggests a statistically significant increase in stopping treatment because of adverse events with ivermectin but agreed that this evidence is of very low certainty.

Other panel considerations

The panel discussed the potential for the occurrence of rare serious adverse events with ivermectin. They considered that the available studies were too small to identify such events.

The panel noted that no studies were from the UK. They commented that some of the treatments (such as hydroxychloroquine, doxycycline, azithromycin and lopinavir–ritonavir) used in the control groups are not used in the UK for COVID-19. Detail on other treatments was lacking in some studies. The panel considered that this limits the applicability of the evidence to UK practice. The panel also discussed that, because dosage varied widely across the included studies, it is uncertain what a safe dose of ivermectin would be.

The panel agreed that the uncertainty around the benefits and safety of ivermectin based on the current evidence means that it cannot be recommended for COVID-19 in people in hospital or community settings. They considered that this was the case for children, young people and adults. The panel were aware of ongoing trials investigating ivermectin, such as the PRINCIPLE trial. They considered that the available evidence for the effectiveness and safety of ivermectin could be improved by evidence from a well-designed randomised controlled trial.

Certainty of the Evidence

Very low

The panel agreed that the certainty of evidence on ivermectin for people with COVID-19 in hospital and in the community is low to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with most studies being at high or unclear risk of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care differing from that in the UK); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Some studies were only available as preprints so have not been peer reviewed.

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on peoples' preferences and values about ivermectin for COVID-19. They discussed that people with COVID-19 may have different views on ivermectin use because of the quality of current evidence, uncertainty over its safety and the availability of recommended treatments for COVID-19 in the UK.

Resources and other considerations

Important issues, or potential issues not investigated

The panel raised concerns about ivermectin being used to treat COVID-19 when there is limited evidence of benefit. They highlighted the importance of not diverting resources away from other evidence-based indications for ivermectin.

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

Equity

Important issues, or potential issues not investigated

No evidence was found for ivermectin use in pregnancy. Limited evidence was identified in children or young people. However, because the overall recommendation is not to offer ivermectin, it is not expected to cause inequity among any groups. The panel considered the issue of equity and did not raise any additional concerns. However, the panel flagged the importance of not diverting ivermectin supply away from existing evidence-based indications in non-UK countries.

Acceptability

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability. Ivermectin is not licensed in the UK for treating COVID-19. The low to very low certainty of current evidence may reduce acceptability.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility. However, the panel noted the current limited availability of ivermectin in the UK.

Rationale

Overall, there is a high degree of uncertainty about whether ivermectin is more effective than control for managing COVID-19 in hospital or community settings. The panel raised concerns about the quality of the studies on ivermectin. They agreed that the certainty of evidence is low to very low for all outcomes. The panel also noted the uncertainty about the overall safety and the possibility of rare serious adverse events with ivermectin. Because of the uncertainty in the current evidence (including small sample sizes and issues with study quality), the panel concluded that ivermectin should only be used to treat COVID-19 in well-conducted clinical trials.

Clinical Question/ PICO

Population: People with COVID-19 (Community)
Intervention: Ivermectin
Comparator: Standard care, standard care plus placebo, or placebo

Summary

There remains a high degree of uncertainty over whether ivermectin is more effective than placebo, placebo plus standard care or standard care for management of COVID-19 in the community.

What is the evidence informing this conclusion?

Evidence comes from 7 randomised control trials (RCTs) that compared ivermectin with placebo, placebo plus standard care or standard care in people with COVID-19 in the community (Biber 2021; Buonfrate 2021; Chaccour 2021; Chachar 2020; Lopez-Medina 2021; Podder 2021; Vallejos 2021).

Publication status

Two studies were preprints (posted on medRxiv on 31 May 2021 (Biber 2021) and posted on Lancet preprints on 6 September 2021 (Buonfrate 2021) and have therefore not been peer reviewed.

Five studies were full publications (Chaccour 2021; Chachar 2020; Lopez-Medina 2021; Podder 2021; Vallejos 2021).

Study characteristics

Sample sizes ranged from 24 (Chaccour 2021) to 501 (Vallejos 2021). The average age of study samples ranged from 26 (Chaccour 2021) to 47 years (Buonfrate 2021). Study samples were mostly male. Standard care within the trials varied.

For COVID-19 disease severity (based on degree of respiratory support): 88% were mild/moderate, 11% asymptomatic and 0.15% severe. The studies defined COVID-19 disease severity using a variety of markers.

Participants were described as outpatients in 2 studies (Buonfrate 2021; Podder 2021), attending COVID-19 clinics and the outpatient department in 1 study (Chachar 2020) and as being non-hospitalised in 2 studies (Biber 2021,Vallejos 2021). In 1 study people were described as attending the emergency room and the trial protocol stated patients isolated at home (Chaccour 2021). One study was a mixed setting of home or hospital, but very few people were hospitalised (Lopez-Medina 2021).

Ivermectin doses varied across the included studies.

For further details see the evidence review.

What are the main results?

Critical outcomes

Discontinuation of treatment due to adverse events was significantly higher with ivermectin compared with control.

The evidence suggests that, compared with control groups in people with COVID-19 in the community, ivermectin does not result in statistically significant differences in any other critical outcomes reviewed.

Important outcomes

No statistically significant differences were seen with ivermectin compared with control in the important outcomes reviewed.

Our confidence in the results

Studies are heterogenous with both clinical and methodological diversity. For some studies insufficient information was available to assess the methods used. Most studies were assessed as being at high or unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care differing from that in the UK); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome).Certainty of evidence was low or very low for all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care, standard care plus placebo, or placebo	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality (day 28) 9 Critical	Relative risk 1 (CI 95% 0.27 — 3.67) Based on data from 899 participants in 2 studies. [1] (Randomized controlled)	9 per 1000 Difference:	9 per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 24 more)		2 studies showed no significant difference in mortality for ivermectin compared with control.
Invasive mechanical ventilation 9 Critical	Relative risk 1.34 (CI 95% 0.3 — 5.92) Based on data from 501 participants in 1 studies. [3] (Randomized controlled)	12 per 1000 Difference:	16 per 1000 **4 more per 1000** (CI 95% 8 fewer — 59 more)	Low Due to serious imprecision, Due to serious indirectness [4]	1 study showed no significant difference in invasive mechanical ventilation for ivermectin compared with control.
Hospitalisation (with Buonfrate lower dose) 9 Critical	Relative risk 0.65 (CI 95% 0.35 — 1.19) Based on data from 634 participants in 3 studies. [5] (Randomized controlled)	78 per 1000 Difference:	51 per 1000 **27 fewer per 1000** (CI 95% 51 fewer — 15 more)	Very low Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision [6]	3 studies showed no significant difference in hospitalisation for ivermectin compared with control.
Hospitalisation (with Buonfrate higher dose) 9 Critical	Relative risk 0.7 (CI 95% 0.39 — 1.27) Based on data from 635 participants in 3 studies. [7] (Randomized controlled)	78 per 1000 Difference:	55 per 1000 **23 fewer per 1000** (CI 95% 48 fewer — 21 more)	Very low Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision [8]	3 studies showed no significant difference in hospitalisation for ivermectin compared with control.
Serious adverse events (end of follow-up) (Buonfrate lower dose) 9 Critical	Relative risk 1.17 (CI 95% 0.23 — 6.08) Based on data from 967 participants in 4 studies. [9] (Randomized controlled)	4 per 1000 Difference:	5 per 1000 **1 more per 1000** (CI 95% 3 fewer — 20 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias [10]	4 studies showed no significant difference in serious adverse events for ivermectin compared with control.
Serious adverse events (end of follow-up) (Buonfrate higher dose) 9 Critical	Relative risk 1.68 (CI 95% 0.36 — 7.97) Based on data from 969 participants in 4 studies. [11] (Randomized controlled)	4 per 1000 Difference:	7 per 1000 **3 more per 1000** (CI 95% 3 fewer — 28 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias [12]	4 studies showed no significant difference in serious adverse events for ivermectin compared with control.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care, standard care plus placebo, or placebo	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Adverse events (end of follow up) 9 Critical	Relative risk 0.92 (CI 95% 0.82 — 1.03) Based on data from 1,039 participants in 4 studies. [13] (Randomized controlled)	427 per 1000 Difference:	393 per 1000 **34 fewer per 1000** (CI 95% 77 fewer — 13 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias [14]	4 studies showed no significant difference in adverse events for ivermectin compared with control.
Discontinuation due to adverse events 9 Critical	Relative risk 2.97 (CI 95% 1.1 — 8.02) Based on data from 899 participants in 2 studies. [15] (Randomized controlled)	11 per 1000 Difference:	33 per 1000 **22 more per 1000** (CI 95% 1 more — 77 more)	Very low Due to serious indirectness, Due to very serious risk of bias [16]	2 studies showed a significant increase in discontinuation due to adverse events for ivermectin compared with control.
Number of patients requiring oxygen 6 Important	Relative risk 0.3 (CI 95% 0.01 — 7.14) Based on data from 89 participants in 1 studies. [17] (Randomized controlled)	24 per 1000 Difference:	7 per 1000 **17 fewer per 1000** (CI 95% 24 fewer — 147 more)	Very low Due to very serious imprecision, Due to serious indirectness, Due to serious risk of bias [18]	1 study showed a non-significant reduction in the number of people requiring oxygen for ivermectin compared with control.
Clinical progression 6 Important	Relative risk 0.57 (CI 95% 0.17 — 1.9) Based on data from 422 participants in 2 studies. [19] (Randomized controlled)	33 per 1000 Difference:	19 per 1000 **14 fewer per 1000** (CI 95% 27 fewer — 30 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias [20]	2 studies showed no significant difference in clinical progression for ivermectin compared with control.
Clinical recovery (21 days) 6 Important	Relative risk 1.04 (CI 95% 0.94 — 1.15) Based on data from 398 participants in 1 studies. [21] (Randomized controlled)	788 per 1000 Difference:	820 per 1000 **32 more per 1000** (CI 95% 47 fewer — 118 more)	Very low Due to serious imprecision, Due to serious indirectness, Due to very serious risk of bias [22]	1 study showed no significant difference in clinical recovery for ivermectin compared with control.
Symptomatic at day 7 6 Important	Relative risk 0.9 (CI 95% 0.44 — 1.83) Based on data from 50 participants in 1 studies. [23] (Randomized controlled)	400 per 1000 Difference:	360 per 1000 **40 fewer per 1000** (CI 95% 224 fewer — 332 more)	Very low Due to very serious imprecision, Due to serious indirectness, Due to very serious risk of bias [24]	1 study showed no significant difference in people symptomatic at day 7 for ivermectin compared with control.
		859 per 1000	850 per 1000		

Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
[25] (Randomized controlled)	Difference:	**9 fewer per 1000** (CI 95% 60 fewer — 52 more)	indirectness, Due to serious inconsistency [26]	compared with control.
Relative risk 1.19 (CI 95% 0.74 — 1.91) Based on data from 43 participants in 1 studies. [27] (Randomized controlled)	600 per 1000 Difference:	714 per 1000 **114 more per 1000** (CI 95% 156 fewer — 546 more)	Very low Due to very serious imprecision, Due to serious indirectness, Due to serious risk of bias [28]	1 study showed no significant difference in virological clearance for ivermectin compared with control.
Relative risk 0.94 (CI 95% 0.56 — 1.59) Based on data from 45 participants in 1 studies. [29] (Randomized controlled)	600 per 1000 Difference:	564 per 1000 **36 fewer per 1000** (CI 95% 264 fewer — 354 more)	Very low Due to serious risk of bias, Due to very serious imprecision, Due to serious indirectness [30]	1 study showed no significant difference in virological clearance for ivermectin compared with control.
Based on data from: 62 participants in 1 studies. [31] (Randomized controlled)	Difference:	**MD 1.41 lower** (CI 95% 3.62 lower — 0.8 higher)	Very low Due to very serious imprecision, Due to serious indirectness, Due to very serious risk of bias [32]	1 study showed no significant difference in recovery for ivermectin compared with control.
Based on data from: 62 participants in 1 studies. [33] (Randomized controlled)	Difference:	**MD 1.02 lower** (CI 95% 2.76 lower — 0.72 higher)	Very low Due to very serious imprecision, Due to serious indirectness, Due to serious risk of bias, Due to very serious risk of bias [34]	1 study showed no significant difference in recovery for ivermectin compared with control.

1. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
3. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: no serious.** less than 33.3% weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
5. Systematic review [133] with included studies: Biber 2021, Vallejos 2021, Buonfrate 2021 600 ug. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: no serious.** less than 33.3% weight came from studies at unclear or high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard care not relevant to UK. **Imprecision: serious.** due to confidence

interval crossing line of no effect. **Publication bias: no serious.**
7. Systematic review [133] with included studies: Biber 2021, Vallejos 2021, Buonfrate 2021 1200 ug. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: no serious.** less than 33.3% weight came from studies at unclear or high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard care not relevant to UK. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
9. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
11. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
13. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
15. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
16. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious. Publication bias: no serious.**
17. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
19. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
21. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
23. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
25. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
26. **Risk of Bias: no serious.** less than 33.3% weight came from studies at unclear or high risk of bias. **Inconsistency: serious.** due to large I-squared value (>50%). **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
27. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
28. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
29. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
30. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
31. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
32. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
33. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
34. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence

interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**

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133. Ivermectin versus standard care for COVID-19.

Clinical Question/ PICO

Population:	People with COVID-19 (Hospitalised)
Intervention:	Ivermectin
Comparator:	Standard care, standard care plus placebo, or placebo

Summary

There remains a high degree of uncertainty over whether ivermectin is more effective than placebo, placebo plus standard care or standard care for management of COVID-19 in hospital.

What is the evidence informing this conclusion?

Evidence comes from 11 randomised control trials (RCTs) that compared ivermectin with placebo, placebo plus standard care or standard care for people hospitalised with COVID-19 (Abd-Elsalam 2021; Ahmed 2021; Bukhari 2021; Gonzalez 2021; Kishoria 2020; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021; Ravikirti 2021; Shahbaznejad 2021; Shakhsi Niaee 2021).

Publication status

Two studies were preprints (posted to medRxiv on 5 February 2021 (Bukhari 2021), and on 23 February 2021 (Gonzalez 2021) and have therefore not been peer reviewed.

Nine studies were full publications (Abd-Elsalam 2021; Ahmed 2021; Kishoria 2020; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021; Ravikirti 2021; Shahbaznejad 2021; Shakhsi Niaee 2021).

Study characteristics
Sample sizes ranged from 31 (Pott-Junior 2021) to 180 (Shakhsi Niaee 2021). The average age of study samples ranged from 35 (Mohan 2021) to 56 years (Gonzalez 2021) and the proportion of women ranged between 10 and 55%. Standard care within the trials varied.

For COVID-19 disease severity (based on degree of respiratory support) the majority of patients were mild/moderate (61%), with 10% severe and 3% asymptomatic. It was not possible to determine severity in 26% of patients. The studies define severity using a variety of measures.

Ivermectin doses varied across the included studies.

For further details see the evidence review.

What are the main results?

Critical outcomes

The evidence suggests that, compared with control groups in people with COVID-19 in hospital, ivermectin does not result in statistically significant differences in the critical outcomes reviewed.

Important outcomes

The evidence suggests that ivermectin does not result in statistically significant differences in number of patients requiring oxygen, clinical improvement, clinical worsening and viral clearance (1-7 days).

The evidence suggests that, compared with control, ivermectin results in a statistically significant reduction in viral clearance (7-12 days), duration of hospitalisation, duration of symptoms and duration to viral clearance.

Our confidence in the results
Studies are heterogenous with both clinical and methodological diversity. For some studies insufficient information was available to assess the methods used. Most studies were assessed as being at high or unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care differing from that in the UK, specifically, the majority of patients had mild/moderate disease so in UK practice would not be hospitalised); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Certainty of evidence was low or very low for all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care, standard care plus placebo, or placebo	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality (day 28) 9 Critical	Relative risk 0.41 (CI 95% 0.16 — 1.07) Based on data from 681 participants in 5 studies. [1] (Randomized controlled)	87 per 1000 Difference:	36 per 1000 **51 fewer per 1000** (CI 95% 73 fewer	Very low Due to very serious risk of bias, Due to serious indirectness, Due to serious	5 studies showed a non-significant reduction in mortality for ivermectin compared with control.

Outcome Timeframe	Study results and measurements	Comparator Standard care, standard care plus placebo, or placebo	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
			— 6 more)	imprecision, Due to serious inconsistency [2]	
Admission to ICU 9 Critical	Relative risk 0.7 (CI 95% 0.26 — 1.91) Based on data from 143 participants in 2 studies. [3] (Randomized controlled)	115 per 1000 Difference:	81 per 1000 **34 fewer per 1000** (CI 95% 85 fewer — 105 more)	**Very low** Due to serious indirectness, Due to very serious imprecision, Due to serious risk of bias [4]	2 studies showed no significant difference in admission to ICU for ivermectin compared with control.
Invasive mechanical ventilation 9 Critical	Relative risk 0.75 (CI 95% 0.29 — 1.95) Based on data from 529 participants in 5 studies. [5] (Randomized controlled)	38 per 1000 Difference:	29 per 1000 **9 fewer per 1000** (CI 95% 27 fewer — 36 more)		5 studies showed no significant difference in invasive mechanical ventilation for ivermectin compared with control.
Discharge from hospital (end of follow-up) 9 Critical	Relative risk 1.04 (CI 95% 0.97 — 1.12) Based on data from 342 participants in 4 studies. [7] (Randomized controlled)	868 per 1000 Difference:	903 per 1000 **35 more per 1000** (CI 95% 26 fewer — 104 more)	**Very low** Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias [8]	4 studies showed no significant difference in discharge from hospital for ivermectin compared with control.
Discharge from hospital (by day 10) 9 Critical	Relative risk 1.09 (CI 95% 0.89 — 1.33) Based on data from 112 participants in 1 studies. [9] (Randomized controlled)	737 per 1000 Difference:	803 per 1000 **66 more per 1000** (CI 95% 81 fewer — 243 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [10]	1 study showed no significant difference in discharge from hospital for ivermectin compared with control.
Serious adverse events (end of follow-up) 9 Critical	Relative risk 1.55 (CI 95% 0.07 — 35.89) Based on data from 242 participants in 3 studies. [11] (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**Very low** Due to serious indirectness, Due to very serious imprecision, Due to serious risk of bias [12]	There were too few who experienced serious adverse events to determine whether ivermectin made a difference.
		51 per 1000 Difference:	65 per 1000 **14 more per 1000** (CI 95% 13 fewer — 59 more)	**Very low** Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias [14]	7 studies showed no significant difference in adverse events for ivermectin compared with control.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care, standard care plus placebo, or placebo	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Number of patients requiring oxygen 6 Important	Relative risk 1.08 (CI 95% 0.5 — 2.32) Based on data from 114 participants in 2 studies. [15] (Randomized controlled)	158 per 1000 Difference:	171 per 1000 **13 more per 1000** (CI 95% 79 fewer — 209 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [16]	2 studies showed no significant difference in the number of patients requiring oxygen for ivermectin compared with control.
Clinical improvement (2 or more decrease WHO) 6 Important	Relative risk 1.07 (CI 95% 0.94 — 1.22) Based on data from 125 participants in 1 studies. [17] (Randomized controlled)	867 per 1000 Difference:	928 per 1000 **61 more per 1000** (CI 95% 52 fewer — 191 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [18]	1 study showed no significant difference in clinical improvement for ivermectin compared with control.
Clinical worsening 6 Important	Relative risk 0.56 (CI 95% 0.17 — 1.84) Based on data from 125 participants in 1 studies. [19] (Randomized controlled)	111 per 1000 Difference:	62 per 1000 **49 fewer per 1000** (CI 95% 92 fewer — 93 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [20]	1 study showed no significant difference in clinical worsening for ivermectin compared with control.
Viral clearance (1-7 days) 6 Important	Relative risk 1.03 (CI 95% 0.55 — 1.91) Based on data from 63 participants in 2 studies. [21] (Randomized controlled)	471 per 1000 Difference:	485 per 1000 **14 more per 1000** (CI 95% 212 fewer — 429 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [22]	2 studies showed no significant difference in viral clearance (1 to 7 days) for ivermectin compared with control.
Viral clearance (7-12 days) 6 Important	Relative risk 1.68 (CI 95% 1.26 — 2.25) Based on data from 203 participants in 2 studies. [23] (Randomized controlled)	378 per 1000 Difference:	635 per 1000 **257 more per 1000** (CI 95% 98 more — 473 more)	Very low Due to very serious risk of bias, Due to serious indirectness, Due to serious inconsistency [24]	2 studies showed a statistically significant improvement in viral clearance (7 to 12 days) for ivermectin compared with control.
Duration of hospitalisation (days) 9 Critical	Based on data from: 278 participants in 3 studies. [25] (Randomized controlled)	Difference:	**MD 1.43 lower** (CI 95% 2.41 lower — 0.44 lower)	Very low Due to serious indirectness, Due to very serious risk of bias [26]	3 studies showed a statistically significant reduction in duration of hospitalisation for ivermectin compared with control.
		5 (Median) Difference:	6 (Median) **1 higher**		

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care, standard care plus placebo, or placebo	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical				imprecision. [27]	
Duration of symptoms 6 Important	Based on data from: 69 participants in 1 studies. [28] (Randomized controlled)	Difference:	**MD 1 lower** (CI 95% 1.14 lower — 0.86 lower)	**Low** Due to serious risk of bias, Due to serious indirectness [29]	1 study showed a statistically significant reduction in duration of symptoms for ivermectin compared with control.
Time to recovery (resolution of symptoms) 6 Important	Based on data from: 125 participants in 1 studies. [30] (Randomized controlled)	Difference:	**MD 0.07 lower** (CI 95% 1.09 lower — 0.95 higher)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [31]	1 study showed no significant difference in time to recovery for ivermectin compared with control.
		Difference:	**MD 3 lower** (CI 95% 5.43 lower — 0.57 lower)		

1. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
3. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
5. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
7. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**
9. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
11. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
13. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no**

serious. Indirectness: serious. standard of care was different to UK setting. **Imprecision: serious.** due to confidence interval crossing line of no effect. **Publication bias: no serious.**

15. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
16. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
17. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
19. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
21. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
23. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: serious.** due to large I-squared value (>50%). **Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious. Publication bias: no serious.**
25. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
26. **Risk of Bias: very serious.** greater than 33.3% of weight came from studies at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious. Publication bias: no serious.**
27. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: serious.** due to uncertainty in estimate. **Publication bias: no serious.**
28. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
29. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious. Publication bias: no serious.**
30. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
31. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: very serious.** due to confidence interval crossing line of no effect, fewer than 300 people contributing to outcome. **Publication bias: no serious.**
32. Systematic review [133] . **Baseline/comparator:** Control arm of reference used for intervention.
33. **Risk of Bias: serious.** greater than 33.3% of weight came from studies at unclear or high risk of bias. **Inconsistency: no serious. Indirectness: serious.** standard of care was different to UK setting. **Imprecision: no serious. Publication bias: no serious.**

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133. Ivermectin versus standard care for COVID-19.

7.15 Ongoing review of therapeutics for COVID-19

Info Box

We are currently reviewing new and existing therapeutics for treating COVID-19 as part of a living guidelines approach. New and updated recommendations will be published for this guideline as they become available (see Update information | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE).

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 the NICE guideline on intravenous fluid therapy in children and young people in hospital.

For information on managing renal replacement therapy for adults who are critically unwell with COVID-19, see the Renal Association's guidelines on renal replacement therapy for critically unwell adults.

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: 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: 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.

Standard prophylactic dose: the prophylactic dose of a low molecular weight heparin (LMWH), as listed in the medicine's summary of product characteristics, for medical patients.

Intermediate dose: double the standard prophylactic dose of an LMWH for medical patients.

A treatment dose: 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.

The Department of Health VTE risk assessment tool is commonly used to develop treatment plans.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel considered evidence from 6 trials evaluating whether higher doses (intermediate or treatment) of anticoagulation improve clinical outcomes in people in hospital with confirmed COVID-19.

Although the evidence did not show a statistically significantly increased risk of bleeding with higher doses of anticoagulation, the panel agreed that the occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. They therefore agreed that risk of bleeding should be assessed as soon as possible using a risk assessment tool to uncover any potential harm to people with a high risk.

Preference and values

Rationale

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 people 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.

Recommended

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

See the NICE recommendation on low molecular weight heparin self-administration.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel agreed that a standard prophylactic dose of a low molecular weight heparin (LMWH) should be offered as soon as possible to manage the risk of VTE based on current standard practice.

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 reported in the studies used was relatively low for adults in hospital with moderate COVID-19 (defined in this guideline as people receiving low flow supplementary oxygen) and severe COVID-19 (defined in this guideline as people receiving high-flow oxygen). Thus the benefits of standard-dose prophylactic anticoagulation may outweigh the potential harms in these populations. The panel also noted that people who are discharged early (before 7 days) could be at risk of clots. They emphasised the importance of continuing treatment after discharge until 7 days has passed to ensure people have had a full dose of a LMWH.

The panel noted that the duration of treatment recommended in NICE's guideline on VTE in over 16s is a minimum of 7 days and thought that it would be acceptable to align treatment duration of a standard prophylactic dose of a LMWH in people with moderate or severe COVID-19 with standard practice.

Certainty of the Evidence

Moderate

The panel was presented with evidence from 3 trials (ACTION, ACTIVE-4A-ATTACC-REMAP-CAP, RAPID) that compared the effectiveness of standard-dose VTE prophylaxis with treatment-dose VTE prophylaxis. The outcomes of ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID were of moderate to very low certainty.

The panel noted that the results from RAPID were preprint results. This meant they had not been peer reviewed, so they interpreted the results with the appropriate caution. Some of the group allocated to the standard prophylactic anticoagulant dose had higher doses in the ACTION and ACTIVE-4a-ATTACC-REMAP-CAP trials (between 26% and 29%), which the panel recognised could have affected the results. However, they considered that the evidence was certain enough to make recommendations to consider standard-dose VTE prophylaxis in young people and adults with moderate or severe COVID-19.

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 possible mortality benefits and increase in organ support-free days for people with COVID-19 who need low-flow or high-flow oxygen, many would choose a standard dose of an anticoagulant.

Resources and other considerations

No important issues with the recommended alternative

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

The panel did not have concerns about opportunity costs when an LMWH is being used for people who need low-flow or high-flow oxygen. The panel decided to recommend that treatment is continued for up to 7 days, including after discharge. This may be a higher resource use of anticoagulation because people who are discharged before 7 days will need to learn how to self-administer LMWH at home and monitor levels.

Equity

No important issues with the recommended alternative

The panel noted an absence of evidence for anticoagulation in children. They 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 are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults.

For people under 16 years the risk of VTE is uncertain in the context of COVID-19. The risk-benefit of VTE and dosing should be discussed by multidisciplinary teams on a case-by-case basis.

Not all heparins are acceptable to people of certain religions because the products are derived from animals. The panel made a recommendation about other treatments that can be used (including fondaparinux sodium, which is not animal derived).

No other equity issues were identified at this update.

Acceptability

No important issues with the recommended alternative

It is anticipated that, when considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with COVID-19, who need low-flow or high-flow oxygen and who do not have an increased bleeding risk might favour standard-dose anticoagulation. However, we have no systematically collected evidence about acceptability.

Feasibility

No important issues with the recommended alternative

Using standard prophylactic doses in young people and adults receiving low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation reflects usual treatment in most

centres. For others, it is a minor treatment adjustment that should be feasible to implement.

Rationale

The panel agreed that a standard prophylactic dose of a low molecular weight heparin (LMWH) should be offered as soon as possible to manage the risk of VTE based on current standard practice. Following standard prophylactic dose administration on admission, a more detailed assessment should be done to see whether people should be offered a treatment dose or not.

The panel also noted that people who are discharged early (before 7 days) could be at risk of clots. They emphasised the importance of continuing treatment after discharge until 7 days has passed to ensure people have had a full dose of a LMWH.

The treatment duration comes from NICE's guideline on VTE in over 16s.

Clinical Question/ PICO

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

Summary

What is the evidence informing this recommendation?

Evidence comes from 3 randomised controlled trials with 3,298 participants included.

One study (ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, reported in Lawler, 2021; n=2,219) compared treatment dose anticoagulant (UFH or LMWH, mainly enoxaparin) with standard dose venous thromboembolism prophylaxis (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) according to local protocols. Treatment dose LMWH or UFH were administered according to local protocols for up to 14 days or until recovery.

In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, most of the intervention group (94.7%) received treatment dose anticoagulation, most commonly enoxaparin and in the control group 71.7% received standard prophylactic dose thromboprophylaxis and 26.5% received intermediate-dose thromboprophylaxis

The second study (ACTION trial, reported in Lopes, 2021, n=614) compared treatment dose anticoagulant (mainly rivaroxaban) for 30 days, with standard prophylactic dose anticoagulant (unfractionated heparin or enoxaparin) given whilst an inpatient and according to local hospital protocols.

Participants in the ACTION trial had a clinical 'stable' condition (93% and 95% in treatment and standard care group respectively), with a small proportion having a clinically 'unstable' condition (7% and 5% in treatment and standard care group respectively).

In the ACTION trial, most of the intervention group (94.8%) received treatment dose anticoagulation (92% rivaroxaban); stable patients were prescribed rivaroxaban 20mg once daily and clinically unstable patients SC enoxaparin 1mg/kg twice daily, or IV UFH.

Mortality and venous thromboembolism outcomes from the ACTION trial were calculated separately due to the usage of rivaroxaban as therapeutic dose anticoagulation not being standard practice in the UK.

The majority of the control group received prophylactic dose anticoagulation during hospitalisation (99.5%); unfractionated heparin/enoxaparin dosed according to local hospital protocols.

The third study (RAPID trial, reported in Sholzberg 2021, n=465) compared treatment dose anticoagulant (LMWH and UFH) with standard dose prophylactic anticoagulant (dose-capped subcutaneous heparin (LMWH or UFH)). Study treatment was continued until the first day of hospital discharge, for 28 days or until study withdrawal/death.

The majority of participants from the RAPID trial intervention group received treatment dose heparin (98.2%) and (93.7%) received prophylactic heparin as allocated in the first 48 hours post-randomisation. Participants were moderately ill hospitalised patients with elevated D-dimer levels

Study Characteristics

The mean age in the studies ranged from 56 to 60, and between 54% and 76% of participants were male. Data for the ACTIVE-4a-ATTACC-REMAP-CAP and RAPID trials were collected from Brazil, Canada, Ireland, Netherlands, Australia, UK, Saudi Arabia, Mexico and USA. The ACTION trial was conducted in Brazil only (31 centres).

The definition of moderate severity varied between the studies. In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, moderate disease severity was defined as hospitalisation for COVID-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU. The ACTION trial defined moderate severity disease patients as those with an oxygen saturation <94%, pulmonary infiltrates <50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300. The RAPID trial defined disease severity as hospitalised patients with elevated D-dimer levels, above the upper limit of normal (ULN) of the local hospital in the presence of an oxygen saturation of ≤93% on room air, or ≥2 times the ULN irrespective of oxygen saturation levels.

The ACTION trial reported 14% of the participants were on high-flow oxygen, the rest were either on no oxygen or low-flow oxygen.

Exclusion criteria varied, but all studies excluded patients with a clinical indication for therapeutic anticoagulation and those who were at high risk of bleeding. The RAPID trial further excluded participants who were pregnant, and any participants that met any of the primary outcomes or would imminently meet them.

Duration of treatment ranged from up to 14 days (ACTIVE-4a-ATTACC-REMAP-CAP) to up to 30 days (RAPID and ACTION).

What are the main results?

Mortality at 30 days

Very low quality evidence from 2 studies found a non-statistically significant reduction in mortality at 30 days with treatment dose anticoagulant (mainly LMWH) compared with standard dose anticoagulant (UFH or LMWH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.50, CI 95% 0.13-1.88; 2,684 people in 2 studies].

Mortality at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.49, CI 95% 0.90 - 2.46; 614 people in 1 study].

All cause mortality or need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.63, CI 95% 0.39 -1.02; 465 people in 1 study].

Death or need for invasive ventilation or non-invasive ventilation or ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.75, CI 95% 0.51 – 1.11; 465 people in 1 study].

Survival

Survival to hospital discharge

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.01, CI 95% 0.99-1.03; 2,219 people in 1 study].

Survival to hospital discharge without major thrombotic events (a composite of freedom from myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival to hospital discharge without any macrovascular thrombotic events (the components of major thrombotic events and symptomatic deep venous thrombosis)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival without organ support 28 days

Moderate quality evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.05, CI 95% 1.01-1.10; 2,221 people in 1 study].

Organ support free days at day 21 (defined as survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21)

Moderate quality evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Mean 25.8 in treatment versus 24.1 standard; CI 95% 0.32 - 3.08; 465 people in 1 study].

VTE

Venous thromboembolism at 30 days

Moderate quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.30 CI 95% 0.06 - 1.41; 465 people in 1 study].

Venous thromboembolism at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.60, CI 95% 0.29-1.24; 614 people in 1 study].

Composite Thrombotic Outcome: Any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events

Moderate quality evidence from 1 study found a non-statistically significant reduction in the composite thrombotic outcome with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.75, CI 95% 0.45-1.26; 614 people in 1 study].

ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.82, CI 95% 0.54-1.24; 465 people in 1 study].

Need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.84. CI 95% 0.49-1.45; 465 people in 1 study].

Adverse events

Major bleeding was defined in both studies according to the International Society on Thrombosis and Haemostasis.

Major bleeding

Low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised with moderate COVID-19. [Relative risk 1.30, CI 95% 0.34- 4.98; 2,692 people in 2 studies].

Major bleeding - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 2.45, CI 95% 0.78-7.73; 614 people in 1 study].

Clinically relevant non-major bleeding - Rivaroxaban

Moderate quality evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 5.23, CI 95% 1.54-17.77; 614 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (RAPID) and two were published manuscripts (ACTION and ACTIVE-4a-ATTACC-REMAP-CAP).

Certainty of the evidence is very low for mortality at 30 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis), serious indirectness (mortality was calculated by NICE by subtracting survival from total number of events) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for mortality at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and serious imprecisions (confidence intervals cross the line of no effect).

Certainty of the evidence is moderate for all cause mortality or need for invasive ventilation and non-invasive ventilation due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for death or need for invasive ventilation or non-invasive ventilation or ICU admission due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence varies for survival outcomes.

Certainty of the evidence is low for survival to hospital discharge, survival to hospital discharge without any major thrombotic events and survival to hospital discharge without any macrovascular thrombotic events, due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for survival without organ support for 28 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis).

Certainty of the evidence is moderate for venous thromboembolism at 30 days due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for venous thromboembolism at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty if the evidence is moderate for Composite Thrombotic Outcome, due to serious imprecision (confidence interval includes the line of no effect).

Certainty of the evidence is low for major bleeding due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for clinically relevant non-major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 30 days 9 Critical	Relative risk 0.5 (CI 95% 0.13 — 1.88) Based on data from 2,684 participants in 2 studies. [1] (Randomized controlled)	81 per 1000 Difference:	41 per 1000 **41 fewer per 1000** (CI 95% 70 fewer — 71 more)	**Very low** Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias [2]	A pooled analysis of 2 studies found a non-statistically significant reduction in mortality after 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					people who were hospitalised.
Mortality - rivaroxaban 30 days 9 Critical	Relative risk 1.49 (CI 95% 0.9 — 2.46) Based on data from 614 participants in 1 studies. [3] (Randomized controlled)	**76** per 1000 Difference:	**113** per 1000 **37 more per 1000** (CI 95% 8 fewer — 111 more)	**Low** Due to serious risk of bias, Due to serious imprecision [4]	Evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised
All-cause mortality or need for IV or NIV 9 Critical	Relative risk 0.63 (CI 95% 0.39 — 1.02) Based on data from 465 participants in 1 studies. [5] (Randomized controlled)	**160** per 1000 Difference:	**101** per 1000 **59 fewer per 1000** (CI 95% 98 fewer — 3 more)	**Moderate** Due to serious imprecision [6]	Evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Death / need for IV or NIV / ICU admission 9 Critical	Relative risk 0.75 (CI 95% 0.51 — 1.11) Based on data from 465 participants in 1 studies. [7] (Randomized controlled)	**215** per 1000 Difference:	**161** per 1000 **54 fewer per 1000** (CI 95% 105 fewer — 24 more)	**Moderate** Due to serious imprecision [8]	Evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised
Survival to hospital discharge 9 Critical	Relative risk 1.01 (CI 95% 0.99 — 1.03) Based on data from 2,219 participants in 1 studies. [9] (Randomized controlled)	**918** per 1000 Difference:	**927** per 1000 **9 more per 1000** (CI 95% 9 fewer — 28 more)	**Low** Due to serious risk of bias, Due to serious imprecision, [10]	Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
		901 per 1000 Difference:	**919** per 1000 **18 more per 1000** (CI 95% 0 fewer	**Low** Due to serious risk of bias, Due to serious imprecision, [12]	Evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical			— 45 more)		anticoagulant compared with standard prophylactic dose anticoagulant for people who were hospitalised.
Survival to hospital discharge without any macrovascular thrombotic events 9 Critical	Relative risk 1.02 (CI 95% 1 — 1.05) Based on data from 2,226 participants in 1 studies. [13] (Randomized controlled)	897 per 1000 Difference:	915 per 1000 **18 more per 1000** (CI 95% 0 fewer — 45 more)	**Low** Due to serious risk of bias, Due to serious imprecision [14]	Evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Venous thromboembolism 30 days 9 Critical	Relative risk 0.3 (CI 95% 0.06 — 1.41) Based on data from 465 participants in 1 studies. [15] (Randomized controlled)	30 per 1000 Difference:	9 per 1000 **21 fewer per 1000** (CI 95% 28 fewer — 12 more)	**Moderate** Due to serious imprecision [16]	Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised. Uncertainty
Venous thromboembolism - rivaroxaban 30 days 9 Critical	Relative risk 0.6 (CI 95% 0.29 — 1.24) Based on data from 615 participants in 1 studies. [17] (Randomized controlled)	59 per 1000 Difference:	35 per 1000 **24 fewer per 1000** (CI 95% 42 fewer — 14 more)	**Low** Due to serious risk of bias, Due to serious imprecision [18]	Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised
		99 per 1000 Difference:	74 per 1000 **25 fewer per 1000** (CI 95% 54 fewer — 26 more)	**Moderate** Due to serious imprecision [20]	Evidence from 1 study found a non-statistically significant reduction in thrombotic events (defined as any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events) with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					hospitalised
Major bleeding 9 Critical	Relative risk 1.3 (CI 95% 0.34 — 4.98) Based on data from 2,692 participants in 2 studies. [21] (Randomized controlled)	10 per 1000 Difference:	13 per 1000 **3 more per 1000** (CI 95% 7 fewer — 40 more)	Low Due to serious risk of bias, Due to serious imprecision [22]	A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Major bleeding - rivaroxaban 9 Critical	Relative risk 2.45 (CI 95% 0.78 — 7.73) Based on data from 614 participants in 1 studies. [23] (Randomized controlled)	13 per 1000 Difference:	32 per 1000 **19 more per 1000** (CI 95% 3 fewer — 87 more)	Low Due to serious risk of bias, , Due to serious imprecision, [24]	Evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised
Survival without organ support 28 days 6 Important	Relative risk 1.3 (CI 95% 1 — 1.61) Based on data from 2,219 participants in 1 studies. [25] (Randomized controlled)	754 per 1000 Difference:	980 per 1000 **226 more per 1000** (CI 95% 0 fewer — 460 more)	Moderate Due to serious risk of bias, [26]	Evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Clinically relevant non-major bleeding - rivaroxaban 6 Important	Relative risk 5.23 (CI 95% 1.54 — 17.77) Based on data from 614 participants in 1 studies. [27] (Randomized controlled)	10 per 1000 Difference:	52 per 1000 **42 more per 1000** (CI 95% 5 more — 168 more)	Moderate Due to serious risk of bias, [28]	Evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
ICU admission 6 Important	Relative risk 0.82 (CI 95% 0.54 — 1.24) Based on data from 465 participants in 1 studies. [29] (Randomized controlled)	177 per 1000 Difference:	145 per 1000 **32 fewer per 1000** (CI 95% 81 fewer — 42 more)	Moderate Due to serious imprecision [30]	Evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Need for IV or NIV 6 Important	Relative risk 0.84 (CI 95% 0.49 — 1.45) Based on data from 465 participants in 1 studies. [31] (Randomized controlled)	110 per 1000 Difference:	92 per 1000 **18 fewer per 1000** (CI 95% 56 fewer — 50 more)	Moderate Due to serious imprecision [32]	Evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Organ support-free days 6 Important	Based on data from: 465 participants in 1 studies. [33] (Randomized controlled)	24.1 (Mean) Difference:	25.8 (Mean) **MD 1.7 higher** (CI 95% 0.32 higher — 3.08 higher)	Moderate Due to serious risk of bias [34]	Evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [84] with included studies: RAPID 2021, REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: serious.** Mortality in REMAP-CAP was calculated by NICE (through subtracting no. survival until discharge from total no. of events). **Imprecision: serious.** 95% CI crossed line of no effect. **Publication bias: no serious.**
3. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Small number of participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
5. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
7. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
9. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**
11. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of no effect. **Publication**

bias: no serious.
13. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**
15. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**
17. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** Due to study design where participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
19. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% confidence interval crossed the line of no effect.. **Publication bias: no serious.**
21. Systematic review [82] with included studies: REMAP-CAP 2021, RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
23. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: serious.** Participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of effect. **Publication bias: no serious.**
25. Systematic review [82] with included studies: [85]. **Baseline/comparator:** Control arm of reference used for intervention.
26. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
27. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
28. **Risk of Bias: serious.** 13% were prescribed treatment beyond hospital discharge. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
29. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
30. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**
31. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
32. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**
33. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
34. **Risk of Bias: serious.** participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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Clinical Question/ PICO

Population:	People with severe COVID-19
Intervention:	Treatment dose VTE prophylaxis
Comparator:	Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 1,089 participants included. Both studies (HESACOVID trial, reported in Lemos, 2020, n=20; and ACTIVE-41, ATACC, REMAP-CAP multiplatform trial, reported in Lawler, 2021, n=1,098) compared treatment dose anticoagulant (unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) with either prophylactic or intermediate dose anticoagulant (mainly enoxaparin).

The comparator group varies between studies. In the HESACOVID trial, half of the comparator group received UFH and half received prophylactic dose enoxaparin. The ACTIVE-41, ATACC, REMAP-CAP trial combines data from three sites, each operating under their own protocols. The protocols are very similar but allow for local practice, meaning that just over 40% of the comparator arm received prophylactic dose enoxaparin, just over 50% received intermediate dose enoxaparin, and 7.4% received either subtherapeutic (dose unclear) or therapeutic dose of either UFH or LMWH. This may reduce the validity of the results from the ACTIVE-41, ATACC, REMAP-CAP trial.

Study characteristics

The mean age in the studies ranged from 55 to 61, and between 68% and 90% of participants were male. Both studies included only adult patients receiving intensive care unit-level respiratory or cardiovascular support. Data was collected from Australia, Brazil, Canada, Ireland, Mexico, Netherlands, New Zealand, Saudi Arabia, UK, and USA.

Exclusion criteria varied, but both studies excluded patients with a separate clinical indication for therapeutic anticoagulation. One study excluded patients over 85.

Duration of treatment was 4-14 days in HESACOVID, and up to 14 days or hospital discharge in ACTIVE-41, ATACC, REMAP-CAP.

What are the main results?

All-cause mortality

Very low quality evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28

days with treatment dose anticoagulant (LMWH or UFH) compared to either prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised. [Relative risk 0.33 CI 95% 0.04 - 2.69; 20 people in 1 study].

Death in hospital

Low quality evidence from a pooled analysis of 2 studies found no significant difference for death in hospital with treatment dose anticoagulant (LMWH at varying doses) compared with either UFH, enoxaparin or usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 1.03, CI 95% 0.89-1.21; 1,118 people in 2 studies].

Survival to hospital discharge

Low quality evidence from 1 study found no significant difference for survival to hospital discharge with treatment dose anticoagulant compared with usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 0.97, CI 95% 0.89-1.06; 1,098 people in 1 study].

Serious Adverse events: Major bleeding

Low quality evidence from a pooled analysis of 2 studies found no significant difference in major bleeding with treatment dose anticoagulant compared with prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised. [Relative risk 1.63, CI 95% 0.82 - 3.25; 1,111 people in 2 studies].

Organ-support free days at 21 days

Low quality evidence from 1 study found no statistically significant difference in organ-support free days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Odds Ratio 0.83, CI 95% 0.67 - 1.03; 1,098 people in 1 study].

Ventilator-free days

Low quality evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 15 versus 0; 20 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. The two studies were published manuscripts (ACTIVE-41, ATACC, REMAP-CAP and HESACOVID). Following the peer reviewed publication of ACTIVE-41,ATACC,REMAP-CAP (26/08/2021), the data for some of the outcomes was updated to reflect the latest figures in the published manuscript.

There were significant deviations from the intended interventions reported in one study (ACTIVE-41, ATACC, REMAP-CAP) whereby a large proportion of the comparator group received intermediate rather than prophylactic dose anticoagulant. In addition, almost 15% of the treatment group received either low or intermediate dose anticoagulant, where the intended intervention was treatment dose anticoagulant. This means the results from this study are unclear.

One study (HESACOVID) contained only 20 participants (10 in each arm). This trial did not have sufficient power to assess a difference in mortality, and results may be due to chance. This should be considered when looking at the increase in ventilator free days in the treatment group reported by this study.

Certainty of the evidence is very low for all-cause mortality due to serious risk of bias (deviation from intended

control group treatment) and very serious imprecision (confidence intervals include the line of no effect and low numbers of participants).

Certainty of the evidence is low for death in hospital due to serious risk of bias, serious inconsistency (high statistical heterogeneity) and serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for survival to hospital discharge due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for major bleeding due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for organ support free days due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for ventilator-free days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality 28 days 9 Critical	Relative risk 0.33 (CI 95% 0.04 — 2.69) Based on data from 20 participants in 1 studies. [1] (Randomized controlled)	300 per 1000 Difference:	99 per 1000 **201 fewer per 1000** (CI 95% 288 fewer — 507 more)	**Very low** Due to serious risk of bias and very serious imprecision [2]	Evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (unfractionated heparin or low molecular weight heparin) compared to either standard prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised.
Death in hospital 9 Critical	Relative risk 1.03 (CI 95% 0.89 — 1.21) Based on data from 1,118 participants in 2 studies. [3] (Randomized controlled)	357 per 1000 Difference:	368 per 1000 **11 more per 1000** (CI 95% 39 fewer — 75 more)	**Low** Due to serious risk of bias, Due to serious imprecision [4]	A pooled analysis of 2 studies found no statistically significant difference in death in hospital with treatment dose anticoagulant (low molecular weight heparin at varying doses) compared to either unfractionated heparin, enoxaparin or standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Survival to hospital disharge 9 Critical	Relative risk 0.97 (CI 95% 0.89 — 1.06) Based on data from 1,098 participants in 1 studies. [5] (Randomized controlled)	645 per 1000 Difference:	626 per 1000 **19 fewer per 1000** (CI 95% 71 fewer — 39 more)	**Low** Due to serious risk of bias, Due to serious imprecision [6]	Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Major bleeding 9 Critical	Relative risk 1.63 (CI 95% 0.82 — 3.25) Based on data from 1,111 participants in 2 studies. [7] (Randomized controlled)	23 per 1000 Difference:	37 per 1000 **14 more per 1000** (CI 95% 4 fewer — 52 more)	**Low** Due to serious risk of bias, Due to serious imprecision [8]	A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Organ support free days 21 days 6 Important	Odds Ratio 0.83 (CI 95% 0.67 — 1.03) Based on data from 1,098 participants in 1 studies. (Randomized controlled)	567 per 1000 Difference:	536 per 1000 **46 fewer per 1000** (CI 95% 100 fewer — 7 more)	**Low** Due to serious risk of bias, Due to serious imprecision [9]	Evidence from 1 study found no statistically significant difference in organ support free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
		0 (Median)	15 (Median) CI 95%	**Low** Due to very serious imprecision [10]	Evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [78] with included studies: HESACOVID 2020, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis), due to [reason]. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No statistically significant effect, and low number of patients., due to [reason]. **Publication bias: no serious.**
3. Systematic review [93] with included studies: HESACOVID 2020, REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-

dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
5. Systematic review [93] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
7. Systematic review [93] with included studies: REMAP-CAP 2021, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
9. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias: no serious.**

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Clinical Question/ PICO

Population:	People with severe COVID-19
Intervention:	Intermediate dose VTE prophylaxis
Comparator:	Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 735 participants included. Both studies (INSPIRATION trial, reported in Sadeghipour 2021 [for 30 day outcomes] and Bikdeli, 2021 [for 90 day outcomes], n=562 and Perepu 2021 n=173) compared intermediate dose enoxoparin (1mg/kg daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30) with prophylactic dose enoxaparin (40mg daily).

The intervention and comparator groups were consistent between the studies. However, Perepu (2021) allowed for cointerventions, and more patients received azithromycin in the intermediate dose arm (29%) than in the prophylactic dose arm (13%).

Study characteristics

The mean age in the studies ranged from 61 to 65, and between 56% and 58% of participants were male. Both studies investigate the effects of the interventions in severe patients, but approximately 45% of the participants in the INSPIRATION trial were receiving low-flow oxygen and would therefore not be classed as having severe COVID-19 by the definitions used in the study protocol. The proportion of participants in Perepu (2021) receiving low-flow oxygen is unclear: it is reported that 62% were admitted to intensive care and 23% received invasive mechanical ventilation.

Data was collected from IRAN (INSPIRATION trial) and the USA (Perepu 2021).. Participants were excluded if they had recent known major bleeding or indications for a therapeutic dose of anticoagulant. Both studies excluded pregnant women. Duration of treatment was until hospital discharge (Perepu 2021) or for 30 and 90 days (INSPIRATION).

What are the main results?

All-cause mortality

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.01, CI 95% 0.84— 1.21; 735 people in 2 studies].

Low quality evidence from 1 study found no significant difference for all-cause mortality at 90 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.07, CI 95% 0.89 - 1.29; 562 people in 1 study]

Serious Adverse events: Major bleeding

Very low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised. [Relative risk 1.53, CI 95% 0.54 -4.28; 735 people in 2 studies]

Venous thromboembolism

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.02, CI 95% 0.52 — 2.00; 735 people in 2 studies]

Low quality evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 0.93, CI 95% 0.38 — 2.26; 562 people in 1 study]

Ventilator-free days

Very low quality evidence from 1 study found no significant difference for ventilator-free days at 30 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 30 days in intermediate dose group versus 30 days in prophylactic dose group; 562 people in 1 study].

Our confidence in the results

Both studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (Perepu, 21). The other study was from published manuscripts that reported 30 day and 90 day outcomes separately (INSPIRATION 2021).

Certainty of the evidence is low or very low for mortality outcomes due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for major bleeding due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for VTE outcomes at 30 days due to serious risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for VTE outcomes at 90 days to serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of evidence is very low for ventilator-free days at 30 days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals) and serious indirectness (dissimilarity between population of interest and those studied).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Intermediate dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality 30 days 9 Critical	Relative risk 1.01 (CI 95% 0.84 — 1.21) Based on data from 735 participants in 2 studies. [1] (Randomized controlled)	363 per 1000 Difference:	367 per 1000 **4 more per 1000** (CI 95% 58 fewer — 76 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [2]	A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
All-cause mortality 90 days 9 Critical	Relative risk 1.07 (CI 95% 0.89 — 1.29) Based on data from 562 participants in 1 studies. [3] (Randomized controlled)	430 per 1000 Difference:	460 per 1000 **30 more per 1000** (CI 95% 47 fewer — 125 more)	**Low** Due to serious indirectness and serious imprecision [4]	Evidence from 1 study found no statistically significant difference in all-cause mortality at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Major bleeding	Relative risk 1.53 (CI 95% 0.54 — 4.28) Based on data from 735	16 per 1000	24 per 1000	**Very low** Due to serious risk of bias,	A pooled analysis of 2 studies found a non-statistically significant

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Intermediate dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical	participants in 2 studies. [5] (Randomized controlled)	Difference:	**8 more per 1000** (CI 95% 7 fewer — 52 more)	serious indirectness and serious imprecision [6]	increase in major bleeding with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised.
VTE 30 days 9 Critical	Relative risk 1.02 (CI 95% 0.52 — 2) Based on data from 735 participants in 2 studies. [7] (Randomized controlled)	43 per 1000 Difference:	44 per 1000 **1 more per 1000** (CI 95% 21 fewer — 43 more)	**Very low** Due to serious risk of bias, serious indirectness and serious imprecision [8]	A pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
VTE 90 days 9 Critical	Relative risk 0.93 (CI 95% 0.38 — 2.26) Based on data from 562 participants in 1 studies. [9] (Randomized controlled)	35 per 1000 Difference:	33 per 1000 **2 fewer per 1000** (CI 95% 22 fewer — 44 more)	**Low** Due to serious indirectness and serious imprecision [10]	Evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
		30 (Median)	30 (Median) CI 95%	**Very low** Due to serious indirectness and very serious imprecision [11]	Evidence from 1 study found no statistically significant difference in ventilator-free days at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [83] with included studies: INSPIRATION 2021, Perepu 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients have moderate in one study have moderate, not severe COVID-19. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**
3. Systematic review [79] with included studies: INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
5. Systematic review [79] with included studies: Perepu 2021, INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency:**

no serious. Indirectness: serious. Some patients in one study have moderate, not severe COVID-19.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
7. Systematic review [79] with included studies: Perepu 2021, INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
9. Systematic review [79] with included studies: INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
11. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied.. **Imprecision: very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias: no serious.**

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Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances.

For people with COVID-19 who do not need low-flow oxygen, follow the recommendations in NICE's guideline on venous thromboembolism in over 16s.

In August 2021, using 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

Small net benefit, or little difference between alternatives

The panel were presented with data from 3 randomised controlled trials (ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID). These trials evaluated whether empiric use of treatment-dose anticoagulation improves clinical outcomes in adults in hospital with confirmed moderate COVID-19 (defined in this guideline as people receiving low-flow supplementary oxygen).

The panel agreed that, for adults with moderate COVID-19, the studies showed a trend towards improved mortality

outcomes with a treatment dose of an anticoagulant compared with the standard prophylactic dose. One study reported no difference in survival to hospital discharge and a statistically significant increase in survival without organ support at 28 days. The panel also emphasised a trend towards a positive effect on VTE at 30 and 90 days, and a statistically significant increase in organ-support-free days.

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 adults in hospital with moderate COVID-19. Thus the benefits of treatment-dose prophylactic anticoagulation may outweigh the potential harms in this population.

The panel noted that the duration of treatment recommended should match the duration of the largest study included, which was 14 days or until discharge, whichever was sooner.

Certainty of the Evidence

Moderate

The outcomes of ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID were of moderate to very low certainty.

The panel noted that the results from RAPID were preprint results. This meant they had not been peer reviewed, so they interpreted the results with the appropriate caution. Some of the group allocated to the standard prophylactic anticoagulant dose had higher doses in the ACTION and ACTIVE-4a-ATTACC-REMAP-CAP trials (between 26% and 29%), which the panel recognised could have affected the results. However, they considered that the evidence was certain enough to make recommendations to consider treatment-dose VTE prophylaxis in young people and adults with moderate COVID-19.

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 possible mortality benefits and increase in organ support-free days for people with COVID-19 who need low-flow oxygen, many would choose a treatment dose of an anticoagulant in spite of a potential increased risk of bleeding.

Resources and other considerations

No important issues with the recommended alternative

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

The panel did not have concerns about opportunity costs when a low molecular weight heparin is being used for people who need low-flow oxygen. The panel decided to recommend that treatment is continued for up to 14 days. This may be longer than the standard treatment duration for acute illness (at least 7 days), so may be a higher resource use of anticoagulation in this group. This is to reflect the duration used in the trials contributing evidence to this recommendation.

Equity

No important issues with the recommended alternative

The panel noted an absence of evidence for anticoagulation in children. They 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 are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults. Additionally, a research recommendation was made for this population.

For people under 16 years the risk of VTE is uncertain in the context of COVID-19. The risk benefit of VTE and dosing should be discussed by multidisciplinary teams on a case-by-case basis.

Not all heparins are acceptable to people of certain religions because the products are derived from animals. The panel made a recommendation about other treatments that can be used (including fondaparinux sodium, which is not animal derived).

No other equity issues were identified at this update.

Acceptability

No important issues with the recommended alternative

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 to very low. However, the panel noted that the direction of effect tended to favour treatment-dose anticoagulation for adults with COVID-19 who need low-flow supplemental oxygen.

It is anticipated that, when considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with COVID-19, who need low-flow oxygen and who do not have an increased bleeding risk might favour treatment-dose anticoagulation.

Feasibility

No important issues with the recommended alternative

Implementing use of treatment-dose VTE prophylaxis in young people and adults in hospital who are receiving low-flow oxygen is expected to be feasible because it represents an increase in the dose and duration of an established treatment.

Rationale

The panel agreed that some young people and adults with COVID-19 who need low-flow oxygen supplementation may benefit from a treatment dose of a low molecular weight heparin (LMWH). The evidence suggests that a treatment dose of an LMWH for adults with COVID-19 who are in hospital and needing low-flow oxygen supplementation may reduce the risk of death and need for organ support compared with a standard prophylactic dose. It also suggests an increased risk in major bleeding compared with a standard prophylactic dose. Because of the fine balance of benefits and harms, the panel agreed that this decision should be carefully considered, and that this choice should be guided by bleeding risk, clinical judgement and local protocols.

The treatment duration in the largest included trial was 14 days or until discharge, whichever was sooner. The panel thought that the timeframe for treatment should reflect the trial evidence.

Clinical Question/ PICO

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

Summary

What is the evidence informing this recommendation?

Evidence comes from 3 randomised controlled trials with 3,298 participants included.

One study (ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, reported in Lawler, 2021; n=2,219) compared treatment dose anticoagulant (UFH or LMWH, mainly enoxaparin) with standard dose venous thromboembolism prophylaxis (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) according to local protocols. Treatment dose LMWH or UFH were administered according to local protocols for up to 14 days or until recovery.

In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, most of the intervention group (94.7%) received treatment dose anticoagulation, most commonly enoxaparin and in the control group 71.7% received standard prophylactic dose thromboprophylaxis and 26.5% received intermediate-dose thromboprophylaxis

The second study (ACTION trial, reported in Lopes, 2021, n=614) compared treatment dose anticoagulant (mainly rivaroxaban) for 30 days, with standard prophylactic dose anticoagulant (unfractionated heparin or enoxaparin) given whilst an inpatient and according to local hospital protocols.

Participants in the ACTION trial had a clinical 'stable' condition (93% and 95% in treatment and standard care group respectively), with a small proportion having a clinically 'unstable' condition (7% and 5% in treatment and standard care group respectively).

In the ACTION trial, most of the intervention group (94.8%) received treatment dose anticoagulation (92% rivaroxaban); stable patients were prescribed rivaroxaban 20mg once daily and clinically unstable patients SC enoxaparin 1mg/kg twice daily, or IV UFH.

Mortality and venous thromboembolism outcomes from the ACTION trial were calculated separately due to the usage of rivaroxaban as therapeutic dose anticoagulation not being standard practice in the UK.

The majority of the control group received prophylactic dose anticoagulation during hospitalisation (99.5%); unfractionated heparin/enoxaparin dosed according to local hospital protocols.

The third study (RAPID trial, reported in Sholzberg 2021, n=465) compared treatment dose anticoagulant (LMWH and UFH) with standard dose prophylactic anticoagulant (dose-capped subcutaneous heparin (LMWH or UFH)). Study treatment was continued until the first day of hospital discharge, for 28 days or until study withdrawal/death.

The majority of participants from the RAPID trial intervention group received treatment dose heparin (98.2%) and (93.7%) received prophylactic heparin as allocated in the first 48 hours post-randomisation. Participants were moderately ill hospitalised patients with elevated D-dimer levels

Study Characteristics

The mean age in the studies ranged from 56 to 60, and between 54% and 76% of participants were male. Data for the ACTIVE-4a-ATTACC-REMAP-CAP and RAPID trials were collected from Brazil, Canada, Ireland, Netherlands, Australia, UK, Saudi Arabia, Mexico and USA. The ACTION trial was conducted in Brazil only (31 centres).

The definition of moderate severity varied between the studies. In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, moderate disease severity was defined as hospitalisation for COVID-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU. The ACTION trial defined moderate severity disease patients as those with an oxygen saturation <94%, pulmonary infiltrates <50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300. The RAPID trial defined disease severity as hospitalised patients with elevated D-dimer levels, above the upper limit of normal (ULN) of the local hospital in the presence of an oxygen saturation of ≤93% on room air, or ≥2 times the ULN irrespective of oxygen saturation levels.

The ACTION trial reported 14% of the participants were on high-flow oxygen, the rest were either on no oxygen or low-flow oxygen.

Exclusion criteria varied, but all studies excluded patients with a clinical indication for therapeutic anticoagulation and those who were at high risk of bleeding. The RAPID trial further excluded participants who were pregnant, and any participants that met any of the primary outcomes or would imminently meet them.

Duration of treatment ranged from up to 14 days (ACTIVE-4a-ATTACC-REMAP-CAP) to up to 30 days (RAPID and ACTION).

What are the main results?

Mortality at 30 days

Very low quality evidence from 2 studies found a non-statistically significant reduction in mortality at 30 days with treatment dose anticoagulant (mainly LMWH) compared with standard dose anticoagulant (UFH or LMWH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.50, CI 95% 0.13-1.88; 2,684 people in 2 studies].

Mortality at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.49, CI 95% 0.90 - 2.46; 614 people in 1 study].

All cause mortality or need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.63, CI 95% 0.39 -1.02; 465 people in 1 study].

Death or need for invasive ventilation or non-invasive ventilation or ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.75, CI 95% 0.51 – 1.11; 465 people in 1 study].

Survival

Survival to hospital discharge

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.01, CI 95% 0.99-1.03; 2,219 people in 1 study].

Survival to hospital discharge without major thrombotic events (a composite of freedom from myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival to hospital discharge without any macrovascular thrombotic events (the components of major thrombotic events and symptomatic deep venous thrombosis)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival without organ support 28 days

Moderate quality evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.05, CI 95% 1.01-1.10; 2,221 people in 1 study].

Organ support free days at day 21 (defined as survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21)

Moderate quality evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Mean 25.8 in treatment versus 24.1 standard; CI 95% 0.32 - 3.08; 465 people in 1 study].

VTE

Venous thromboembolism at 30 days

Moderate quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.30 CI 95% 0.06 - 1.41; 465 people in 1 study].

Venous thromboembolism at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or

enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.60, CI 95% 0.29-1.24; 614 people in 1 study].

Composite Thrombotic Outcome: Any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events

Moderate quality evidence from 1 study found a non-statistically significant reduction in the composite thrombotic outcome with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.75, CI 95% 0.45-1.26; 614 people in 1 study].

ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.82, CI 95% 0.54-1.24; 465 people in 1 study].

Need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.84. CI 95% 0.49-1.45; 465 people in 1 study].

Adverse events

Major bleeding was defined in both studies according to the International Society on Thrombosis and Haemostasis.

Major bleeding

Low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised with moderate COVID-19. [Relative risk 1.30, CI 95% 0.34- 4.98; 2,692 people in 2 studies].

Major bleeding - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 2.45, CI 95% 0.78-7.73; 614 people in 1 study].

Clinically relevant non-major bleeding - Rivaroxaban

Moderate quality evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 5.23, CI 95% 1.54-17.77; 614 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of

objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (RAPID) and two were published manuscripts (ACTION and ACTIVE-4a-ATTACC-REMAP-CAP).

Certainty of the evidence is very low for mortality at 30 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis), serious indirectness (mortality was calculated by NICE by subtracting survival from total number of events) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for mortality at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and serious imprecisions (confidence intervals cross the line of no effect).

Certainty of the evidence is moderate for all cause mortality or need for invasive ventilation and non-invasive ventilation due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for death or need for invasive ventilation or non-invasive ventilation or ICU admission due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence varies for survival outcomes.

Certainty of the evidence is low for survival to hospital discharge, survival to hospital discharge without any major thrombotic events and survival to hospital discharge without any macrovascular thrombotic events, due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for survival without organ support for 28 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis).

Certainty of the evidence is moderate for venous thromboembolism at 30 days due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for venous thromboembolism at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty if the evidence is moderate for Composite Thrombotic Outcome, due to serious imprecision (confidence interval includes the line of no effect).

Certainty of the evidence is low for major bleeding due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for clinically relevant non-major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 30 days 9 Critical	Relative risk 0.5 (CI 95% 0.13 — 1.88) Based on data from 2,684 participants in 2 studies. [1] (Randomized controlled)	81 per 1000 Difference:	41 per 1000 **41 fewer per 1000** (CI 95% 70 fewer — 71 more)	**Very low** Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias [2]	A pooled analysis of 2 studies found a non-statistically significant reduction in mortality after 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Mortality - rivaroxaban 30 days 9 Critical	Relative risk 1.49 (CI 95% 0.9 — 2.46) Based on data from 614 participants in 1 studies. [3] (Randomized controlled)	76 per 1000 Difference:	113 per 1000 **37 more per 1000** (CI 95% 8 fewer — 111 more)	**Low** Due to serious risk of bias, Due to serious imprecision [4]	Evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised
All-cause mortality or need for IV or NIV 9 Critical	Relative risk 0.63 (CI 95% 0.39 — 1.02) Based on data from 465 participants in 1 studies. [5] (Randomized controlled)	160 per 1000 Difference:	101 per 1000 **59 fewer per 1000** (CI 95% 98 fewer — 3 more)	**Moderate** Due to serious imprecision [6]	Evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Death / need for IV or NIV / ICU admission 9 Critical	Relative risk 0.75 (CI 95% 0.51 — 1.11) Based on data from 465 participants in 1 studies. [7] (Randomized controlled)	215 per 1000 Difference:	161 per 1000 **54 fewer per 1000** (CI 95% 105 fewer — 24 more)	**Moderate** Due to serious imprecision [8]	Evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Survival to hospital discharge 9 Critical		918 per 1000 Difference:	927 per 1000 **9 more per 1000** (CI 95% 9 fewer — 28 more)	Low Due to serious risk of bias, Due to serious imprecision, [10]	Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Survival to hospital discharge without major thrombotic events 9 Critical		901 per 1000 Difference:	919 per 1000 **18 more per 1000** (CI 95% 0 fewer — 45 more)	Low Due to serious risk of bias, Due to serious imprecision, [12]	Evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant compared with standard prophylactic dose anticoagulant for people who were hospitalised.
Survival to hospital discharge without any macrovascular thrombotic events 9 Critical		897 per 1000 Difference:	915 per 1000 **18 more per 1000** (CI 95% 0 fewer — 45 more)	Low Due to serious risk of bias, Due to serious imprecision [14]	Evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Venous thromboembolism 30 days 9 Critical		30 per 1000 Difference:	9 per 1000 **21 fewer per 1000** (CI 95% 28 fewer — 12 more)	Moderate Due to serious imprecision [16]	Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised. Uncertainty
		59 per 1000 Difference:	35 per 1000 **24 fewer per 1000** (CI 95% 42 fewer — 14 more)	Low Due to serious risk of bias, Due to serious imprecision [18]	Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					dose anticoagulant for people who were hospitalised
Composite Thrombotic Outcome 9 Critical	Relative risk 0.75 (CI 95% 0.45 — 1.26) Based on data from 614 participants in 1 studies. [19] (Randomized controlled)	99 per 1000 Difference:	74 per 1000 **25 fewer per 1000** (CI 95% 54 fewer — 26 more)	**Moderate** Due to serious imprecision [20]	Evidence from 1 study found a non-statistically significant reduction in thrombotic events (defined as any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events) with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised
Major bleeding 9 Critical	Relative risk 1.3 (CI 95% 0.34 — 4.98) Based on data from 2,692 participants in 2 studies. [21] (Randomized controlled)	10 per 1000 Difference:	13 per 1000 **3 more per 1000** (CI 95% 7 fewer — 40 more)	**Low** Due to serious risk of bias, Due to serious imprecision [22]	A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Major bleeding - rivaroxaban 9 Critical	Relative risk 2.45 (CI 95% 0.78 — 7.73) Based on data from 614 participants in 1 studies. [23] (Randomized controlled)	13 per 1000 Difference:	32 per 1000 **19 more per 1000** (CI 95% 3 fewer — 87 more)	**Low** Due to serious risk of bias, , Due to serious imprecision, [24]	Evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised
Survival without organ support 28 days 6 Important	Relative risk 1.3 (CI 95% 1 — 1.61) Based on data from 2,219 participants in 1 studies. [25] (Randomized controlled)	754 per 1000 Difference:	980 per 1000 **226 more per 1000** (CI 95% 0 fewer — 460 more)	**Moderate** Due to serious risk of bias, [26]	Evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Clinically relevant non-major bleeding - rivaroxaban	Relative risk 5.23 (CI 95% 1.54 — 17.77) Based on data from 614 participants in 1 studies.	10 per 1000	52 per 1000	**Moderate** Due to serious risk of bias, [28]	Evidence from 1 study found a statistically significant increase in clinically relevant non-

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	[27] (Randomized controlled)	Difference:	**42 more per 1000** (CI 95% 5 more — 168 more)		major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
ICU admission 6 Important	Relative risk 0.82 (CI 95% 0.54 — 1.24) Based on data from 465 participants in 1 studies. [29] (Randomized controlled)	177 per 1000 Difference:	145 per 1000 **32 fewer per 1000** (CI 95% 81 fewer — 42 more)	Moderate Due to serious imprecision [30]	Evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Need for IV or NIV 6 Important	Relative risk 0.84 (CI 95% 0.49 — 1.45) Based on data from 465 participants in 1 studies. [31] (Randomized controlled)	110 per 1000 Difference:	92 per 1000 **18 fewer per 1000** (CI 95% 56 fewer — 50 more)	Moderate Due to serious imprecision [32]	Evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
		24.1 (Mean) Difference:	25.8 (Mean) **MD 1.7 higher** (CI 95% 0.32 higher — 3.08 higher)	Moderate Due to serious risk of bias [34]	Evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [84] with included studies: RAPID 2021, REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: serious.** Mortality in REMAP-CAP was calculated by NICE (through subtracting no. survival until discharge from total no. of events). **Imprecision: serious.** 95% CI crossed line of no effect. **Publication bias: no serious.**
3. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Small number of participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
5. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
7. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
9. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**
11. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of no effect. **Publication bias: no serious.**
13. Systematic review [82] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**
15. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**
17. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** Due to study design where participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
19. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% confidence interval crossed the line of no effect.. **Publication bias: no serious.**
21. Systematic review [82] with included studies: REMAP-CAP 2021, RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
23. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
24. **Risk of Bias: serious.** Participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of effect. **Publication bias: no serious.**
25. Systematic review [82] with included studies: [85]. **Baseline/comparator:** Control arm of reference used for intervention.
26. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
27. Systematic review [82] with included studies: ACTION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
28. **Risk of Bias: serious.** 13% were prescribed treatment beyond hospital discharge. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

29. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
30. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**
31. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
32. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**
33. Systematic review [82] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of reference used for intervention.
34. **Risk of Bias: serious.** participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

References

84. Heparins for COVID-19.

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Only in research settings

Only offer an intermediate or treatment dose of a low molecular weight heparin to young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation as part of a clinical trial.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel were presented with data from 4 open-label randomised controlled trials (INSPIRATION, ATTACC, ACTIV-4a, REMAP-CAP, HESACOVID and Perepu [2021]). These trials evaluated the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults having care for severe COVID-19 (that is, receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation).

Intermediate-dose anticoagulant

Two studies compared intermediate-dose anticoagulation with the standard prophylactic dose (INSPIRATION and Perepu [2021]). The panel agreed that, for adults with severe COVID-19, the studies showed no statistically significant benefit for mortality, VTE prophylaxis or ventilator-free days with an intermediate dose of an anticoagulant compared with the standard prophylactic dose. There was, however, no indication of increased bleeding with an intermediate dose compared with the standard prophylactic dose.

Treatment-dose anticoagulant

Two studies compared a treatment dose of an anticoagulant with the standard prophylactic dose (HESACOVID and ATTACC-ACTIV-4a-REMAP-CAP). The panel agreed that, for adults with severe COVD-19, the studies showed no statistically significant benefit for mortality or organ support-free days with a treatment dose of an anticoagulant compared with the standard prophylactic dose. There was no sign of increased bleeding with a treatment dose compared with the standard prophylactic dose.

Other considerations

The panel noted that 1 study showed an increase in ventilator-free days with treatment-dose anticoagulation. However, they agreed that the results were not certain enough to base a recommendation on because the study was very small.

The panel recommended not to base prophylactic dosing of heparin on levels of D-dimer because 1 trial presented evidence showing that a person's D-dimer measurements did not influence the effects of VTE prophylaxis.

Based on the lack of clear benefit with intermediate- or treatment-dose anticoagulation, the panel concluded that young people and adults with severe COVID-19 should be offered standard prophylactic-dose anticoagulation, and that intermediate- or treatment-dose VTE prophylaxis should not be used apart from as part of a clinical trial.

The panel discussed what to do if someone is already on treatment-dose anticoagulation at admission. They 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 an intensive care unit.

Certainty of the Evidence

Low

INSPIRATION, REMAP-CAP, HESACOVID and Perepu et al. (2021) evaluated the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults having care for severe COVID-19.

The panel noted that the interventions that people had were mixed because of the local practices of the sites taking part in the trial. The panel recognised that the HESACOVID trial was very small and likely to be underpowered for the results it presented. Around 45% of people in INSPIRATION did not match the definition of 'severe COVID-19' used here. This was reflected in the lower rates of VTE than the committee expected to see in a population with severe COVID-19. The panel took these factors into account when considering the evidence.

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 lack of clear benefit of intermediate- or treatment-dose anticoagulation, most would choose a standard prophylactic dose of an anticoagulant.

Resources and other considerations

No important issues with the recommended alternative

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

The panel recommended that standard prophylactic-dose anticoagulation is used, rather than higher doses. This means there is expected to be no increase in cost related to the treatment.

Equity

No important issues with the recommended alternative

The panel noted an absence of evidence for anticoagulation in children. They 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 are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults. Additionally, a research recommendation was made for this population.

For people under 16 years, the risk of VTE is uncertain in the context of COVID-19. The risk benefit of VTE and dosing should preferably be discussed in multidisciplinary teams on a case-by-case basis considering all risk factors.

Not all heparins are acceptable to people of certain religions because the products are derived from animals. The panel made a recommendation about other treatments that can be used (including fondaparinux sodium, which is not animal derived).

No other equity issues were identified at this update.

Acceptability

No important issues with the recommended alternative

It is anticipated that, after considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with severe COVID-19 would choose to have standard prophylactic-dose anticoagulation. However, we have no systematically collected evidence about acceptability.

Feasibility

No important issues with the recommended alternative

Using standard prophylactic doses in young people and adults receiving high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation reflects usual treatment in some centres. For others, it is a minor treatment adjustment that should be feasible to implement.

Rationale

Based on the lack of clear benefit with intermediate- or treatment-dose anticoagulation, the panel concluded that young people and adults with severe COVID-19 should be offered standard prophylactic-dose anticoagulation. They also concluded that intermediate- or treatment-dose VTE prophylaxis should only be used as part of a clinical trial.

The panel were aware of ongoing trials of low molecular weight heparins (LMWHs) that use intermediate or treatment doses in this group of people, including REMAP-CAP. They agreed that intermediate- or treatment- dose LMWHs should only be used for VTE prophylaxis in this group as part of a clinical trial to support recruitment into these trials.

Clinical Question/ PICO

Population: People with severe COVID-19
Intervention: Treatment dose VTE prophylaxis
Comparator: Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 1,089 participants included. Both studies (HESACOVID trial, reported in Lemos, 2020, n=20; and ACTIVE-41, ATACC, REMAP-CAP multiplatform trial, reported in Lawler, 2021, n=1,098) compared treatment dose anticoagulant (unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) with either prophylactic or intermediate dose anticoagulant (mainly enoxaparin).

The comparator group varies between studies. In the HESACOVID trial, half of the comparator group received UFH and half received prophylactic dose enoxaparin. The ACTIVE-41, ATACC, REMAP-CAP trial combines data from three sites, each operating under their own protocols. The protocols are very similar but allow for local practice, meaning that just over 40% of the comparator arm received prophylactic dose enoxaparin, just over 50% received intermediate dose enoxaparin, and 7.4% received either subtherapeutic (dose unclear) or therapeutic dose of either UFH or LMWH. This may reduce the validity of the results from the ACTIVE-41, ATACC, REMAP-CAP trial.

Study characteristics

The mean age in the studies ranged from 55 to 61, and between 68% and 90% of participants were male. Both

studies included only adult patients receiving intensive care unit-level respiratory or cardiovascular support. Data was collected from Australia, Brazil, Canada, Ireland, Mexico, Netherlands, New Zealand, Saudi Arabia, UK, and USA.

Exclusion criteria varied, but both studies excluded patients with a separate clinical indication for therapeutic anticoagulation. One study excluded patients over 85.

Duration of treatment was 4-14 days in HESACOVID, and up to 14 days or hospital discharge in ACTIVE-41, ATACC, REMAP-CAP.

What are the main results?

All-cause mortality

Very low quality evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (LMWH or UFH) compared to either prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised. [Relative risk 0.33 CI 95% 0.04 - 2.69; 20 people in 1 study].

Death in hospital

Low quality evidence from a pooled analysis of 2 studies found no significant difference for death in hospital with treatment dose anticoagulant (LMWH at varying doses) compared with either UFH, enoxaparin or usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 1.03, CI 95% 0.89-1.21; 1,118 people in 2 studies].

Survival to hospital discharge

Low quality evidence from 1 study found no significant difference for survival to hospital discharge with treatment dose anticoagulant compared with usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 0.97, CI 95% 0.89-1.06; 1,098 people in 1 study].

Serious Adverse events: Major bleeding

Low quality evidence from a pooled analysis of 2 studies found no significant difference in major bleeding with treatment dose anticoagulant compared with prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised. [Relative risk 1.63, CI 95% 0.82 - 3.25; 1,111 people in 2 studies].

Organ-support free days at 21 days

Low quality evidence from 1 study found no statistically significant difference in organ-support free days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Odds Ratio 0.83, CI 95% 0.67 - 1.03; 1,098 people in 1 study].

Ventilator-free days

Low quality evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 15 versus 0; 20 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. The two studies were published manuscripts (ACTIVE-41, ATACC, REMAP-CAP and HESACOVID). Following the peer reviewed publication of ACTIVE-41,ATACC,REMAP-CAP (26/08/2021), the data for some of the outcomes was updated to reflect the latest figures in the published manuscript.

There were significant deviations from the intended interventions reported in one study (ACTIVE-41, ATACC, REMAP-CAP) whereby a large proportion of the comparator group received intermediate rather than prophylactic dose anticoagulant. In addition, almost 15% of the treatment group received either low or intermediate dose anticoagulant, where the intended intervention was treatment dose anticoagulant. This means the results from this study are unclear.

One study (HESACOVID) contained only 20 participants (10 in each arm). This trial did not have sufficient power to assess a difference in mortality, and results may be due to chance. This should be considered when looking at the increase in ventilator free days in the treatment group reported by this study.

Certainty of the evidence is very low for all-cause mortality due to serious risk of bias (deviation from intended control group treatment) and very serious imprecision (confidence intervals include the line of no effect and low numbers of participants).

Certainty of the evidence is low for death in hospital due to serious risk of bias, serious inconsistency (high statistical heterogeneity) and serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for survival to hospital discharge due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for major bleeding due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for organ support free days due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for ventilator-free days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality 28 days 9 Critical	Relative risk 0.33 (CI 95% 0.04 — 2.69) Based on data from 20 participants in 1 studies. [1] (Randomized controlled)	300 per 1000 Difference:	99 per 1000 **201 fewer per 1000** (CI 95% 288 fewer — 507 more)	**Very low** Due to serious risk of bias and very serious imprecision [2]	Evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (unfractionated heparin or low molecular weight heparin) compared to either standard prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death in hospital 9 Critical	Relative risk 1.03 (CI 95% 0.89 — 1.21) Based on data from 1,118 participants in 2 studies. [3] (Randomized controlled)	357 per 1000 Difference:	368 per 1000 **11 more per 1000** (CI 95% 39 fewer — 75 more)	**Low** Due to serious risk of bias, Due to serious imprecision [4]	A pooled analysis of 2 studies found no statistically significant difference in death in hospital with treatment dose anticoagulant (low molecular weight heparin at varying doses) compared to either unfractionated heparin, enoxaparin or standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Survival to hospital disharge 9 Critical	Relative risk 0.97 (CI 95% 0.89 — 1.06) Based on data from 1,098 participants in 1 studies. [5] (Randomized controlled)	645 per 1000 Difference:	626 per 1000 **19 fewer per 1000** (CI 95% 71 fewer — 39 more)	**Low** Due to serious risk of bias, Due to serious imprecision [6]	Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Major bleeding 9 Critical	Relative risk 1.63 (CI 95% 0.82 — 3.25) Based on data from 1,111 participants in 2 studies. [7] (Randomized controlled)	23 per 1000 Difference:	37 per 1000 **14 more per 1000** (CI 95% 4 fewer — 52 more)	**Low** Due to serious risk of bias, Due to serious imprecision [8]	A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.
Organ support free days 21 days 6 Important	Odds Ratio 0.83 (CI 95% 0.67 — 1.03) Based on data from 1,098 participants in 1 studies. (Randomized controlled)	567 per 1000 Difference:	536 per 1000 **46 fewer per 1000** (CI 95% 100 fewer — 7 more)	**Low** Due to serious risk of bias, Due to serious imprecision [9]	Evidence from 1 study found no statistically significant difference in organ support free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
		0 (Median)	15 (Median) CI 95%	**Low** Due to very serious imprecision [10]	Evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Treatment dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important					dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [78] with included studies: HESACOVID 2020, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis), due to [reason]. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No statistically significant effect, and low number of patients., due to [reason]. **Publication bias: no serious.**
3. Systematic review [93] with included studies: HESACOVID 2020, REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
5. Systematic review [93] with included studies: REMAP-CAP 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
7. Systematic review [93] with included studies: REMAP-CAP 2021, HESACOVID 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**
9. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias: no serious.**

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99. Zarychanski R, Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, et al. : Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. The New England journal of medicine 2021;385(9):777-789 Pubmed Journal

Clinical Question/ PICO

Population: People with severe COVID-19

Intervention: Intermediate dose VTE prophylaxis
Comparator: Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 735 participants included. Both studies (INSPIRATION trial, reported in Sadeghipour 2021 [for 30 day outcomes] and Bikdeli, 2021 [for 90 day outcomes], n=562 and Perepu 2021 n=173) compared intermediate dose enoxoparin (1mg/kg daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30) with prophylactic dose enoxaparin (40mg daily).

The intervention and comparator groups were consistent between the studies. However, Perepu (2021) allowed for cointerventions, and more patients received azithromycin in the intermediate dose arm (29%) than in the prophylactic dose arm (13%).

Study characteristics

The mean age in the studies ranged from 61 to 65, and between 56% and 58% of participants were male. Both studies investigate the effects of the interventions in severe patients, but approximately 45% of the participants in the INSPIRATION trial were receiving low-flow oxygen and would therefore not be classed as having severe COVID-19 by the definitions used in the study protocol. The proportion of participants in Perepu (2021) receiving low-flow oxygen is unclear: it is reported that 62% were admitted to intensive care and 23% received invasive mechanical ventilation.

Data was collected from IRAN (INSPIRATION trial) and the USA (Perepu 2021).. Participants were excluded if they had recent known major bleeding or indications for a therapeutic dose of anticoagulant. Both studies excluded pregnant women. Duration of treatment was until hospital discharge (Perepu 2021) or for 30 and 90 days (INSPIRATION).

What are the main results?

All-cause mortality

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.01, CI 95% 0.84— 1.21; 735 people in 2 studies].

Low quality evidence from 1 study found no significant difference for all-cause mortality at 90 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.07, CI 95% 0.89 - 1.29; 562 people in 1 study]

Serious Adverse events: Major bleeding

Very low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised. [Relative risk 1.53, CI 95% 0.54 -4.28; 735 people in 2 studies]

Venous thromboembolism

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.02, CI 95% 0.52 — 2.00; 735 people in 2 studies]

Low quality evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 0.93, CI 95% 0.38 — 2.26; 562 people in 1 study]

Ventilator-free days

Very low quality evidence from 1 study found no significant difference for ventilator-free days at 30 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 30 days in intermediate dose group versus 30 days in prophylactic dose group; 562 people in 1 study].

Our confidence in the results

Both studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (Perepu, 21). The other study was from published manuscripts that reported 30 day and 90 day outcomes separately (INSPIRATION 2021).

Certainty of the evidence is low or very low for mortality outcomes due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for major bleeding due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for VTE outcomes at 30 days due to serious risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for VTE outcomes at 90 days to serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of evidence is very low for ventilator-free days at 30 days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals) and serious indirectness (dissimilarity between population of interest and those studied).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Intermediate dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality 30 days 9 Critical	Relative risk 1.01 (CI 95% 0.84 — 1.21) Based on data from 735 participants in 2 studies. [1] (Randomized controlled)	363 per 1000 Difference:	367 per 1000 **4 more per 1000** (CI 95% 58 fewer — 76 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [2]	A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to standard prophylactic

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Intermediate dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					dose anticoagulant for people who were hospitalised.
All-cause mortality 90 days 9 Critical	Relative risk 1.07 (CI 95% 0.89 — 1.29) Based on data from 562 participants in 1 studies. [3] (Randomized controlled)	430 per 1000 Difference:	460 per 1000 **30 more per 1000** (CI 95% 47 fewer — 125 more)	**Low** Due to serious indirectness and serious imprecision [4]	Evidence from 1 study found no statistically significant difference in all-cause mortality at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
Major bleeding 9 Critical	Relative risk 1.53 (CI 95% 0.54 — 4.28) Based on data from 735 participants in 2 studies. [5] (Randomized controlled)	16 per 1000 Difference:	24 per 1000 **8 more per 1000** (CI 95% 7 fewer — 52 more)	**Very low** Due to serious risk of bias, serious indirectness and serious imprecision [6]	A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised.
VTE 30 days 9 Critical	Relative risk 1.02 (CI 95% 0.52 — 2) Based on data from 735 participants in 2 studies. [7] (Randomized controlled)	43 per 1000 Difference:	44 per 1000 **1 more per 1000** (CI 95% 21 fewer — 43 more)	**Very low** Due to serious risk of bias, serious indirectness and serious imprecision [8]	A pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
VTE 90 days 9 Critical	Relative risk 0.93 (CI 95% 0.38 — 2.26) Based on data from 562 participants in 1 studies. [9] (Randomized controlled)	35 per 1000 Difference:	33 per 1000 **2 fewer per 1000** (CI 95% 22 fewer — 44 more)	**Low** Due to serious indirectness and serious imprecision [10]	Evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.
		30 (Median)	30 (Median) CI 95%	**Very low** Due to serious indirectness and very serious imprecision [11]	Evidence from 1 study found no statistically significant difference in ventilator-free days at 30 days with intermediate dose anticoagulant compared

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard dose VTE prophylaxis	**Intervention** Intermediate dose VTE prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					to standard prophylactic dose anticoagulant for people who were hospitalised.

1. Systematic review [83] with included studies: INSPIRATION 2021, Perepu 2021. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients have moderate in one study have moderate, not severe COVID-19. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**
3. Systematic review [79] with included studies: INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
5. Systematic review [79] with included studies: Perepu 2021, INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
7. Systematic review [79] with included studies: Perepu 2021, INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19.. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
9. Systematic review [79] with included studies: INSPIRATION 2021. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** No statistically significant effect.. **Publication bias: no serious.**
11. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied.. **Imprecision: very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias: no serious.**

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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 sections for the recommendation for treatment-dose VTE prophylaxis for young people and adults with COVID-19 who are receiving low-flow supplementary oxygen and the recommendation for treatment- and intermediate-dose VTE prophylaxis for young people and adults who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Preference and values

Rationale

The panel agreed that D-dimer levels do not influence peoples' response to anticoagulation.

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

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 low molecular weight heparins.

Consensus recommendation

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

8.3.1.1 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.

8.3.2 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.

8.3.3 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.

9. Identifying and managing co-infections

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).

9.1 Bacterial pneumonia

9.1.1 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.

9.1.2 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.

9.1.3 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.

9.1.4 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.

9.1.5 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.

9.2 COVID-19-associated pulmonary aspergillosis (CAPA)

New

Info Box

For people who are critically ill and have, or have had, COVID-19 as part of their acute illness:

- CAPA is a recognised cause of someone's condition not improving despite treatment (for example, antibiotic therapy, ventilatory support)
- there are no specific combinations of signs or symptoms for diagnosing CAPA
- the risk of having CAPA may increase with age and chronic lung disease.

9.2.1 Diagnosing CAPA

Consensus recommendation

When deciding whether to suspect CAPA in someone who is critically ill and has, or has had, COVID-19 as part of their acute illness:

- base your decisions on individual risk factors and the person's clinical condition
- involve a multidisciplinary team, including infection specialists
- refer to local protocols on diagnosing and managing CAPA.

Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel were presented with evidence from one systematic review (Chong 2021) and two primary studies (Prattes 2021 and Segrelles-Calvo 2021). The studies presented evidence on the risk factors and signs and symptoms associated with people developing CAPA.

The panel agreed that there was insufficient evidence to define specific risk factors or signs and symptoms of CAPA. Although the studies suggest that increasing age and chronic lung disease may increase the risk of developing CAPA, the panel considered that the evidence was not strong enough to include these specific risk factors in a diagnostic recommendation. They also agreed that, while studies suggest that people who receive invasive mechanical ventilation are at increased risk of CAPA, the thresholds for mechanical ventilation vary across centres and invasive mechanical ventilation may not be considered an independent risk factor for CAPA. The panel also considered the evidence around whether taking long-term immunosuppressants can increase the risk of CAPA, but concluded that the evidence was not strong enough to list 'long-term immunosuppressants' as an independent risk factor for CAPA.

The panel highlighted the need to use clinical judgement and assess the individual needs of people who are suspected to have CAPA, before progressing further with their diagnosis and management.

The panel considered whether existing clinical algorithms for the diagnosis of invasive pulmonary aspergillosis could be applied to CAPA. In particular, the panel discussed the AspICU algorithm, which is a clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. However, the panel agreed not to recommend use of the AspICU algorithm for CAPA because of a lack of evidence of its use in this condition and meaningful differences between the people for which the AspICU algorithm is typically used and the people who are at risk of developing CAPA.

The panel discussed that from their experience, a diagnosis of CAPA should usually be made as part of a multidisciplinary team, with input from infection specialists (for example, medical microbiologists or infectious disease specialists).

Certainty of the Evidence

Very low

The certainty of the evidence was rated as low to very low for all outcomes. This was due to serious risk of bias, serious indirectness, and serious inconsistency. The panel discussed that heterogeneity of the study participants, and the variations in local practice in reporting and case definitions of CAPA also reduced their certainty in the results.

In particular, the panel discussed that the association shown between invasive mechanical ventilation and CAPA is likely to be at risk of bias from confounding due to the difference in diagnostic approach between those who are invasively mechanically ventilated and those who are not.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data about the preferences and values in people who are suspected to have CAPA.

Resources and other considerations

Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. The panel recommended that decisions about whether to suspect CAPA should be made as part of a multidisciplinary team which includes infection specialists, which may not currently be in place in all settings where people who are critically ill are cared for.

Equity

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill and have, or have had, COVID-19 as part of their acute illness.

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 the acceptability of assessing for suspicion of CAPA.

Feasibility

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about feasibility, but agreed that this approach should be feasible, particularly where a multidisciplinary team which includes infection specialists is already in place.

Rationale

The panel agreed that the evidence was not strong enough to recommend specific factors that increase the risk of CAPA. They noted the importance of multidisciplinary decision making and using local protocols when deciding whether to suspect CAPA.

Clinical Question/ PICO

Population: Risk factors for People hospitalised with confirmed COVID-19 and CAPA
Intervention: People with CAPA
Comparator: People without CAPA

Summary

There remains a high degree of uncertainty over possible risk factors that are associated with people developing COVID-19-associated pulmonary aspergillosis.

What is the evidence informing this conclusion?

Evidence comes from 2 studies. The first (Chong 2021) was a systematic review and meta-analysis of cohort studies comparing the clinical characteristics of people with CAPA to people without CAPA. The systematic review included cohort studies that investigated the clinical characteristics and outcomes of people who are hospitalised with proven or probable CAPA and confirmed COVID-19 (Bartoletti 2020; Delliere 2021; Gangneux 2020; Lahmer 2021; Segrelles-Calvo 2021; Van Biesen 2021; Velez Pintado 2021; Wang 2020).

The second study identified in this review (Prattes 2021) was a multinational cohort study that evaluated the risk factors associated with developing CAPA in people hospitalised and admitted to the intensive care for COVID-19 acute respiratory failure.

Publication status

The two studies included in this review were full publications (Chong 2021 and Prattes 2021). All 8 of the studies included in the systematic review (Chong 2021) were full publications as well.

Study characteristics

The Chong 2021 systematic review included 8 cohort studies, with 729 participants and ages ranging from 59-71 years. It included people who developed COVID-19 and were admitted to hospitals and later diagnosed with CAPA. The included studies collected data from participants during the early surges of COVID-19 in March-August 2020.

Prattes 2021 evaluated 592 participants, with 109/592 with proven, probable or possible CAPA who were admitted to ICU for COVID-19 acute respiratory failure. Participants in Prattes 2021 were aged between 54-75 years and were admitted between March 2020 – April 2021.

Both studies compared the clinical characteristics, or risk factors, of people with COVID-19 and confirmed CAPA with those without CAPA. The majority of participants in both studies were male (Chong 2021- 71.5% male and Prattes 2021 - 70.8% male), and were adults who were hospitalised with confirmed COVID-19. Participants were diagnosed with CAPA as defined by the ECMM criteria and the AspICU algorithm criteria.

For further details see the evidence review for risk factors of CAPA.

What are the main results?

The results from the studies indicated that there is a possible association between CAPA incidence and increasing age, long-term corticosteroid treatment, higher sequential organ failure assessment (SOFA) score, progression to invasive mechanical ventilation and COVID-19 treatment with tocilizumab. There is an association of borderline significance between the presence of underlying chronic obstructive pulmonary disease (COPD) and CAPA.

Our confidence in the results

The certainty of the evidence for these risk factors was rated as low to very low, due to serious risk of bias with the studies controlling variables, due to serious indirectness (Prattes 2021) from the inclusion of people with possible CAPA (not proven or probable) and due to serious inconsistency as Chong 2021 analysed studies that varied methodologically.

The risk factors in the systematic review and the single cohort study are reported in general terms and not in detail. Details on confounding variables, such as diagnostic criteria and treatment regimens were not clearly defined. It was also unclear how these different variables were controlled in both the CAPA and non-CAPA groups, and how they were accounted for throughout data collection and analysis.

As both studies evaluated people from different waves of the COVID-19 pandemic, it is possible that changes in practice (e.g. treatments for COVID-19 in different centres, different diagnostic criteria for CAPA) throughout the COVID-19 pandemic context (e.g. surges and recovery periods in COVID-19 waves, take-up of vaccinations), may affect the number of people who contracted COVID-19 and CAPA.

Currently, there is limited evidence that identifies the associations between patient characteristics and CAPA development in COVID-19 disease and the current evidence base is small.

Outcome Timeframe	**Study results and measurements**	**Comparator** No CAPA	**Intervention** CAPA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Risk factor - Age per 5 years 9 Critical	Hazard Ratio 1.18 (CI 95% 1.08 — 1.28) Based on data from 592 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Low** Due to serious risk of bias, Due to serious indirectness [1]	Increasing age is associated with developing CAPA in people hospitalised with COVID-19
Risk factor - Sex (Female) 9 Critical	Hazard Ratio 0.68 (CI 95% 0.42 — 1.09) Based on data from 592 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [2]	Sex is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Sex (Male) 9 Critical	Odds Ratio 0.82 (CI 95% 0.43 — 1.55) Based on data from 514 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [3]	Sex is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Number of coexisting	Hazard Ratio 0.92 (CI 95% 0.76 — 1.1) Based on data from 592 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious	Increasing numbers of coexisting conditions are not associated with an increased risk of

Outcome Timeframe	**Study results and measurements**	**Comparator** No CAPA	**Intervention** CAPA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
conditions 9 Critical				imprecision, Due to serious indirectness [4]	developing CAPA in people hospitalised with COVID-19.
Risk factor - History of smoking 9 Critical	Hazard Ratio 1.36 (CI 95% 0.76 — 2.44) Based on data from 529 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [5]	Smoking is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Obesity 9 Critical	Hazard Ratio 0.89 (CI 95% 0.54 — 1.44) Based on data from 592 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [6]	Obesity is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Diabetes 9 Critical	Odds Ratio 1.2 (CI 95% 0.71 — 2.01) Based on data from 506 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [7]	Diabetes is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Diabetes 9 Critical	Hazard Ratio 1.12 (CI 95% 0.73 — 1.73) Based on data from 529 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [8]	Diabetes is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Cancer 9 Critical	Odds Ratio 2.25 (CI 95% 0.68 — 5.07) Based on data from 332 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [9]	Cancer is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - COPD 9 Critical	Odds Ratio 2.75 (CI 95% 1 — 7.52) Based on data from 514 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Low** Due to serious risk of bias, Due to serious inconsistency [10]	COPD is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Active malignant	Hazard Ratio 1.56 (CI 95% 0.81 — 3) Based on data from 529		CI 95%	**Very low** Due to serious risk of bias, Due	Active malignant disease is not associated with an

Outcome Timeframe	**Study results and measurements**	**Comparator** No CAPA	**Intervention** CAPA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
disease 9 Critical	participants in 1 studies.			to serious imprecision, Due to serious indirectness [11]	increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Cardiovascular disease 9 Critical	Hazard Ratio 1.2 (CI 95% 0.81 — 1.78) Based on data from 529 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [12]	Cardiovascular disease is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Pulmonary disease 9 Critical	Hazard Ratio 1.42 (CI 95% 0.89 — 2.24) Based on data from 529 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [13]	Pulmonary disease is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Solid organ transplantation 9 Critical	Hazard Ratio 2.2 (CI 95% 0.9 — 5.42) Based on data from 529 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [14]	Solid organ transplantation is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Long term corticosteroid use 9 Critical	Odds Ratio 3.53 (CI 95% 1.16 — 10.69) Based on data from 250 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Low** Due to serious risk of bias, Due to serious inconsistency [15]	Long-term corticosteroid is associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Long term immunosuppressant 9 Critical	Odds Ratio 1.87 (CI 95% 0.28 — 12.29) Based on data from 142 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [16]	Long-term immunosuppressant use is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Non-invasive ventilation 9 Critical	Hazard Ratio 0.08 (CI 95% 0.02 — 0.33) Based on data from 529 participants in 1 studies.		CI 95%	**Low** Due to serious risk of bias,, Due to serious indirectness [17]	Non-invasive ventilation is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Extracorporeal	Hazard Ratio 0.8 (CI 95% 0.37 — 1.7)		CI 95%	**Low** Due to serious	Extracorporeal Membrane Oxygenation

Outcome Timeframe	**Study results and measurements**	**Comparator** No CAPA	**Intervention** CAPA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Membrane Oxygenation (ECMO) 9 Critical	Based on data from 529 participants in 1 studies.			risk of bias, Due to serious indirectness [18]	(ECMO) is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Invasive mechanical ventilation 9 Critical	Hazard Ratio 2.53 (CI 95% 1.53 — 4.17) Based on data from 529 participants in 1 studies.		CI 95%	**Low** Due to serious risk of bias, Due to serious indirectness [19]	Invasive mechanical ventilation is significantly associated with an increased risk of developing CAPA in people hospitalized with COVID-19.
Risk factor - Any invasive ventilation 9 Critical	Hazard Ratio 2.93 (CI 95% 1.6 — 5.35) Based on data from 529 participants in 1 studies.		CI 95%	**Low** Due to serious risk of bias, Due to serious indirectness [20]	Invasive ventilation of any kind is associated with an increased risk of developing CAPA in people hospitalized with COVID-19.
Risk factor - COVID-19 treatment with tocilizumab 9 Critical	Odds Ratio 1.85 (CI 95% 0.88 — 3.89) Based on data from 514 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [21]	Treatment with tocilizumab for COVID-19 is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - COVID-19 treatment tocilizumab 9 Critical	Hazard Ratio 2.34 (CI 95% 1.03 — 4.06) Based on data from 529 participants in 1 studies.		CI 95%	**Low** Due to serious risk of bias, Due to serious indirectness [22]	Treatment with tocilizumab for COVID-19 is associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - COVID-19 treatment with corticosteroid 9 Critical	Odds Ratio 0.69 (CI 95% 0.19 — 2.58) Based on data from 510 participants in 1 studies.		CI 95%	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [23]	Treatment with corticosteroids for COVID-19 is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
			CI 95%		

Outcome Timeframe	**Study results and measurements**	**Comparator** No CAPA	**Intervention** CAPA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Risk factor - COVID-19 treatment with antibiotic 9 Critical	Odds Ratio 0.88 (CI 95% 0.39 — 1.97) Based on data from 542 participants in 1 studies. (Observational (non-randomized))		CI 95%	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [25]	Treatment of COVID-19 with antibiotics is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - COVID-19 treatment with hydroxychloroquine 9 Critical	Odds Ratio 0.43 (CI 95% 0.07 — 2.68) Based on data from 514 participants in 1 studies.		CI 95%	**Very low** Due to serious inconsistency, Due to serious risk of bias, Due to serious imprecision [26]	Treatment of COVID-19 with hydroxychloroquine is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - COVID-19 treatment with azithromycin 9 Critical	Hazard Ratio 0.63 (CI 95% 0.33 — 1.21) Based on data from 529 participants in 1 studies.		CI 95%	**Low** Due to serious risk of bias, Due to serious imprecision [27]	Treatment of COVID-19 with azithromycin is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Risk factor - Age 9 Critical	Based on data from: 729 participants in 1 studies.	59.25 (Mean) Difference:	66.58 (Mean) **MD 7.52 more** (CI 95% 2.02 more — 13.03 more)	**Low** Due to serious risk of bias, Due to serious inconsistency, [28]	Increasing age is associated with developing CAPA in people hospitalised with COVID-19
Risk factor - BMI 9 Critical	Based on data from: 729 participants in 1 studies.	27.88 (Mean) Difference:	27.8 (Mean) **MD 0.46 fewer** (CI 95% -1.93 fewer — 1.02 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [29]	Increasing BMI is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
Sequential Organ Failure Assessment (SOFA) score 9 Critical		7.27 (Mean) Difference:	9.37 (Mean) **MD 2.57 higher** (CI 95% 1.46 higher — 3.68 higher)	**Low** Due to serious risk of bias, Due to serious inconsistency [30]	Increasing SOFA score is associated with an increased risk of developing CAPA in people hospitalised with COVID-19.

1. **Risk of Bias: serious.** Unclear how variables in the study were controlled. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
2. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious.**

Indirectness: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**

3. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
4. **Risk of Bias: serious.** Unclear how variables were controlled.. **Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line o fno effect.
5. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
6. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
7. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
8. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
9. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
10. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
11. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
12. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
13. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
14. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
15. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
16. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious.** Differences amongst the populations included within the study. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
17. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
18. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
19. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious.**

Indirectness: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**

20. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
21. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
22. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: serious.** Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision: no serious. Publication bias: no serious.**
23. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious.** Differences amongst the populations included within the study. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
24. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
25. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: serious.** Differences amongst the populations included within the study. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
26. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
27. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
28. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
29. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**
30. **Risk of Bias: serious.** Unclear how variables are controlled throughout the study. **Inconsistency: serious.** Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

References

131. Chong WH, Saha BK, Neu KP : Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis. Infection 2021; Pubmed Journal

132. Prattes J, Wauters J, Giacobbe DR, Salmanton-García J, Maertens J, Bourgeois M, et al. : Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients-a multinational observational study by the European Confederation of Medical Mycology. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2021; Pubmed Journal

Clinical Question/ PICO

Population: Signs and symptoms of people hospitalised with COVID-19 and with CAPA
Intervention: NA
Comparator: NA

Summary

There is very limited evidence on symptoms of invasive pulmonary aspergillosis (IPA) in people who have or, as part of their acute illness, have had confirmed COVID-19.

What is the evidence informing this conclusion?

Evidence comes from one small, retrospective cohort study aiming to determine the prevalence of IPA and risk factors for IPA in people admitted to ICU due to severe SARS-CoV-2 infection (Segrellos-Calvo 2021).

Publication status

The included study has been published and peer-reviewed.

Study characteristics

The included study had seven participants. Their ages ranged from 42 to 75. Two participants (29%) were female. All had PCR-confirmed COVID-19. They were diagnosed with IPA using bronchoalveolar lavage using an Aspergillus EIA assay. All participants had been admitted to respiratory ICU.

For further details see the evidence review for signs and symptoms of CAPA.

What are the main results?

Critical outcomes

Fever, dyspnoea and cough were the most common symptoms among the participants (affecting 100%, 86% and 86% respectively).

Important outcomes

All outcomes for this review were classified as critical outcomes

Our confidence in the results

The evidence is extremely sparse and the results could be due to chance. The study was at high risk of bias due to a lack of detail about how outcomes were measured. There could also be variation over time or between people assessing symptoms, potentially introducing bias.

Outcomes were also downgraded twice for imprecision, as the precision of the result was not reported and could not be calculated.

The symptoms reported are also associated with COVID-19, and therefore it is not possible to attribute the symptoms to COVID-19 associated pulmonary aspergillosis (CAPA) alone.

Outcome Timeframe	**Study results and measurements**	**Comparator** NA	**Intervention** NA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Symptom: Fever During ICU admission 9 Critical	Based on data from: 7 participants in 1 studies. [1] (Observational (non-randomized))	7/7 (100%) of participants with CAPA had fever. No comparator group.		Very low Due to serious risk of bias, Due to very serious imprecision [2]	The prevalence of fever in people diagnosed with CAPA is uncertain.
Symptom:	Based on data from: 7	6/7 (86%) of participants with CAPA		Very low	The prevalence of

Outcome Timeframe	**Study results and measurements**	**Comparator** NA	**Intervention** NA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Dyspnoea During ICU admission 9 Critical	participants in 1 studies. (Observational (non-randomized))	had dyspnoea. No comparator group.		Due to serious risk of bias, Due to very serious imprecision [3]	dyspnoea in people diagnosed with CAPA is uncertain.
Symptom: Cough During ICU admission 9 Critical	Based on data from: 7 participants in 1 studies. (Observational (non-randomized))	6/7 (86%) of participants with CAPA had cough. No comparator group.		**Very low** Due to serious risk of bias, Due to very serious imprecision [4]	The prevalence of cough in people diagnosed with CAPA is uncertain.
Symptom: Malaise During ICU admission 9 Critical	Based on data from: 7 participants in 1 studies. (Observational (non-randomized))	3/7 (43%) of participants with CAPA had malaise. No comparator group.		**Very low** Due to serious risk of bias, Due to very serious imprecision [5]	The prevalence of malaise in people diagnosed with CAPA is uncertain.
Symptom: Sputum During ICU admission 9 Critical	Based on data from: 7 participants in 1 studies. (Observational (non-randomized))	1/7 (14%) of participants with CAPA had sputum. No comparator group.		**Very low** Due to serious risk of bias, Due to very serious imprecision [6]	The prevalence of sputum in people diagnosed with CAPA is uncertain.
Symptom: Diarrhoea During ICU admission 9 Critical	Based on data from: 7 participants in 1 studies. (Observational (non-randomized))	1/7 (14%) of participants with CAPA had diarrhoea. No comparator group.		**Very low** Due to serious risk of bias, Due to very serious imprecision [7]	The prevalence of diarrhoea in people diagnosed with CAPA is uncertain.
Symptom: Headache During ICU admission 9 Critical	Based on data from: 7 participants in 1 studies. (Observational (non-randomized))	1/7 (14%) of participants with CAPA had headache. No comparator group.		**Very low** Due to serious risk of bias, Due to very serious imprecision [8]	The prevalence of headache in people diagnosed with CAPA is uncertain.

1. Primary study **Supporting references:** [129],
2. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
3. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
4. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute

the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
5. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
6. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
7. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**
8. **Risk of Bias: serious.** The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No CIs could be reported. **Publication bias: no serious.**

References

129. Segrelles-Calvo G, Araújo GRS, Llopis-Pastor E : Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia. Mycoses 2021; Pubmed Journal

Not recommended

Do not do diagnostic tests for CAPA if there is low clinical suspicion of the condition.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel were presented with information from a taskforce report by Verweij et al. on diagnosing and managing CAPA that prevalence of CAPA in people being treated in ICU was between 0% and 33% (the average across included studies was 9.3%). They discussed that this prevalence included possible as well as probable and proven CAPA, and was therefore likely to be an overestimation. The panel agreed that in their experience, prevalence of CAPA is low, and so testing for CAPA should only take place if there is clinical suspicion of the condition.

The panel were also presented with evidence from 2 systematic reviews (Chong 2021 and Dimopoulos 2021) and 2 primary studies (Meawed 2021 and van Grootveld 2021). The panel discussed the most common types of diagnostic tests and also referred to the taskforce report by Verweij et al.

The evidence showed that a range of different diagnostic test types are conducted to confirm CAPA diagnosis. The panel agreed that some of the common tests for diagnosing CAPA, for example bronchoalveolar lavage (BAL), are invasive and so the risks of carrying out the test should be considered against the benefit of a potential diagnosis.

Certainty of the Evidence

It was not possible to apply GRADE to the outcomes in this review, because the outcomes were descriptive rather than analytical.

The panel agreed that the studies were at moderate to high risk of bias due to high heterogeneity between study participants and variations in practice between study centres. The panel also agreed that the taskforce document was an up to date and relevant source of information on the diagnosis and treatment of CAPA. However, the panel also acknowledged that the evidence identified by the taskforce was sparse.

Based on this evidence the panel agreed that it would not be possible to determine the best diagnostic tests to request when CAPA was suspected. The panel agreed that unless CAPA was suspected clinically, further investigations for CAPA should not be carried out.

Preference and values

Substantial variability is expected or uncertain

The panel considered that some of the diagnostic tests for CAPA, for example a bronchoscopy or BAL, may involve clinical risk or patient discomfort and some people may be apprehensive about having it done. Therefore these tests should be carried out following an appropriate multidisciplinary discussion and decision on the clinical suspicion of CAPA.

The panel were not aware of any systematically collected data on preferences and values of people in relation to bronchoalveolar lavage sampling.

Resources and other considerations

Important issues, or potential issues not investigated

This recommendation advises against investigation when suspicion is low, so has potential for savings in resource use from unnecessary procedures. Cost-effectiveness was not assessed as part of this evidence review.

Equity

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that investigations should take place in the same way for all people who are critically ill because of current or previous 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 the acceptability of assessing for suspicion of CAPA.

Feasibility

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about feasibility. They agreed that testing for CAPA only in cases where there is a clinical suspicion of CAPA should be feasible, especially where it results in a reduction in testing.

Rationale

Because the incidence of CAPA is low, there is a lack of evidence on how to diagnose the condition. Also, there are no specific combinations of signs and symptoms for diagnosing it. The panel concluded that the likelihood of CAPA should be considered when deciding whether to do diagnostic tests.

Clinical Question/ PICO

Population: Diagnostics for CAPA
Intervention: NA
Comparator: NA

Summary

This review aimed to determine the diagnostic tests that should be used to diagnose CAPA in people with COVID-19. The evidence highlighted the range of tests that are used in clinical practice.

What is the evidence informing this conclusion?

Evidence comes from 2 systematic reviews that evaluate different diagnostic investigations for people with COVID-19 and suspected CAPA (Chong 2021 and Dimopoulos 2021). A further 2 studies were included in this evidence review to supplement the findings of the included systematic reviews: a cross-sectional study (Meawed 2021) and a cohort study (van Grootveld 2021).

Publication status

All included studies were full publications (Chong 2021, Dimopoulos 2021, Meawed 2021 and van Grootveld 2021).

Study characteristics

Study participant numbers ranged from 63 people (van Grootveld 2021) to 1494 people (Chong 2021b). The average age of participants ranged from 62 to 63 years. The proportion of male participants ranged from 34% to 80% of the study population. All participants had a wide range of underlying comorbidities (for example, hypertension, diabetes, chronic pulmonary disease, cardiovascular disease, and active malignancies).

Most participants (94%; n= 2829/3026) were hospitalised and admitted to ICU with severe COVID-19 and only 6% had moderate COVID-19 (197/3026). Disease severity was mostly scored against the WHO Clinical Progression Scale.

For further details see the evidence review for diagnostics for CAPA.

What are the main results?

The evidence described the use of bronchoalveolar lavage (BAL), endotracheal aspirates (ETA), serum, non-directed bronchial lavage (NBL) and sputum to diagnose CAPA. The different microbiological investigations performed on each sample (such as tissue culture, galactomannan and beta-d-glucan biomarker levels, PCR) were also described in the literature.

CT imaging, serum assays (galactomannan (GM) and beta-d-glucan (BDG)), ETA culture and BAL are commonly used to support CAPA diagnosis. Further BAL sample investigations such as microscopy, culture, GM, BDG and PCR are also commonly used to support CAPA diagnosis.

The evidence shows that sputum sampling, NBL and ETA investigations like GM, BDG and PCR are not as commonly used to diagnose CAPA, as their prevalence was relatively low when compared to that of CT imaging, BAL, and serum assays.

The findings of this review are consistent with existing recommendations on diagnosing CAPA (Verweij et al. 2021). The Verweij et al. 2021 report states that bronchoscopy alongside BAL is recommended to diagnose CAPA and states that ETA and sputum should not be relied on solely to diagnose CAPA.

Our confidence in the results

GRADE could not be conducted on the results of this review because the results were descriptive rather than analytical.

There were some concerns about risk of bias due to unclear reporting of participant eligibility criteria in all studies (Chong 2021b, Dimopoulous 2021, Meawed 2021 and van Grootveld 2021). There was also insufficient information to assess the data collection and data analysis methods used in Chong 2021b and Dimopoulous 2021 and as such, risk of bias was rated as high for both studies.

The two systematic reviews contained studies from international centres and as such, there may have been differences in standard of care as well as diagnostic investigations and assessment criteria. As such, there is risk of the evidence being indirect to the UK context.

Although Chong 2021b defined clear eligibility criteria to limit the heterogeneity, studies are heterogeneous with epidemiological, clinical, and methodological diversity, meaning that it may not be possible to generalise the prevalence results.

Conclusion

The review has found that CT imaging, serum assays of biomarkers, ETA culture and BAL are the most common investigations for diagnosing CAPA.

The findings of this review are consistent with current recommendations on diagnosing CAPA.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention**	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
CT Imaging	Based on data from: 1,792 participants in 3 studies.	Three studies (n=1792) found that 10%- 43% of participants had undergone a CT imaging investigation to support CAPA diagnosis.			Evidence from four studies found that CT imaging is a common investigation used to support CAPA diagnosis.
Serum Galactomannan	Based on data from: 957 participants in 2 studies.	Two studies (n=957) found that 25%-47% of participants had undergone a serum galactomannan investigation to support CAPA diagnosis.			Evidence from two studies found that serum galactomannan is a common investigation used to support CAPA diagnosis.
Serum beta-D-glucan	Based on data from: 636 participants in 2 studies.	Two studies (n= 636) found that 3% - 47% of participants had undergone a serum beta-d-glucan investigation to support CAPA diagnosis.			Evidence from two studies found that serum beta-d-glucan is a common investigation used to support CAPA diagnosis.
Endotracheal Aspirate Culture	Based on data from: 370 participants in 3 studies.	Three studies (n = 370) found that 8% - 100% of a participants had undergone a endotracheal aspirate microscopy investigation to support CAPA diagnosis.			Evidence from three studies found that endotracheal aspirate culture is a common investigation used to support CAPA diagnosis
Endotracheal Aspirate Beta-d-glucan	Based on data from: 52 participants in 2 studies.	Two studies (n = 52) found that 4%-5% of participants had undergone a endotracheal aspirate beta-d-glucan investigation to support CAPA diagnosis.			Evidence from two studies found that endotracheal aspirate culture is not commonly used to support CAPA diagnosis.
Endotracheal Aspirate PCR	Based on data from: 63 participants in 1 studies.	One study (n = 63) found that 100% of patients had undergone a endotracheal aspirate PCR investigation to support CAPA diagnosis.			Evidence from one study found that endotracheal aspirate PCR is not commonly used to support CAPA diagnosis
Non-directed Bronchial Lavage Culture	Based on data from: 217 participants in 2 studies.	Two studies (n = 217) found that 5% - 10% of participants had undergone a non-directed bronchial lavage culture investigation to support CAPA diagnosis.			Evidence from two studies found that non-directed bronchial lavage culture is not commonly used to support CAPA diagnosis

Outcome Timeframe	**Study results and measurements**			**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Non-directed Bronchial Lavage Galactomannan					
Non-directed Bronchial Lavage PCR					
Bronchoalveolar Lavage Microscopy		One study (n=16) found tha1% of participants had undergone a bronchoalveolar lavage microscopy investigation to support CAPA diagnosis.			Evidence from one study found that bronchoalveolar lavage microscopy is not commonly used to support CAPA diagnosis
Bronchoalveolar Lavage Culture					Evidence from three studies found that bronchoalveolar lavage culture is a common investigation to support CAPA diagnosis
Bronchoalveolar Lavage Galactomannan	Based on data from: 518 participants in 3 studies.				Evidence from one study found that bronchoalveolar lavage galactomannan is a common investigation used to support CAPA diagnosis
Bronchoalveolar Lavage PCR	Based on data from: 540 participants in 4 studies.	Four studies (n=540) found that 4%-24% of participants had undergone a bronchoalveolar lavage PCR investigation to support CAPA diagnosis.			Evidence from four studies found that bronchoalveolar lavage PCR is a common investigation to support CAPA diagnosis
Sputum	Based on data from: 241 participants in 3 studies.	Three studies (n=241) found that 1%-100% of participants had undergone a sputum investigation to support CAPA diagnosis.			Evidence from three studies found that sputum sampling is not commonly used to support CAPA diagnosis

References

148. Chong WH, Neu KP : Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. The Journal of hospital infection 2021;113 115-129 Pubmed Journal

149. Dimopoulos G, Almyroudi M-P, Myrianthefs P, Rello J : COVID-19-Associated Pulmonary Aspergillosis (CAPA). Journal of Intensive Medicine 2021; Journal Website

151. van Grootveld R, van Paassen J, de Boer MGJ, Claas ECJ, Kuijper EJ, van der Beek MT : Systematic screening for COVID-19 associated invasive aspergillosis in ICU patients by culture and PCR on tracheal aspirate. Mycoses 2021;64(6):641-650 Pubmed Journal

Recommended

When investigating suspected CAPA:

- use a range of tests to increase the likelihood of making a confident diagnosis
- if possible, include bronchoalveolar lavage (BAL) as part of diagnostic testing, taking into account the risks of BAL in relation to the person's clinical condition
- discuss the diagnostic testing strategy and final diagnosis with a multidisciplinary team that includes infection specialists.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel were presented with evidence from 2 systematic reviews (Chong 2021 and Dimopoulos 2021), and 2 primary studies (Meawed 2021 and van Grootveld 2021). The panel also considered a taskforce report by Verweij et al. on diagnosing and managing CAPA.

The evidence described the frequency of diagnostic tests that are used to investigate CAPA. It showed that bronchoalveolar lavage (BAL) is one of the most commonly used diagnostic tests for diagnosing CAPA. Of the studies included, 55% of people had a BAL carried out, with further investigations on the sample (for example culture, galactomannan and PCR). The panel noted that BAL is carried out in intensive care units in people who are critically ill and invasively mechanically ventilated to investigate infectious lung disease.

The taskforce report discussed by the panel, recommends bronchoscopy with BAL, stating that it is the most important tool to diagnose invasive pulmonary aspergillosis, including in people who are critically ill and have, or have had, COVID-19 as part of their acute illness. The panel acknowledged that BAL is an invasive procedure that is not risk-free and may not be feasible to carry out in all patients, particularly in patients who remain on non-invasive ventilation.

The reviewed studies and the taskforce report also reported that other tests such as endotracheal aspirates, serological assays for beta-D-glucan and galactomannan (fungal biomarkers) are used to diagnose CAPA. Overall, the panel agreed that there are variations in the sensitivity and specificity of diagnostic tests, but that BAL may perform most favourably for the diagnosis of CAPA.

The panel concluded that BAL is the preferred diagnostic approach for investigating a CAPA diagnosis, but the risks and harms from carrying out the procedure need to be carefully assessed and other tests should be used alongside BAL or if BAL is not possible.

The panel discussed that, in their experience, a diagnosis of CAPA should usually be made as part of a multidisciplinary team with input from infection specialists, for example medical microbiologists or infectious disease specialists.

The panel agreed that the approach for diagnosing CAPA in children and young people should be the same as the approach for adults, however the levels of serum biomarkers may be different.

Certainty of the Evidence

It was not possible to apply GRADE to the outcomes in this review, because the outcomes were descriptive rather than analytical.

The panel agreed that the studies were at moderate to high risk of bias due to high heterogeneity between study participants and variations in local practice in study centres. The panel agreed that the evidence informing the taskforce report by Verweij et al.on diagnosing and managing CAPA was sparse.

Based on the evidence, the panel agreed that it was not possible to identify with certainty which tests, and in which order, should be used to diagnose CAPA. They agreed with the taskforce report that a BAL is likely to be the most accurate test for diagnosing CAPA based on the evidence of comparisons of diagnostic tests in IPA more broadly.

Preference and values

No substantial variability expected

The panel agreed that people may experience discomfort during a bronchoalveolar lavage (BAL), and some people may be apprehensive about having it done. They suggested that the risks and patient experience may be different if the person is already on invasive mechanical ventilation. The panel suggested that people's preferences and values should be considered as part of the shared-decision making process with the patients and their families

The panel were not aware of any systematically collected data on preferences and values of people in relation to the different investigations that are used to diagnose CAPA.

Resources and other considerations

Important issues, or potential issues not investigated

The panel discussed the need for timely testing and diagnostics to investigate CAPA. Since BAL is a commonly used diagnostic test for the assessment of pulmonary aspergillosis, it is not expected that this recommendation will lead to significant changes in resource utilisation.

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

Equity

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous COVID-19.

No other equity issues were identified.

Acceptability

Important issues, or potential issues not investigated

The panel discussed that, in their experience, there are few issues with acceptance of BAL as a diagnostic tool for CAPA among people who are critically ill and have, or have had, COVID-19 as part of their acute illness. However, the panel noted that in some cases, people may reject BAL or bronchoscopy as it may cause some discomfort.

Feasibility

No important issues with the recommended alternative

The panel identified several potential barriers to feasibility for this recommendation. They noted that while BAL is recommended to diagnose CAPA, a wait is required for the results of BAL to become available. The panel noted that bronchoscopy may not always be feasible to carry out in patients with suspected CAPA. The panel addressed these feasibility concerns by ensuring that other diagnostic tests for CAPA were also included in the recommendation.

Rationale

There is a lack of evidence on diagnosing CAPA, including on what diagnostic tests to use, how frequently to test and the diagnostic value of the different investigations. The panel noted that using a range of tests, including bronchoalveolar lavage

(BAL), follows current best practice recommended in a taskforce report by Verweij et al., (2021) on diagnosing and managing CAPA.

Because BAL is an invasive procedure, it is important that any benefits or harms are considered before using it to investigate CAPA. The panel noted that BAL may not always be suitable or feasible. They agreed that other tests could be used instead of BAL, such as serological assays, non-bronchoscopic lavage or endotracheal aspirates.

Clinical Question/ PICO

Population: Diagnostics for CAPA
Intervention: NA
Comparator: NA

Summary

This review aimed to determine the diagnostic tests that should be used to diagnose CAPA in people with COVID-19. The evidence highlighted the range of tests that are used in clinical practice.

What is the evidence informing this conclusion?

Evidence comes from 2 systematic reviews that evaluate different diagnostic investigations for people with COVID-19 and suspected CAPA (Chong 2021 and Dimopoulos 2021). A further 2 studies were included in this evidence review to supplement the findings of the included systematic reviews: a cross-sectional study (Meawed 2021) and a cohort study (van Grootveld 2021).

Publication status

All included studies were full publications (Chong 2021, Dimopoulos 2021, Meawed 2021 and van Grootveld 2021).

Study characteristics

Study participant numbers ranged from 63 people (van Grootveld 2021) to 1494 people (Chong 2021b). The average age of participants ranged from 62 to 63 years. The proportion of male participants ranged from 34% to 80% of the study population. All participants had a wide range of underlying comorbidities (for example, hypertension, diabetes, chronic pulmonary disease, cardiovascular disease, and active malignancies).

Most participants (94%; n= 2829/3026) were hospitalised and admitted to ICU with severe COVID-19 and only 6% had moderate COVID-19 (197/3026). Disease severity was mostly scored against the WHO Clinical Progression Scale.

For further details see the evidence review for diagnostics for CAPA.

What are the main results?

The evidence described the use of bronchoalveolar lavage (BAL), endotracheal aspirates (ETA), serum, non-directed bronchial lavage (NBL) and sputum to diagnose CAPA. The different microbiological investigations performed on each sample (such as tissue culture, galactomannan and beta-d-glucan biomarker levels, PCR) were also described in the literature.

CT imaging, serum assays (galactomannan (GM) and beta-d-glucan (BDG)), ETA culture and BAL are commonly used to support CAPA diagnosis. Further BAL sample investigations such as microscopy, culture, GM, BDG and PCR are also commonly used to support CAPA diagnosis.

The evidence shows that sputum sampling, NBL and ETA investigations like GM, BDG and PCR are not as commonly used to diagnose CAPA, as their prevalence was relatively low when compared to that of CT imaging, BAL, and serum assays.

The findings of this review are consistent with existing recommendations on diagnosing CAPA (Verweij et al. 2021). The Verweij et al. 2021 report states that bronchoscopy alongside BAL is recommended to diagnose CAPA and states that ETA and sputum should not be relied on solely to diagnose CAPA.

Our confidence in the results

GRADE could not be conducted on the results of this review because the results were descriptive rather than analytical.

There were some concerns about risk of bias due to unclear reporting of participant eligibility criteria in all studies (Chong 2021b, Dimopoulous 2021, Meawed 2021 and van Grootveld 2021). There was also insufficient information to assess the data collection and data analysis methods used in Chong 2021b and Dimopoulous 2021 and as such,

risk of bias was rated as high for both studies.

The two systematic reviews contained studies from international centres and as such, there may have been differences in standard of care as well as diagnostic investigations and assessment criteria. As such, there is risk of the evidence being indirect to the UK context.

Although Chong 2021b defined clear eligibility criteria to limit the heterogeneity, studies are heterogeneous with epidemiological, clinical, and methodological diversity, meaning that it may not be possible to generalise the prevalence results.

Conclusion

The review has found that CT imaging, serum assays of biomarkers, ETA culture and BAL are the most common investigations for diagnosing CAPA.

The findings of this review are consistent with current recommendations on diagnosing CAPA.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention**	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
CT Imaging	Based on data from: 1,792 participants in 3 studies.	Three studies (n=1792) found that 10%- 43% of participants had undergone a CT imaging investigation to support CAPA diagnosis.			Evidence from four studies found that CT imaging is a common investigation used to support CAPA diagnosis.
Serum Galactomannan	Based on data from: 957 participants in 2 studies.	Two studies (n=957) found that 25%-47% of participants had undergone a serum galactomannan investigation to support CAPA diagnosis.			Evidence from two studies found that serum galactomannan is a common investigation used to support CAPA diagnosis.
Serum beta-D-glucan	Based on data from: 636 participants in 2 studies.	Two studies (n= 636) found that 3% - 47% of participants had undergone a serum beta-d-glucan investigation to support CAPA diagnosis.			Evidence from two studies found that serum beta-d-glucan is a common investigation used to support CAPA diagnosis.
Endotracheal Aspirate Culture	Based on data from: 370 participants in 3 studies.	Three studies (n = 370) found that 8% - 100% of a participants had undergone a endotracheal aspirate microscopy investigation to support CAPA diagnosis.			Evidence from three studies found that endotracheal aspirate culture is a common investigation used to support CAPA diagnosis
Endotracheal Aspirate Beta-d-glucan	Based on data from: 52 participants in 2 studies.	Two studies (n = 52) found that 4%-5% of participants had undergone a endotracheal aspirate beta-d-glucan investigation to support CAPA diagnosis.			Evidence from two studies found that endotracheal aspirate culture is not commonly used to support CAPA diagnosis.
Endotracheal	Based on data from: 63	One study (n = 63) found that 100%			Evidence from one

Outcome Timeframe	Study results and measurements	Comparator	Intervention	Certainty of the Evidence (Quality of evidence)	Plain language summary
Aspirate PCR		of patients had undergone a endotracheal aspirate PCR investigation to support CAPA diagnosis.			study found that endotracheal aspirate PCR is not commonly used to support CAPA diagnosis
Non-directed Bronchial Lavage Culture					
Non-directed Bronchial Lavage Galactomannan					
Non-directed Bronchial Lavage PCR					
Bronchoalveolar Lavage Microscopy		One study (n=16) found tha1% of participants had undergone a bronchoalveolar lavage microscopy investigation to support CAPA diagnosis.			Evidence from one study found that bronchoalveolar lavage microscopy is not commonly used to support CAPA diagnosis
Bronchoalveolar Lavage Culture					Evidence from three studies found that bronchoalveolar lavage culture is a common investigation to support CAPA diagnosis
Bronchoalveolar Lavage Galactomannan	Based on data from: 518 participants in 3 studies.	Three studies (n=518) found that 17%-30% of participants had undergone a bronchoalveolar lavage galactomannan investigation to support CAPA diagnosis.			Evidence from one study found that bronchoalveolar lavage galactomannan is a common investigation used to support CAPA diagnosis
Bronchoalveolar Lavage PCR	Based on data from: 540 participants in 4 studies.	Four studies (n=540) found that 4%-24% of participants had undergone a bronchoalveolar lavage PCR investigation to support CAPA			Evidence from four studies found that bronchoalveolar lavage PCR is a common

Outcome Timeframe	Study results and measurements	Comparator	Intervention	Certainty of the Evidence (Quality of evidence)	Plain language summary
		diagnosis.			investigation to support CAPA diagnosis
Sputum	Based on data from: 241 participants in 3 studies.	Three studies (n=241) found that 1%-100% of participants had undergone a sputum investigation to support CAPA diagnosis.			Evidence from three studies found that sputum sampling is not commonly used to support CAPA diagnosis

References

148. Chong WH, Neu KP : Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. The Journal of hospital infection 2021;113 115-129 Pubmed Journal

149. Dimopoulos G, Almyroudi M-P, Myrianthefs P, Rello J : COVID-19-Associated Pulmonary Aspergillosis (CAPA). Journal of Intensive Medicine 2021; Journal Website

151. van Grootveld R, van Paassen J, de Boer MGJ, Claas ECJ, Kuijper EJ, van der Beek MT : Systematic screening for COVID-19 associated invasive aspergillosis in ICU patients by culture and PCR on tracheal aspirate. Mycoses 2021;64(6):641-650 Pubmed Journal

Consensus recommendation

Test for antifungal resistance if an Aspergillus isolate is cultured from a CAPA test sample.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel discussed the risks of antifungal resistance and agreed on the importance of testing for antifungal resistance to guide treatment decisions for CAPA. Resistance to azoles, a type of antifungal treatment, would affect the treatment options available and the panel therefore agreed that resistance should be tested for as soon as possible.

The panel understood that waiting for the results of antifungal resistance tests could lead to a delay in effective treatment. Therefore, the panel advised that CAPA treatment could be started based on clinical judgement while waiting for test results. However, the panel emphasised the importance of using the results of antifungal resistance testing to guide definitive treatment.

The panel was not aware of any harms posed to patients from testing for antifungal resistance, but agreed that there were strong benefits from carrying out antifungal resistance testing as it could aid in identifying the optimal treatment for a CAPA patient.

Certainty of the Evidence

No evidence was identified on antifungal resistance testing and diagnostic investigations for CAPA. However, the panel

highlighted the need for a recommendation and stated that despite the lack of evidence on antifungal resistance in CAPA, based on their experience and expertise, this recommendation should be made to guide clinical management and decision making.

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on preferences and values of people in relation to testing for antifungal resistance.

Resources and other considerations

Important issues, or potential issues not investigated

The panel discussed the need for timely testing and diagnostics to investigate CAPA and agreed that testing was important to guide the need for further intervention, and any resource implications may be offset by savings from prompt treatment.

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

Equity

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous 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 the acceptability of testing for antifungal resistance.

Feasibility

No important issues with the recommended alternative

The panel discussed that testing for antifungal resistance may not be routine in all centres, and that feasibility will require access to laboratory expertise.

Rationale

In clinical practice, microbiological investigations can be used to assess antifungal resistance of isolates cultured from test samples. The panel noted the importance of testing for azole resistance to support clinical management decisions and ensure that suitable antifungal treatments are used. They agreed that treatment can be started before test results are confirmed, but should be reviewed when test results are available.

See the British Society for Medical Mycology's guidance on therapeutic drug monitoring of antifungal agents.

Consensus recommendation

Commissioners and local trusts should ensure that results of diagnostic tests for CAPA are available in a timeframe that informs and supports clinical decision making.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel highlighted the benefits of tests results being available quickly. They agreed that this would more often allow treatment to be started only after a confirmed diagnosis, rather than either starting treatment before diagnosis or accepting delays to treatment. Timely test results would reduce the frequency of treatment being used where diagnosis of CAPA is later determined to be negative, supporting antifungal stewardship aims.

Certainty of the Evidence

The panel did not review any evidence related to the time to availability of diagnostic tests for CAPA but advised that a recommendation was needed on this topic to ensure improved standardisation across centres. The panel's recommendation was based on their experience observing the variability in arrangements for processing diagnostic tests for CAPA.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on preferences and values of people in relation to testing for CAPA.

Resources and other considerations

Important issues, or potential issues not investigated

The panel discussed the need for timely testing and diagnostics to investigate CAPA. They were aware that this might require additional resources, or changes to current processes in some areas, but concluded that the impact would be offset by the savings from appropriate diagnosis and treatment for people with CAPA, which could result in fewer days in hospital and reduced mortality among people with CAPA.

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

Equity

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but agreed testing should take place in the same way for all people who are critically ill because of current or previous COVID-19.

No other equity issues were identified.

Acceptability

Important issues, or potential issues not investigated

The panel were not aware of any barriers to acceptability in ensuring test results for CAPA are available in a timeframe that supports clinical decision-making.

Feasibility

No important issues with the recommended alternative

The panel acknowledged that while some centres can already provide rapid turnaround of tests for CAPA, other centres may be required to make changes to practice to adhere to this recommendation, which may be challenging to implement. However, these changes will support improved care for people who are critically ill and have suspected CAPA.

Rationale

The panel noted that results of laboratory tests, in particular fungal antigen tests, are needed to diagnose CAPA. They also noted that if test results are not timely, there could be a delay in treatment or people could have treatments that they do not need. They highlighted the importance of having test results available in an appropriate timeframe to support clinical

decision making and to improve people's outcomes.

Consensus recommendation

Monitor and report testing for, and diagnosis and management of, CAPA in line with local protocols.

Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel discussed the fact that there is insufficient evidence around the prevalence and management of CAPA. The panel agreed that monitoring and reporting on CAPA in line with local protocols would therefore provide useful information which could be used to improve identification and management of people with CAPA in the future.

Certainty of the Evidence

There was no evidence on the monitoring and reporting of diagnostics used for CAPA. As such, the panel highlighted the importance of monitoring and reporting the prevalence and management of CAPA.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data about the preferences and values for monitoring and reporting testing, in people who are suspected to have CAPA.

Resources and other considerations

No important issues with the recommended alternative

The panel discussed the need for monitoring and reporting clinical management of CAPA. Although this could require additional resource demands, the panel concluded that the information being recorded could inform and improve future testing, diagnosis, and management of CAPA through better understanding of when to test and treat.

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

Equity

Important issues, or potential issues not investigated

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous 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 the acceptability of monitoring and reporting for CAPA.

Feasibility

No important issues with the recommended alternative

The panel acknowledged that while some centres already have processes in place to support reporting of CAPA testing, diagnosis, and management, other centres may be required to make changes to practice in order to adhere to this recommendation, which may be challenging to implement. However, these changes could support continuous improvement of care.

Rationale

There is a lack of evidence on the tests used to diagnose CAPA and on treatments for CAPA in people who are critically ill and have, or have had, COVID-19 as part of their acute illness. So, the panel agreed that local protocols should be developed to collect more information on the current prevalence of CAPA and practices for diagnosing and managing the condition.

9.2.2 Treating CAPA

Consensus recommendation

Only use antifungal treatments to treat CAPA if:

- diagnostic investigations support a diagnosis of CAPA or
- the results of diagnostic investigations are not available yet, but CAPA is suspected, and a multidisciplinary team or local protocols support starting treatment.

See NICE's recommendations on diagnosing CAPA.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel considered that there are risks from inappropriate use of antifungal agents, including antifungal resistance and adverse drug effects. The panel concluded that the harms of antifungal therapies used for CAPA outweigh the benefits in people who do not have evidence of invasive pulmonary aspergillosis. The panel agreed that antifungal treatments for CAPA should not be offered unless CAPA has been diagnosed or there is clinical suspicion of CAPA and a local multidisciplinary team including infection specialists (for example, medical microbiologists or infectious disease specialists) support starting treatment.

Certainty of the Evidence

The panel reviewed evidence on the effectiveness of treatments for people with CAPA. A review of the evidence only found one study available that directly investigates the effect of a specific treatment for patients with CAPA, and the panel agreed that the certainty of the evidence was very low. The study did not present evidence on when antifungal treatments for CAPA should be started.

The panel decision was based on their experience and prior knowledge of the clinical use of antifungal agents and when treatment with these agents should be started. They also drew on expertise about antifungal resistance when making this recommendation.

Preference and values

Substantial variability is expected or uncertain

The panel were not aware of any systematically collected data on people's preferences and values.

The panel agreed that it was likely that people would not want to take a treatment with no known benefits but well-

established side effects in situations when there is a low suspicion of CAPA.

Resources and other considerations

Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. However, it is possible that this recommendation will result in a reduction in the use of antifungals when there is low clinical suspicion or before investigations take place.

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

Equity

Important issues, or potential issues not investigated

This recommendation is not expected to cause inequity in any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA.

The panel recognised that the effectiveness and safety of antifungals may differ in pregnant women and children but that there was no evidence in this area.

No other equity issues were identified.

Acceptability

Important issues, or potential issues not investigated

While there was no systematically collected evidence about acceptability, the panel acknowledged that not giving antifungal treatment until CAPA is diagnosed or testing is underway may mean treatment is started later, or not at all, for some people. They acknowledged that clinicians treating people who are hospitalised with COVID-19 will seek to improve people's health outcomes as much as possible, and that families and carers of people who are hospitalised with COVID-19 would be likely to want to ensure that appropriate measures are taken to support people.

Feasibility

No important issues with the recommended alternative

This recommendation may reflect usual practice in some centres. For others it may require adjustments to practice which should be feasible to implement, as this recommendation seeks to ensure appropriate practice and potentially reduce over prescribing.

Rationale

The panel noted that there are risks with antifungal treatments for CAPA, including antifungal resistance and adverse effects. They agreed that treatment should only be started if investigations support a diagnosis of CAPA, or a multidisciplinary team agrees to start treatment.

Clinical Question/ PICO

Population: People hospitalised with COVID-19 and with CAPA
Intervention: Voriconazole
Comparator: Other

Summary

What is the evidence informing this conclusion?

Evidence comes from one cohort study (Bartoletti 2020) that compared the survival outcomes of people hospitalised with COVID-19 and CAPA, who had, or did not have, treatment with voriconazole.

Publication status

The study referenced in this review was a full publication that had been peer-reviewed.

Study characteristics

Bartoletti 2020 was a prospective, multicentre cohort study that aimed to describe the incidence and outcomes of CAPA in a larger cohort of people hospitalised with COVID-19 and receiving mechanical ventilation. A total of 108 people with COVID-19 that were treated in hospitals in Bologna, Italy, between February and March 2020 were screened for CAPA using bronchoalveolar lavage (BAL). Of these, 30 people were identified as having COVID-19 and CAPA.

For further details see the evidence review for treatments for CAPA.

What are the main results?

Of the 30 people who were identified as having COVID-19 and CAPA, 13 were treated with voriconazole, an antifungal therapy. Another 3 patients were treated with a different antifungal therapy, and the study authors do not state what treatment the remaining 14 patients received. Survival at 10, 20, and 30 days after ICU admission was captured for the 30 people with COVID-19 and CAPA, and differences were noted between the group of patients that were treated with voriconazole (n=13) vs. those not treated with voriconazole (n=17). At the end of the 30 days, 7 patients were still alive in each group.

Our confidence in the results

The certainty of the evidence for differences in survival between voriconazole treated CAPA patients vs. CAPA patients not treated with voriconazole was rated as very low, due to the small sample size, serious risk of confounding and imprecision.

The study found that there was no statistically significant difference in survival between CAPA patients treated with voriconazole compared with those not treated with voriconazole at 10, 20, and 30 days after ICU admission. However, the study was not powered to detect a difference for this outcome.

Study authors do not provide baseline characteristics for patients by treatment group, nor do they explain the methods used to assign patients to treatment groups. Since it is unclear if the patients treated with voriconazole are different from patients not treated with voriconazole with regards to characteristics that might impact their survival, there is a serious risk of confounding.

Conclusion

There was low quality evidence from one cohort study (Bartoletti 2020) reporting on possible treatments for CAPA.

The study showed that, in people with COVID-19 and CAPA, there were no statistically significant differences in survival for those treated with voriconazole compared with those not treated with voriconazole, at 10, 20, and 30 days from ICU admission.

Outcome Timeframe	**Study results and measurements**	**Comparator** Other	**Intervention** Voriconazole	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
10-Day Survival 9 Critical	Relative risk 1.43 (CI 95% 0.97 — 2.1) Based on data from 30 participants in 1 studies. [1] (Observational (non-randomized))	647 per 1000 Difference:	925 per 1000 **278 more per 1000** (CI 95% 19 fewer — 712 more)	Very low Due to very serious risk of bias and very serious imprecision [2]	One study found no statistically significant difference in 10- day survival in people having voriconazole compared with people not having voriconazole
20-Day Survival	Relative risk 1.05 (CI 95% 0.58 — 1.88) Based on data from 30 participants in 1 studies.	588 per 1000	617 per 1000	Very low Due to very serious risk of bias and very	One study found no statistically significant difference in 20- day survival in people

Outcome Timeframe	Study results and measurements	Comparator Other	Intervention Voriconazole	Certainty of the Evidence (Quality of evidence)	Plain language summary
9 Critical	[3] (Observational (non-randomized))	Difference:	**29 more per 1000** (CI 95% 247 fewer — 517 more)	serious imprecision [4]	having voriconazole compared with people not having voriconazole
30-Day Survival 9 Critical	Relative risk 1.31 (CI 95% 0.61 — 2.79) Based on data from 30 participants in 1 studies. [5]	412 per 1000 Difference:	540 per 1000 **128 more per 1000** (CI 95% 161 fewer — 737 more)	**Very low** Due to very serious risk of bias and very serious imprecision [6]	One study found no statistically significant difference in 30- day survival in people having voriconazole compared with people not having voriconazole

1. Systematic review [145] with included studies: Bartoletti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 10-day survival between patients treated with voriconazole vs. other therapies.. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.
3. Systematic review [145] with included studies: Bartoletti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 20-day survival between patients treated with voriconazole vs. other therapies., Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.
5. Systematic review [145] with included studies: Bartoletti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 30-day survival between patients treated

with voriconazole vs. other therapies., Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.

References

144. Bartoletti M, Pascale R : Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study. Clinical Infectious Diseases 2020; Pubmed Journal Website

145. Voriconazole versus [not] for CAPA.

Recommended

When considering antifungal treatment for CAPA:

- discuss treatment options with a multidisciplinary team that includes infection specialists
- follow local protocols that include best practice guidance on treating invasive aspergillosis.

There is not enough evidence to recommend specific antifungal treatments for CAPA.

The panel noted the importance of national antifungal stewardship guidance, such as NICE's guideline on antimicrobial stewardship.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel agreed that there is not enough evidence to recommend specific treatments for people with CAPA. Currently there is only one study available that directly investigates the effect of a specific treatment for patients with CAPA. This study (Bartoletti 2021) shows no statistically significant effect of voriconazole on the survival of people with CAPA. The panel noted that this was a small study with 30 participants, and that it provided limited insights on the benefits or harms of voriconazole. No safety outcomes are explored in this study. Based on this information, the panel recommended that decisions around treatments for people with CAPA be discussed with a multidisciplinary team that includes infection specialists, for example medical microbiologists or infectious disease specialists. Decisions around treatments for CAPA should also align with local protocols that include guidance on treating invasive aspergillosis.

The panel acknowledged that in many cases, antifungal therapies may be considered for the management of CAPA. They discussed the risks of antifungal resistance and agreed that the national antifungal stewardship strategy should be consulted if antifungal therapies are being considered for CAPA.

See the NICE's guideline on antimicrobial stewardship for more on the risks from antifungal resistance and recommendations for best practice.

Certainty of the Evidence

Very low

The overall certainty of the evidence for treatments for CAPA is very low.

Currently there is only one study available that directly investigates the effect of a specific treatment for patients with CAPA. In this non-randomised study (Bartoletti 2021), 30 people hospitalised with CAPA were treated either with voriconazole or another treatment, based on clinician discretion. The control group had either no treatment, or another unspecified antifungal.

The panel reviewed this study and found that there is significant risk of bias in the results due to lack of randomisation, and significant imprecision due to the small study size. Additionally, there is a lack of clarity around the comparators used in this study. Evidence did not include young people and children, therefore it was not possible for the panel to discuss differences that might be required between adults and young people

Ultimately, the panel agreed that there is not enough evidence to recommend voriconazole or any other specific antifungal treatment for managing CAPA.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on peoples' preferences about treatments for CAPA. They discussed that, in view of the lack of clear evidence about the treatments, most people would prefer for treatment decisions to be made based on best practice and relevant expertise.

Resources and other considerations

Important issues, or potential issues not investigated

Cost effectiveness was not assessed as part of the evidence review and no formal analysis of resource impact has been carried out. The panel recommended further research on cost-effectiveness of CAPA treatment as part of the research recommendations.

Equity

Important issues, or potential issues not investigated

This recommendation is not expected to cause inequity among any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA

The panel recognised that the effectiveness and safety of antifungals may differ in pregnant women and children, but that there was no evidence in this area.

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. Since this recommendation does not recommend a specific treatment and instead defers to best practice and relevant expertise, it is not expected that there are significant barriers to acceptability. There may be variation in existing practice that the development of local protocols will need to resolve.

The panel acknowledged that some clinicians may feel that voriconazole should be recommended for treatment of CAPA. However, the panel agreed that there is not enough evidence to support the use of voriconazole, and decisions should be taken after discussing with multidisciplinary team.

Feasibility

No important issues with the recommended alternative

This recommendation refers to local protocols and decision-making as part of a multidisciplinary team, and therefore should be feasible to implement.

Rationale

The panel noted the lack of evidence on treatments for CAPA. They agreed that treatment decisions, including on when to start treatment, should be guided by advice from infection specialists, and in line with local protocols and best practice guidelines.

For information on monitoring antifungal treatments, see the British Society for Medical Mycology's guidance on therapeutic drug monitoring of antifungal agents.

Clinical Question/ PICO

Population: People hospitalised with COVID-19 and with CAPA
Intervention: Voriconazole
Comparator: Other

Summary

What is the evidence informing this conclusion?

Evidence comes from one cohort study (Bartoletti 2020) that compared the survival outcomes of people hospitalised with COVID-19 and CAPA, who had, or did not have, treatment with voriconazole.

Publication status

The study referenced in this review was a full publication that had been peer-reviewed.

Study characteristics

Bartoletti 2020 was a prospective, multicentre cohort study that aimed to describe the incidence and outcomes of CAPA in a larger cohort of people hospitalised with COVID-19 and receiving mechanical ventilation. A total of 108 people with COVID-19 that were treated in hospitals in Bologna, Italy, between February and March 2020 were screened for CAPA using bronchoalveolar lavage (BAL). Of these, 30 people were identified as having COVID-19 and CAPA.

For further details see the evidence review for treatments for CAPA.

What are the main results?

Of the 30 people who were identified as having COVID-19 and CAPA, 13 were treated with voriconazole, an antifungal therapy. Another 3 patients were treated with a different antifungal therapy, and the study authors do not state what treatment the remaining 14 patients received. Survival at 10, 20, and 30 days after ICU admission was captured for the 30 people with COVID-19 and CAPA, and differences were noted between the group of patients that were treated with voriconazole (n=13) vs. those not treated with voriconazole (n=17). At the end of the 30 days, 7 patients were still alive in each group.

Our confidence in the results

The certainty of the evidence for differences in survival between voriconazole treated CAPA patients vs. CAPA patients not treated with voriconazole was rated as very low, due to the small sample size, serious risk of confounding and imprecision.

The study found that there was no statistically significant difference in survival between CAPA patients treated with voriconazole compared with those not treated with voriconazole at 10, 20, and 30 days after ICU admission. However, the study was not powered to detect a difference for this outcome.

Study authors do not provide baseline characteristics for patients by treatment group, nor do they explain the methods used to assign patients to treatment groups. Since it is unclear if the patients treated with voriconazole are different from patients not treated with voriconazole with regards to characteristics that might impact their survival, there is a serious risk of confounding.

Conclusion

There was low quality evidence from one cohort study (Bartoletti 2020) reporting on possible treatments for CAPA.

The study showed that, in people with COVID-19 and CAPA, there were no statistically significant differences in survival for those treated with voriconazole compared with those not treated with voriconazole, at 10, 20, and 30 days from ICU admission.

Outcome Timeframe	Study results and measurements	Comparator Other	Intervention Voriconazole	Certainty of the Evidence (Quality of evidence)	Plain language summary
10-Day Survival 9 Critical	Relative risk 1.43 (CI 95% 0.97 — 2.1) Based on data from 30 participants in 1 studies. [1] (Observational (non-randomized))	647 per 1000 Difference:	925 per 1000 **278 more per 1000** (CI 95% 19 fewer — 712 more)	Very low Due to very serious risk of bias and very serious imprecision [2]	One study found no statistically significant difference in 10- day survival in people having voriconazole compared with people not having voriconazole
20-Day Survival 9 Critical	Relative risk 1.05 (CI 95% 0.58 — 1.88) Based on data from 30 participants in 1 studies. [3] (Observational (non-randomized))	588 per 1000 Difference:	617 per 1000 **29 more per 1000** (CI 95% 247 fewer — 517 more)	Very low Due to very serious risk of bias and very serious imprecision [4]	One study found no statistically significant difference in 20- day survival in people having voriconazole compared with people not having voriconazole
30-Day Survival 9 Critical	Relative risk 1.31 (CI 95% 0.61 — 2.79) Based on data from 30 participants in 1 studies. [5]	412 per 1000 Difference:	540 per 1000 **128 more per 1000** (CI 95% 161 fewer — 737 more)	Very low Due to very serious risk of bias and very serious imprecision [6]	One study found no statistically significant difference in 30- day survival in people having voriconazole compared with people not having voriconazole

1. Systematic review [145] with included studies: Bartoletti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 10-day survival between patients treated with voriconazole vs. other therapies.. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.
3. Systematic review [145] with included studies: Bartoletti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 20-day survival between patients treated with voriconazole vs. other therapies., Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study

focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.
5. Systematic review [145] with included studies: Bartoletti 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 30-day survival between patients treated with voriconazole vs. other therapies., Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.

References

144. Bartoletti M, Pascale R : Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study. Clinical Infectious Diseases 2020; Pubmed Journal Website

145. Voriconazole versus [not] for CAPA.

Consensus recommendation

For people having antifungal treatment for suspected CAPA, stop treatment if the results of investigations do not support a diagnosis of CAPA and a multidisciplinary team agrees.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The panel noted that, on occasion, people will start antifungal treatments for CAPA while a diagnosis of CAPA is being confirmed. The panel agreed that antifungal treatments should usually be stopped if subsequent test results do not support a diagnosis of CAPA.

However, the panel also acknowledged that the performance of diagnostic tests for CAPA is variable and may be influenced by the clinical context. Therefore, the panel recommended that, in cases where treatment has been started before a diagnosis of CAPA is confirmed, a multidisciplinary team including infection specialists (for example, medical microbiologists or infectious disease specialists) should review test results. Where tests do not support a diagnosis of CAPA, consider stopping antifungal treatment.

Certainty of the Evidence

The panel decision was based on their experience and prior knowledge of the patient harms of antifungal treatments and national antimicrobial resistance strategies. The panel were not aware of any studies directly investigating the patient harms and risks of antifungal resistance from the use of antifungals for the treatment of CAPA.

Preference and values

No substantial variability expected

The panel were not aware of any systematically collected data on people's preferences and values.

The panel agreed that it was likely that people would not want to continue taking a treatment with no known benefits but well-established side effects where diagnostic testing does not support a diagnosis of CAPA.

Resources and other considerations

Important issues, or potential issues not investigated

No formal analysis of resource impact has been carried out. However, it is possible that this recommendation will result in a shorter course of antifungals for some people.

Cost effectiveness was not assessed as part of the evidence review, but the panel recommended further research on this topic.

Equity

Important issues, or potential issues not investigated

This recommendation is not expected to cause inequity in any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA.

Acceptability

Important issues, or potential issues not investigated

The panel were not aware of any systematically collected evidence about acceptability of stopping treatment for CAPA. It is likely that stopping treatment where results of investigations do not support a diagnosis of CAPA will be acceptable to most people when considering the recognised risk of adverse drug effects and the important antifungal stewardship implications.

Feasibility

No important issues with the recommended alternative

The panel were not aware of any systematically collected evidence about feasibility. This recommendation aims to reduce variation, so there may be a need for a change in practice in some centres.

Rationale

The panel noted the importance of good antifungal stewardship for reducing the risk of adverse effects and antifungal resistance, particularly when treatment is started before diagnosis is confirmed. They wanted to ensure that antifungal treatment would be stopped when investigations do not support a diagnosis of CAPA. However, the panel were aware that interpreting diagnostic test results and confirming a diagnosis of CAPA can be challenging. So, they recommended a multidisciplinary approach when deciding whether to stop treatment.

10. Discharge, follow up and rehabilitation

Info Box

NICE is monitoring evidence on follow up, discharge and rehabilitation. 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.

11. Palliative care

11.1 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.

11.2 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

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**
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.

12. 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*

Is high-flow nasal oxygen effective in reducing breathlessness compared with standard care or conventional oxygen therapy for people in hospital with COVID-19 and respiratory failure when it is agreed that treatment will not be escalated beyond non-invasive respiratory support or palliative care is needed?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: adults over 18 years with COVID-19 having treatment for respiratory failure

I: high-flow nasal oxygen

C:

- *standard care*
- *conventional oxygen therapy*

O:

- *patient experience*
- *symptom improvement*
- *frequency of coughing*
- *assessment of breathing pattern disorder*
- *impact of breathlessness on activities of daily living such as eating, drinking and movement*
- *recovery of sense of smell*
- *practicalities of maintaining high-flow nasal oxygen at home for patients who wish their end of life care to occur at home.*

Subgroups: palliative care

Does a multidisciplinary team agreed approach to weaning from continuous positive airway pressure improve weaning times and result in stopping continuous positive airway pressure for people with COVID-19 and acute respiratory failure?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people with COVID-19 having continuous positive airway pressure for respiratory support

I: multidisciplinary team agreed approach to weaning

C:

- *standard care*
- *different multidisciplinary team approaches*

O:

- *patient experience*
- *symptom improvement*
- *length of time to wean*

What is the effectiveness, cost effectiveness and safety of using a combination of casirivimab and imdevimab at doses other than 8 g for treating COVID-19?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people hospitalised because of COVID-19

I: treatment with different doses of casirivimab and imdevimab

C:

- *recommended dose against different doses*
- *standard care against recommended dose and/or different doses*

O:

- *mortality*
- *progression to invasive mechanical ventilation*
- *progression to non-invasive respiratory support*
- *duration of hospitalisation*
- *adverse events*
- *costs of treatment*
- *health-related quality of life*

What is the effectiveness, cost effectiveness and safety of the combination of casirivimab and imdevimab for treating COVID-19 in people with particular clinical characteristics (for example, people who are seropositive, of unknown serostatus, immunocompromised, or with specific comorbidities and within both the seropositive and seronegative groups, according to vaccination status or history of natural infection)?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people hospitalised because of COVID-19

I: treatment with a combination of casirivimab and imdevimab

C:

- *treatment in people with different clinical characteristics (for example, people who are seropositive, of unknown serostatus, immunocompromised, or with specific comorbidities and within both the seropositive and seronegative groups, according to vaccination status or history of natural infection)*

O:

- *mortality*
- *progression to invasive mechanical ventilation*
- *progression to non-invasive respiratory support*
- *duration of hospitalisation*
- *adverse events*
- *costs of treatment*
- *health-related quality of life*

What is the clinical and cost effectiveness of budesonide for treating COVID-19 in the community in adults, young people and children?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: Adults, young people and children who have COVID-19 and are not in hospital

Subgroups of particular interest:

- *People 18 to 49 years*
- *Children and young people*

I: Inhaled budesonide

C: Inhaled placebo (to accommodate blinding)

O:

- *All-cause mortality*
- *Hospitalisation*
- *Need for oxygen therapy (including thresholds for this decision)*
- *Costs of treatment*
- *Time to recovery*
- *Health-related quality of life*
- *Adverse events*

What risk factors in people who are critically ill and have, or have had, COVID-19 as part of their acute illness are associated with developing COVID-19-associated pulmonary aspergillosis (CAPA)?

Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness. Subgroups of particular interest include children and young people, and pregnant women.

Exposure: any

Outcomes:

- *association of CAPA with individual factors (for example, age, sex, ethnicity, comorbidities, COVID-19 vaccination status,)*
- *association of CAPA with COVID-19 treatments (for example, respiratory support for COVID-19, high-dose corticosteroids, interleukin-6 inhibition)*
- *association of CAPA with length of stay in hospital*

What are the possible outcomes for people who are critically ill and have COVID-19-associated pulmonary aspergillosis (CAPA)?

Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and who have CAPA. Subgroups of particular interest: young people and children, pregnant women, ethnicity, immunosuppression and subgroups who have higher rates of COVID-19

Outcomes:

- *presence of fungal serum biomarkers (for example galactomannan and beta-D-glucan)*
- *measures of inflammation (for example C-reactive protein)*
- *need for respiratory support (for example, invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO])*
- *hospitalisation metrics (for example, mortality, length of hospital stay, admission to and length of stay in intensive care)*
- *long-term morbidity outcomes, functional measures and patient outcomes*
- *results may be stratified (for example, disease severity, use of ECMO)*

In people with suspected COVID-19-associated pulmonary aspergillosis (CAPA), what are the most accurate tests for diagnosing the infection and when should they be done?

Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and suspected CAPA. Subgroups of particular interest include young people and children, and pregnant women.

Diagnostic tests:

- *any methods used to diagnose pulmonary aspergillosis (for example, CT imaging, testing of bronchoalveolar lavage, non-bronchoscopic lavage, endotracheal aspirate, sputum samples, serum assays)*

Reference standard:

- *lung biopsy or postmortem diagnosis*

Target condition:

- *CAPA*

Outcomes:

- *sensitivity and specificity*
- *positive and negative likelihood ratios*

Analysis:

- *optimal time of diagnostic testing*

What are the views, preferences and experiences of people with COVID-19-associated pulmonary aspergillosis (CAPA), and their families or carers, on:

- available tests for diagnosing CAPA
- available treatments for CAPA?

Suggested PIC (Population, Interest, Context)

P: people who have been diagnosed with and treated for CAPA, and their families or carers. Subgroups of particular interest include young people and children, and pregnant women.

I: tests for diagnosing CAPA and treatments for CAPA

C: people who have been diagnosed with, and had treatment for, CAPA in hospital

What are the clinical and cost effectiveness, and the safety, of specific antifungal treatments for treating suspected or confirmed COVID-19-associated pulmonary aspergillosis (CAPA), and the optimal treatment duration? When should treatment be started, stopped or modified?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness and have probable or diagnosed CAPA. Subgroups of particular interest: children and young people, pregnant women, ethnicity, immunosuppression, and subgroups who have higher rates of COVID-19.

I: voriconazole, isavuconazole, liposomal amphotericin B, posaconazole, echinocandins (for example, caspofungin, anidulafungin) and amphotericin B deoxycholate

C: Standard care (usually voriconazole)

O:

- *all-cause mortality (at any time during treatment)*
- *number of people having 1 or more serious adverse events*
- *number of days without respiratory or organ support (organ support includes use of vasopressors and renal replacement therapy)*
- *length of stay in intensive care*
- *number of people having 1 or more adverse events*
- *treatment duration*
- *timing of starting treatment*
- *need for treatment modification*
- *length of hospital stays*
- *need for and duration of invasive mechanical ventilation*
- *need for switching, starting or restarting antifungal treatment*

New

What is the effectiveness and safety of neutralising monoclonal antibodies against different SARS-CoV-2 variants?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people being treated for acute COVID-19 disease and who are not hospitalised with COVID-19

Subgroups of particular interest:

- *ethnicity*
- *children and young people*
- *pregnant women*
- *vaccination status*
- *people with comorbidities*
- *people who are immunocompromised*

I: neutralising monoclonal antibodies

- *combination of casirivimab and imdevimab*
- *sotrovimab*
- *any neutralising monoclonal antibodies that are granted marketing authorisation in the future*

C:

- *standard care*
- *other neutralising monoclonal antibodies*

O:

- *health-related quality of life*
- *adverse events*
- *progression to invasive mechanical ventilation*
- *progression to non-invasive respiratory support*
- *hospitalisation and duration of hospitalisation*
- *mortality*

13. Equality considerations

13.1 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.

13.2 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.

13.3 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.

14. 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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170. Remdesivir for early treatment of COVID-19.

171. Molnupiravir for Covid-19.

172. Molnupiravir for Covid-19.

173. Molnupiravir for Covid-19.

174. Molnupiravir for Covid-19.

175. Remdesivir for early treatment of COVID-19.

176. Molnupiravir for Covid-19.

177. Molnupiravir for Covid-19.

178. Molnupiravir for Covid-19.

179. Molnupiravir for Covid-19.

180. Molnupiravir for Covid-19.

181. Respiratory support for COVID-19.

182. Molnupiravir for Covid-19.

183. Respiratory support for COVID-19.

184. Molnupiravir for Covid-19.

185. Prone positioning for COVID-19.

186. Prone positioning for COVID-19.

187. Respiratory support for COVID-19.

188. Molnupiravir for Covid-19.

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Circular HSC (SQSD) (NICE NG201) 2/22

Subject: NICE Clinical Guideline NG201 - Antenatal care (updates and replaces CG62)

Circular Reference: HSC (SQSD) (NICE NG201) 2/22

Date of Issue: 13 January 2022

Related documents:
HSC (SQSD) 3/13
HSC (SQSD) (NICE NG194) 27/21

For action by:
Chief Executive of HSC Board – **for distribution to:**
All HSC Board Directors – for cascade to relevant staff

Director of Integrated Care, HSC Board – **for cascade to**:
Head of Dental Services
Head of Ophthalmic Services
Head of Pharmacy and Medicines Management
Family Practitioner Services Leads – for cascade to relevant Family Practitioner groups

Chief Executive of Public Health Agency – **for distribution to:**
Director of Public Health and Medical Director – for cascade to relevant staff
Director of Nursing and AHPs – for cascade to relevant staff

Chief Executives of HSC Trusts – **for distribution to:**
Medical Directors – for cascade to relevant staff
Directors of Nursing – for cascade to relevant staff
Heads of Pharmaceutical Services – for cascade to relevant staff
Directors of Acute Services – for cascade to relevant staff
HSC Clinical and Social Governance Leads
Directors of Social Services – for cascade to relevant staff
Directors of Finance – for cascade to relevant staff
AHP Leads – for cascade to relevant staff

Chief Executive, Regulation & Quality Improvement Authority – **for cascade to:** relevant independent healthcare establishments

Chief Executives of HSC Special Agencies and NDPBs

For Information to:
Chair of HSC Board
Chair of Public Health Agency
Chairs of HSC Trusts
Chair of RQIA
NICE Implementation Facilitator NI
Members of NI NICE Managers' Forum

Superseded documents
HSC (SQSD) (NICE CG62) 55/2008

Summary of Contents:
This guideline covers the routine antenatal care that women and their babies should receive. It aims to ensure that pregnant women are offered regular check-ups, information and support.

Status of Contents:
Action

Enquiries:
Any enquiries about the content of this Circular should be addressed to:
Quality Regulation and Improvement Branch
Department of Health
Room D1.4
Castle Buildings
Stormont Estate
Belfast
BT4 3SQ

SGU-NICEGuidance@health-ni.gov.uk

Implementation:
As per circular. Generally, Clinical Guidelines should be implemented within 12 months of endorsement.

Additional copies:
Available to download from
https://www.health-ni.gov.uk/topics/safety-and-quality-standards/national-institute-health-and-care-excellence-nice

Dear Colleagues

NICE Clinical Guideline NG201 - Antenatal care (updates and replaces CG62) - https://www.nice.org.uk/guidance/ng201

The Department has recently reviewed the above NICE guidance and has formally endorsed it as applicable in Northern Ireland.

In accordance with the process outlined in circular HSC (SQSD) 3/13, the following actions should be taken (https://www.health-ni.gov.uk/sites/default/files/publications/dhssps/hsc-sqsd-3-13.pdf)

1. HSC Board / PHA
    a. Identify a Professional Lead who will consider the commissioning implications of the Clinical Guideline and co-ordinate with any other relevant commissioning teams. This Lead will identify any areas where regional planning / investment / commissioning are required, or where there is material risk to safety or quality. These will then be actioned immediately through normal commissioning arrangements or through bespoke arrangements reflecting the nature of the issue / risk.
    b. Ensure that relevant guidance is sent to the appropriate Family Practitioners and other Integrated Care Services as appropriate/relevant.
    c. Seek positive assurance from the HSC Trusts and Integrated Care that the required initial actions have been undertaken within a 3 month period, and that the Guideline has been implemented within a further 9 months (unless otherwise notified by the HSC Trusts).
    d. Where significant investment/ commissioning needs cannot be met within the usual timeframe, agree appropriate arrangements with HSC Trusts. Report to DoH as required at 6 monthly accountability meetings.

2. HSC Trusts
    a. Proceed with targeted dissemination, agree a clinical/management lead to coordinate implementation and consider what has to be done to achieve implementation using a risk based assessment and baseline review as appropriate to support planning. These initial actions should be undertaken within a three month period.
    b. Implement the Guideline within a further 9 months (apart from any elements where significant issues have been raised with the HSC Board/PHA).
    c. Provide positive assurances to the HSC Board that required initial actions have been taken within the 3 month planning period and that the Guideline has been implemented within a further 9 months, where appropriate.
    d. Where significant investment/ commissioning needs cannot be met within the usual timeframe, notify the HSC Board/PHA at the earliest opportunity through the bi-monthly director level meetings and agree appropriate arrangements with them to achieve implementation.

3. RQIA
    a. Disseminate the Guideline to the independent sector as appropriate.

4. HSC Special Agencies and NDPBs
    a. Take account of this Guideline in training and other developments as appropriate.

To inform the planning process, please find attached details from the Departmental review. You should consider and take account of other relevant Departmental policies and strategies in your planning, as well as any legislative / policy caveats identified in the course of the Departmental review.

A full current list of NICE guidance endorsed for application in Northern Ireland can be found on the Department's website at https://www.health-ni.gov.uk/topics/safety-and-quality-standards/national-institute-health-and-care-excellence-nice

Dr Lourda Geoghegan
Deputy Chief Medical Officer

Appendix 1

Endorsed NICE guidance - Details from Departmental review

Reference Number	NICE Clinical Guideline – NG201 https://www.nice.org.uk/guidance/ng201
Title	**Antenatal care**
Summary of guidance	This guideline updates and replaces NICE Clinical Guideline CG62 - Antenatal care (endorsed by DoH in October 2008). The guideline covers the routine antenatal care that women and their babies should receive. It aims to ensure that pregnant women are offered regular check-ups, information and support. This guideline includes recommendations on: • organisation and delivery of antenatal care • routine antenatal clinical care • information and support for pregnant women and their partners • interventions for common problems during pregnancy The guideline uses the terms 'woman' or 'mother' throughout. These should be taken to include people who do not identify as women but who are pregnant. Similarly, where the term 'parents' is used, this should be taken to include anyone who has main responsibility for caring for a baby. **NICE have also published a Clinical Guideline on Postnatal Care which covers the topics of emotional attachment and baby feeding:** ➢ NG194 - Postnatal care (endorsed by DoH in October 2021) - https://www.nice.org.uk/guidance/ng194
Related strategically relevant DoH/ HSC policies	Maternity Strategy for Northern Ireland (2012-2018) https://www.health-ni.gov.uk/articles/maternity-strategy-northern-ireland-2012-2018
Inter-Departmental interest	None

Legislative / policy caveats	This advice does not override or replace the individual responsibility of health professionals to make appropriate decisions in the circumstances of their individual patients, in consultation with the patient and/or guardian or carer. This would, for example, include situations where individual patients have other conditions or complications that need to be taken into account in determining whether the NICE guidance is fully appropriate in their case. **Where this guidance makes reference to Public Health England/NHS screening programmes, Northern Ireland healthcare professionals should refer to Northern Ireland specific information. Available at:** https://www.nidirect.gov.uk/articles/antenatal-infectious-disease-screening https://www.publichealth.hscni.net/publications/pregnancy-book-0 This guidance refers to the *NHS Accessible Information Standard*. Northern Ireland healthcare professionals should refer to *Making Communication Accessible for All - A Guide for Health & Social Care (HSC) Staff*. Available at: http://www.hscboard.hscni.net/download/PUBLICATIONS/PHYSICAL%20AND%20SENSORY%20DISABILITY/Making-Communication-Accessible-for-All-Guide.pdf This guidance refers to some NICE Public Health Guidance which pre-dates the introduction of the DoH process for endorsing Public Health Guidelines. All Public Health Guidance endorsed by DoH can be found at: https://www.health-ni.gov.uk/articles/nice-public-health-guidance This guidance makes reference to NICE Diagnostic Guidance which is not covered under the current service level agreement between the Department and NICE and therefore not endorsed by the DoH. This guidance makes reference to NICE Medicines Practice guidance which is not covered under the current service level agreement between the Department and NICE and therefore not endorsed by the DoH.

Southern Health and Social Care Trust

SHSCT Assurance Response

Reference	**HSC 17/2020** **NatPSA/2020/006/NHSPS**
	Foreign body aspiration during intubation, advanced airway management or ventilation
Date Received from Corporate Governance Office	**24 September 2020**
	01 June 2021
Actual Date of Submission to HSCB	**28 May 2021**
	Melanie McClements – Director of Acute Services **Dr Maria O'Kane – Interim Director of MHD** **Paul Morgan – Director of CYPS**
Clinical Change Lead/ Designation	**MDT working group – Anaesthetics / Cardiology including resuscitation team / Acute Mental Health (ECT) / ED / Acute Paediatrics** **Also working in partnership with PaLS, SHSCT Purchasing and Medical Technical Services**

Loose items unintentionally introduced into the airway during intubation, ventilation or advanced airway management (known as foreign body aspiration [FBA]) can lead to partial or complete airway blockage or obstruction. If the cause is not suspected, this can be fatal.1 Complications following FBA may not be immediately recognised due to sedation and anaesthesia and may be postoperatively misdiagnosed as asthma, chronic obstructive pulmonary disease (COPD), or stridor.

In a recent six-year period, five incidents were identified where a foreign body (FB) was aspirated, and a further four incidents where the FB was identified during intubation and removed. The most common types of FB identified in incident reports were transparent backing plastic from electrocardiogram (ECG) electrodes and plastic caps of unclear origin. This is likely to be an under-estimate of the true number of incidents as many may go unrecognised

Notes

A. NHS Supply Chain are working with suppliers to support availability of products within the compliance timeframe.

B. This Alert does not require changing to the large sheet/coloured/patterned type in areas other than those specified in actions 1a and 1b. However, changing to them across the whole organisation will likely be easier; compared with maintaining ongoing checks and barriers against one type being unintentionally reintroduced into the areas where they should never be used.

C. Caps for breathing system hoses are available, either as a separate item within the system packaging, or pre-attached on a hinge joint for some coaxial systems. The circuit mount on anaesthetic machines should be used in line with manufacturer instructions for use (IFU) and infection control guidance.

Recommendation 1 Amend current supply arrangements, and introduce ongoing controls on purchasing, to ensure ECG/ECT electrodes have either large sheet backing for multiple electrodes or fully coloured or patterned individual backing in: a) all areas where intubation or advanced airway management regularly	Procurement and Logistics Service (PaLS) have confirmed that they have contacted the following suppliers (Ambu, Skintact, Kendell Coviden and 3M) to ascertain if they were aware of the PSA and to clarify what actions these supplier intend to take to manage the risks outlined in the alert. It has been confirmed these suppliers are in the process of changing the specification of their product to ensure clear backing on		The SHSCT has confirmation from PaLS that the new electrode products will be issued from 01/06/21. This will be monitored and any concerns secondary to a delay will be escalated to PaLS by the SHSCT CAG representative.	PaLS	01/06/2021

occurs (including theatres, emergency departments, ECT suites, and emergency ambulances). b) all resuscitation trolleys / emergency response kits containing intubation or advanced airway equipment and containing ECG electrodes	electrodes is changed to coloured / patterned backing, as per the PSA recommendations. This, once done is a sustainable way to prevent aspiration of foreign body. Follow up correspondence with PaLS in May 2021 has confirmed the new products will be issued from 01/06/21. Checks have been carried out within the SHSCT to ensure these listed clinical specialities only use those products on contract. A spreadsheet has been developed to hold a record of this information. As an interim measure until the new specification of ECG electrode becomes available a local decision has been taken in higher risk clinical areas to use a different stock item has a more visible electrode backing.				

Recommendation 2 Identify a named individual to take executive responsibility for coordinating the delivery of the actions required within this patient safety alert and this circular	Within the SHSCT a cross directorate MDT task and finish group has been established to review and implement the requirements of this PSA. This has required involvement from Finance, Acute Services, Mental Health and CYPS directorates.		A meeting has been arranged with PaLS for 10/06/2021 to ascertain how best to manage these alerts going forward given that PaLS are a key stakeholder in the required implementation plan and as such interagency working is pivotal to ensure these alerts are managed appropriately and effectively.	Alison Rutherford (AD – Finance) Caroline Beattie (Interim Senior Manager – Risk and Learning)	10/06/2021
Recommendation 3 Amend current purchasing, and introduce ongoing controls on purchasing, to ensure all breathing system components have either no port or ports with tethered caps	Engagement both within the SHSCT task and finish group and regionally with other Trust colleagues has identified that this action has significant scope and requires stakeholder engagement with PaLS to support a regional co-ordinated approach in this. All contracts awarded by PALS have contract adjudication representatives from Trusts involved (where regional) who input to the specification of the goods being purchased by PALS. It is therefore important that staff nominated to represent the Trust on the CAG ensure the correct specification of products.		A meeting has been arranged with PaLS for 10/06/2021 to ascertain how best to manage patient safety alerts going forward given that PaLS are a key stakeholder and as such interagency working is pivotal to ensure these alerts are managed appropriately and effectively. As part of this meeting the timescales for when the new ECG electrode products will be available for use is to be confirmed.	Alison Rutherford (AD – Finance) Caroline Beattie (Interim Senior Manager – Risk and Learning)	10/06/2021

Recommendation 4 Review other equipment used for, or alongside, intubation and advanced airway management during resuscitation, anaesthesia or ventilation, and if any include small loose components, purchase safer alternatives if available.	A SHSCT short life working group has been established with representatives from ED, ATICS, Maternity, Cardiology, ECT (MHD), Acute Paediatrics (CYPS) with ongoing discussions with Directorate of Finance regarding how best to progress recommendations 1-3. Each of the group representatives has shared the alert with their respective teams. It has also been an ongoing agenda discussion at the Acute S&G Forum and Acute Professional Leads forum. It has also been disseminated by the Directorate Governance teams. Following contact with PaLS a list of stock electrodes used within the Trust was provided. These items were reviewed by the SHSCT working group at the inaugural meeting held on 9 March 2021. Further follow up on a number of other manufacturer products was undertaken with PaLS and confirmed as stock items. Within the Trust electrode specification was confirmed for Acute Mental Health (ECT), Emergency Departments, Cardiology		Ongoing discussions required regionally in relation to purchasing of safer alternatives – to be discussed at PaLS meeting on 10 June 2021	MDT Working Group including discussion with PaLS	10/06/2021

	services, ATICS, Radiology, Paediatrics / NNU and resuscitation service. As an interim measure, a decision was taken within ATICS to use the L-00-S electrode product instead of the M-00-S as the white backing provided more visibility and reduced the risk of accidental entry into any airway equipment. A list of what products are currently being used in each of the clinical specialities has been collated.				
Recommendation 5 Develop or amend local protocols to include: a) a process step that requires any pre-prepared intubation and advanced airway management devices to be covered or protected until used; this may include reinserting them in their packaging. b) a process step to close the end of the reusable breathing system hose in between patient cases; either using bespoke caps supplied with the system or by attaching to the circuit mount.	Dissemination of this SAI has been ongoing and will continue to be brought to the appropriate staff's attention through department/ clinical areas safety meetings and staff meetings. Following discussion at meeting 23/03/2021 it was the consensus that is outlined in this recommendation is seen as best practice. All intubation equipment is single/ individual use and kept in packaging until needed. Closing off the end of the breathing system hose forms part of standard clinical practice.		Ongoing monitoring and review		

	It has also been confirmed that the ECG monitoring electrodes (3 lead monitoring) stocked on the resuscitation trolley should be placed on the top of the trolley along with the defibrillation pads. They should not be stored in the airway drawer of the trolley. All equipment stocked on the resuscitation trolley should be kept in the product packaging until such times as required. Breathing circuits are not stocked on the resuscitation trolleys. As a further safeguard to ensure there is ongoing safety awareness of this risk the SHSCT Crash trolley checklist form has been updated to ensure the safety message in this alert is included against the ECG electrode check section. Within ATICS the existing protocol has been updated to include relevant safety information relating to this recommendation.				

	CYP Position: • *Any prep-prepared intubation and advanced airway management devices to be covered or protected until used, this may include reinserting them into their packaging* It can be confirmed that all air way/ intubation products are single use and individually wrapped. These are not opened until required. **Neonatal Position:** • *Any prep-prepared intubation and advanced airway management devices to be covered or protected until used, this may include reinserting them into their packaging* In neonatal items are supplied in individual packages and are only opened at the point of use. Items are not opened and left prepared for use for any period longer than immediate use.				

	• *A process to close the end of the reusable breathing system hose in between patient cases; either using bespoke caps supplied with the system or by attaching to the circuit mount* In neonatal the breathing system hose is single patient use and is changed between each patient. When the breathing system hose is set up ready for use , the end is replaced with a flow sensor and an artificial test lung . No caps are used				
Ensure implementation by 1 June 2021	Following approval this Assurance response was submitted to the HSCB Safety Alerts team on 28 May 2021				

Compliance Scale

100% Compliance	**70-99% Compliance**	**40-69% Compliance**	**0-39% Compliance**	**Pending**	**Not Applicable**

From the Acting Head of Safety Strategy Unit
David Wilson

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

Reference: HSC (SQSD) 17/20 **Date of Issue: 24 September 2020**

Foreign body aspiration during intubation, advanced airway management or ventilation

For Action:

Chief Executives HSC Trusts
Chief Executive HSCB
Chief Executive PHA
Chief Executive BSO
Chief Executive RQIA

Related documents:

Implementation: 1st June 2021

DoH Safety and Quality Circulars including Patient Safety Alerts can be accessed on: https://www.health-ni.gov.uk/topics/safety-andquality-standards/safety-and-quality-standards circulars

SUMMARY

NHS E&I has issued Patient Safety Alert **NatPSA/2020/006/NHSPS (attached at TAB A).**

This alert highlights that loose items may be unintentionally introduced into the airway during intubation, ventilation or advanced airway management (known as foreign body aspiration [FBA]) and this can lead to partial or complete airway blockage or obstruction. This can be fatal if the cause is not detected. The alert also highlights that complications following FBA may not be immediately recognised due to sedation and anaesthesia and may be postoperatively misdiagnosed as asthma, chronic obstructive pulmonary disease (COPD), or stridor.

ACTION

Chief Executives of HSC Trusts are asked to:

Chief Executives of HSC Trusts are asked to work with BSO Procurement and Logistics Service to**:**

1. Amend current supply arrangements, and introduce ongoing controls on procurement, to ensure ECG/ECT electrodes have either large sheet backing for multiple electrodes or fully coloured or patterned individual backing in:

   a) all areas where intubation or advanced airway management regularly occurs (including theatres, emergency departments, ECT suites, and emergency ambulances).

b) all resuscitation trolleys/emergency response kits containing intubation or advanced airway equipment and containing ECG electrodes.

2. Identify a named individual to take executive responsibility for coordinating the delivery of the actions required within this patient safety alert and this circular.

3. Amend current procurement specifications, and introduce ongoing controls on procurement of these items, to ensure all breathing system components have either or no port or ports with tethered caps.

4. Review other equipment used for, or alongside, intubation and advanced airway management during resuscitation, anaesthesia or ventilation, and if any include small loose components, purchase safer alternatives if available.

5. Develop or amend local procedures to include:

   a) a process step that requires any pre-prepared intubation and advanced airway management devices to be covered or protected until used; this may include reinserting them in their packaging.

   b) a process step to close the end of the reusable breathing system hose in between patient cases; either using bespoke caps supplied with the system or by attaching to the circuit mount.

Chief Executives, HSCB and PHA should:

- Disseminate this circular to any relevant HSCB/PHA staff
- Consider it through the normal HSCB/PHA processes for assuring implementation of safety and quality alerts

BACKGROUND

In a recent six-year period, NHS Improvement have identified five incidents where a foreign body (FB) was aspirated, and a further four incidents where the FB was identified during intubation and removed. The most common types of FB identified in incident reports were transparent backing plastic from electrocardiogram (ECG) electrodes and plastic caps of unclear origin.

During their investigation they also identified that:

- some breathing circuit components with untethered caps are still available to purchase
- airway trays for routine or planned procedures are frequently prepared in advance, but left uncovered, and as a result loose FBs may become attached to breathing system devices

- the ends of breathing system hoses are not routinely closed between patient cases; allowing the potential for loose plastic objects to enter the breathing hose system.

NHS E&I believe that the number of reported incidents is likely to be below the true number of incidents occurring as FBs introduced during ventilation, intubation or advanced airway management may not always be recognised at the time and post-procedure, symptoms are unlikely to be specifically associated with the potential for a FBA.

Enquiries:

Any enquiries about the content of this circular should be addressed to:

Safety Strategy Unit
Department of Health
Room D1.4
Castle Buildings
BELFAST
BT4 3SQ
Personal Information redacted by the USI

Yours sincerely

Personal information redacted by USI

David Wilson
Acting Head of Safety Strategy Unit

From the Interim Chief Nursing Officer
Linda Kelly

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

VIA EMAIL:

Care Home Providers
Chief Executives & Directors of Nursing
(Trusts)

Department of Health
C4.20
Castle Buildings
Stormont Estate
Belfast BT4 3SQ
Tel: Personal Information redacted by the USI
Email: Personal Information redacted by the USI

Date: 14 January 2022

Dear Colleagues,

LATEST REVIEW OF "VISITING WITH CARE – A PATHWAY"

The Public Health Expert Reference Group within the Public Health Agency has recently completed its latest formal review of surveillance information as required in "Visiting With Care – A Pathway".

Review Outcome
Based on the analysis of that surveillance information (see details at Annex A), I can confirm that the Public Health advice is that we should remain at the second full stage of the Pathway – "Gradual Easing". The next 4-weekly review will be completed in early February and we expect to be able to issue a further update shortly thereafter.

Key Messages
I would like to take this opportunity to reinforce the key message that, since the effectiveness of COVID-19 vaccines and vaccine coverage is apparent at this stage in reducing the severity of COVID-19 infections and the risk of hospitalisation, it is crucial that care home mangers and Trusts continue to encourage uptake of the COVID-19 vaccination (including booster) for care home staff and continued engagement with the regular testing programmes for staff, visitors and Care Partners.

Care Partner Scheme
It is also important to reaffirm that when a Care Home is experiencing an outbreak, care partner arrangements can continue in place for those care partners who are demonstrably infection free. Ongoing participation in the regular testing regime by anyone seeking to maintain a care partner status will allow this assessment to be made.

I would ask that this update be circulated appropriately to facilities, residents/families and staff as soon as possible. Thank you all, once again, for the efforts you continue to make to deliver top quality care in these difficult times.

Yours sincerely,

LINDA KELLY
Interim Chief Nursing Officer

cc: Trust Directors of Older People Services
Sean Holland
Dr Michael McBride
Dr Lourda Geoghegan
Tim Johnston
Debbie Murray
Geraldine Traynor
William Stewart
Janet Humphries
Pauline Shepherd – IHCP
Leslie-Anne Newton – ARC
Vivian McConvey - PCC
Sandra Aitcheson – PHA
Malachy Finnegan - RQIA

Annex A

Summary of Public Health Expert Reference Group Findings:

Care Home Outbreaks

There has been a rapid increase in COVID-19 cases and outbreaks in care homes since the end of December 2021. Over one third of all care homes in NI are now reporting active COVID-19 outbreaks in NI, with 177 confirmed outbreaks as of 5 January 2022. The majority of outbreaks are declared due to infections in staff members or care partners (73%), 31% due to staff and residents, and 6% in residents only. The vast majority of the outbreaks are small with only a very small number (<5) of homes have experienced high numbers of cases.

Importantly, the severity of illness is low overall to date, with very small numbers of hospital admissions noted.

Community Incidence

The Omicron variant has spread at an unprecedented rate throughout the community, replacing Delta as the dominant COVID-19 variant with 94% of new cases now being identified as Omicron. NI has recorded the highest rates of new confirmed cases of COVID-19 across the UK in the past 2 weeks. The 7 day rolling average 407.5 per 100,000 population on 30 December 2021, (UK 282.8 on same day). This level of infection in NI is unprecedented.

Mortality associated with COVID-19 in care home settings:

Continued low levels of mortality associated with COVID-19 in care home settings are noted. 5 deaths in Care homes where COVID-19 was listed on the death certificate are reported in the 5 weeks between 19th November and 17 December 2021 (NISRA). The highest number of deaths in a single week during this wave was 10 as compared to 35 in the second wave and 72 in the first wave.

Care home deaths as a proportion of total deaths where COVID-19 is noted on Death certificates remains significantly lower than in all previous waves (NISRA).

Hospital admissions

Data on severity of disease associated with Omicron remains limited, however, early indications suggest that it is associated with milder illness, even for hospital admissions. However, whilst disease severity may be less, the sheer volume of infection with Omicron across the population is likely to result in more admissions to hospital. In addition normal winter pressures associated with respiratory illness are also to be expected across the HSC system (very low rates of influenza circulating).

Whilst numbers of admissions to hospital from Care Homes remain very small, data on disease severity will continue to be monitored closely in the coming weeks in the care home population.

ICU occupancy has remained relatively stable since the beginning of October with 31 ICU inpatients on the 3 January 2022.

Vaccine uptake rates

Early evidence suggests that a third booster dose is required to provide vaccine effectiveness against symptomatic disease with the Omicron variant i.e. 2 doses which were effective against Delta variant may not be enough to protect against severe illness with Omicron.

Care home reported uptake rates indicate that:

- 95% residents have had 2 doses, 89% have received a booster.
- 80% staff have had 2 doses, 58% have received a booster.

Information on vaccination uptake has been shared with Trusts to support continued work to further increase levels of vaccine cover.

HSCB Service Notification for the managed entry of new medicines and technologies

Health and Social Care Board

1.	**Treatment & Condition** Budesonide orodispersible tablet for inducing remission of eosinophilic oesophagitis
2.	**Associated appraisal body *&* Summary of ruling** Technology appraisal guidance [TA708] Published: 23 June 2021 https://www.nice.org.uk/guidance/TA708 • Budesonide as an orodispersible tablet (ODT) is recommended as an option for inducing remission of eosinophilic oesophagitis in adults. This recommendation is not intended to affect treatment with budesonide ODT that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.
3.	**Number of people in Northern Ireland expected to take up service/therapy** According to the NICE Resource Impact Statement that accompanies NICE TA708, eosinophilic oesophagitis is a rare condition affecting around 13,000 people in England. By a pro rata calculation this equates to an estimated patient number in NI of 39 people.
4.	**Patient Access Scheme Availability** (Yes/No) Not applicable
5.	**Infrastructure Requirements** Any additional infrastructure costs associated will be dealt with as part of the routine commissioning process.
6.	**Expected implementation period** There is no impediment to immediate implementation for new patients.
7.	**Commissioning arrangements** Budesonide as an orodispersible tablet for this indication is commissioned by HSCB. Providers are HSC hospital trusts, and primary care.
8.	**Monitoring arrangements** Through usual monitoring of primary care drug budgets.

9.	**DoH (NI) Legislative/Policy Caveats** This advice does not override or replace the individual responsibility of health professionals to make appropriate decisions in the circumstances of their individual patients, in consultation with the patient and/or guardian or carer. This would, for example, include situations where individual patients have other conditions or complications that need to be taken into account in determining whether the NICE guidance is fully appropriate in their case. The Rural Needs Act NI 2016 has been considered and this guidance, which is purely of a technical nature, is not regarded as falling within the scope of the act.

NICE National Institute for Health and Care Excellence

NICE guidance

Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban

Technology appraisal guidance
Published: 12 May 2021
www.nice.org.uk/guidance/ta697

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so 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.

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.

Contents

1 Recommendations

1.1 Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if:

- the bleed is in the gastrointestinal tract, and
- the company provides andexanet alfa according to the commercial arrangement.

1.2 Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator.

Why the committee made these recommendations

Apixaban and rivaroxaban are anticoagulants used for preventing and treating thromboembolism (blood clots). They can increase the risk of major bleeding, which may be life-threatening. If someone has a major bleed the anticoagulation effects need to be reversed. Andexanet alfa aims to reverse the effects of apixaban and rivaroxaban, in case of uncontrolled or life-threatening bleeding.

There is no clinical trial evidence directly comparing andexanet alfa with existing treatments, including prothrombin complex concentrate. An indirect comparison suggests that andexanet alfa improves survival in people with gastrointestinal bleeding or ICH, but lowers survival for people with bleeds in other parts of the body. However, there are differences between the populations in the 2 studies, so the results of the indirect comparison are uncertain. There is no robust evidence that andexanet alfa reduces long-term disability in ICH.

Because of the limitations of the clinical evidence, the cost-effectiveness estimates for andexanet alfa are uncertain. They are likely to be within what NICE considers a cost-effective use of NHS resources for gastrointestinal bleeding, but not for ICH or bleeds in other parts of the body. Therefore, andexanet alfa for reversing anticoagulation is recommended for routine use only in gastrointestinal bleeding. It is recommended only in research in ICH.

2 Information about andexanet alfa

Marketing authorisation indication

2.1 Andexanet alfa (Ondexxya, Alexion) has a conditional marketing authorisation for 'adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price for andexanet alfa is £11,100 per 4-vial pack of 200 mg of powder for solution for infusion (excluding VAT, BNF online accessed March 2021). The average cost of a course of treatment at list price is £15,000 per patient.

2.4 The company has a commercial arrangement. This makes andexanet alfa available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Portola Pharmaceuticals, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

In March 2020, the appraisal committee decided not to recommend andexanet alfa within its marketing authorisation. In June 2020 and February 2021 the committee discussed the following issues, some of which were new issues that were not included in the first appraisal consultation document.

Treatment pathway and clinical need

Direct anticoagulants are associated with a serious risk of major bleeding

3.1 Direct anticoagulants such as apixaban and rivaroxaban are used for preventing and treating thromboembolism in conditions such as deep vein thrombosis and pulmonary embolism, and for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. Although anticoagulants have a greater overall benefit than risk, major bleeding is a serious risk. People with a major bleed are at an increased risk of death and an increased risk of subsequent thrombotic events when anticoagulation is interrupted. The patient experts explained that thrombotic events can have a substantial physical and psychological effect on people's lives. Treatment for a thrombosis can affect employment, family planning, travel and social life. Also, many people fear having further blood clots. Anticoagulants therefore are of benefit to people, but they increase the risk of a major bleeding event. The committee concluded that direct anticoagulants are associated with a risk of major bleeding events.

There is a clinical need for effective anticoagulation reversal agents

3.2 The patient experts explained that anticoagulation treatments are accepted by people because they are lifesaving, but there are concerns about safely managing anticoagulation if a major bleed happens. If bleeding is life-threatening then anticoagulation needs to be reversed. Treatment is challenging

if there is no reversal agent and relies on treating symptoms until the effects of the anticoagulant stop, in line with the normal half-life of the drug. The clinical experts explained that established clinical management often includes prothrombin complex concentrate (PCC), which is used outside of its marketing authorisation to reverse a major bleed. However, there is limited clinical evidence to support its use. The patient experts explained that there is an unmet need for a safe reversal agent for direct factor Xa anticoagulants such as apixaban and rivaroxaban. The committee concluded that the availability of an effective reversal agent would be greatly valued by people and healthcare professionals.

Clinical need is increasing because of changes in clinical practice

3.3 The patient experts explained that the recently published NICE guideline on venous thromboembolic diseases recommends offering apixaban or rivaroxaban as first choice for anticoagulation, including for people with cancer-associated thrombosis. Also, NHS England's clinical guide for managing anticoagulation services has been updated for the COVID-19 pandemic. This has resulted in more people starting or switching treatment to a direct oral anticoagulant. The patient experts explained that anxiety will be high because of COVID-19 and a reversal agent not being available would increase people's concerns. The committee concluded that because more people are having direct oral anticoagulants there is an increased need for a specific reversal agent.

Most relevant population

It is not appropriate to combine all bleed types for decision making

3.4 The clinical evidence came from ANNEXA-4, a single-arm trial of andexanet alfa in people taking a direct factor Xa inhibitor who had an acute major bleed. Initially, the company submitted results for 3 groups: the whole trial population, a cohort of people with intracranial haemorrhage (ICH) and severe gastrointestinal bleeds, and a cohort of people with ICH alone. After technical engagement, the company also provided results for a cohort of people with severe gastrointestinal bleeds alone. The clinical experts explained that different types of bleeds should be considered separately because the nature of the bleeds, their treatment and outcomes vary. The clinical experts explained

that most gastrointestinal bleeds can be managed using measures such as endoscopy, embolisation or surgery. The committee noted that ICH may happen within the brain tissue (intracerebral) or outside the brain (subdural or subarachnoid) and can lead to mortality and long-term disability. They differ from gastrointestinal bleeds in that they happen into a closed rigid structure, the skull, rather than into an air-containing space like the gastrointestinal tract. Treatment options are very limited for ICH, particularly if the bleed is in the brain tissue where damage happens at the time of the bleed and surgery is not usually feasible. The clinical experts explained that outcomes and risk of further bleeding after initial treatment varies depending on the location and cause of an ICH. The effect of bleeding at sites of the body other than intracranial or the gastrointestinal tract would vary considerably, depending on where the bleed happened. For example, a bleed into the eye could lead to blindness in that eye. The committee concluded that different types of bleeds should be considered separately for decision making.

Clinical evidence

The evidence on clinical events is limited to 30-day mortality

3.5 The committee noted that the 2 primary outcomes in the trial were both haematological: change in 'anti-factor Xa activity' and haemostatic efficacy. The only outcome related to clinical events was the safety end point of 30-day mortality. However, the trial excluded all patients with an expected lifespan of less than 1 month. For ICH there were additional exclusions related to larger bleeds (volume over 60 ml) and reduced consciousness (a Glasgow Coma Score below 7). Therefore, the generalisability of the 30-day mortality data from ANNEXA-4 to routine NHS practice is questionable, particularly for ICH. In their response to technical engagement, the clinical experts also questioned the definitions of haemostatic efficacy in relation to intracerebral haemorrhage (ICH). A poor outcome was defined in ANNEXA-4 as more than 35% increase in haematoma volume. The experts considered that haemostatic efficacy as defined in the trial could not be considered directly predictive of clinical outcomes. The clinical expert explained that ICH types are heterogenous and have different management strategies and outcomes. They noted that outcomes after ICH are related to bleed volume. A large bleed volume at first presentation is a poor prognostic sign, and patients with large bleeds were excluded from ANNEXA-4. At the first committee meeting, the clinical experts stated that not

all bleeds increase in size. However, at the third committee meeting, 1 expert stated that an increase in bleed size would be likely for people taking an anticoagulant. The committee noted that no data on ICH growth was available for people on anticoagulants not treated with andexanet alfa. The clinical experts agreed that it is difficult to say that an increase of less than 35% for ICH can be considered a positive outcome or good haemostatic efficacy as defined in the trial. At the second consultation, the company submitted the results of a Delphi panel survey of clinical experts that supported the assumption that limiting haematoma expansion would improve morbidity and quality-of-life outcomes. The company noted that this was in line with results from a meta-analysis from Davis et al. (2006). However, the committee agreed that the Delphi panel represented opinion rather than offering robust evidence on key areas of uncertainty, and that the results should be interpreted with caution. The committee concluded that the clinical evidence available for andexanet alfa was limited to only 30-day mortality in a trial that had several potentially relevant exclusion criteria.

There is no evidence directly comparing andexanet alfa with established clinical management and the indirect comparison has limitations

3.6 Because ANNEXA-4 is a single-arm trial there is no direct evidence for the efficacy of andexanet alfa compared with other treatments, which added to the uncertainty about its benefit in clinical practice. The company used the ORANGE study for the comparison with established clinical management. ORANGE was a UK observational study in people taking anticoagulants who were admitted to hospital with a major bleed. The company used a subgroup from the ORANGE study who had had PCC, which the company considered included people with severe enough bleeds to have andexanet alpha in clinical practice. These data were used in an indirect treatment comparison with andexanet alpha. ORANGE did not exclude patients with an expected survival less than 1 month, or those with the most severe intracranial bleeds, that is an intracerebral bleed volume of more than 60 ml or a Glasgow Coma Score lower than 7, which were exclusion criteria for ANNEXA-4. The committee noted that this could affect the comparability of results for 30-day mortality, particularly in the case of intracerebral bleeds for which there were added exclusion criteria. The company explained that the proportion of patients excluded based on the 30-day survival criterion was extremely low. However, the committee noted

that some patients may not have been screened for inclusion if the clinicians considered that they were too ill to meet the criteria or the intracerebral bleed was too severe. The clinical expert pointed out that every patient with a life-threatening gastrointestinal bleed should have been screened for inclusion unless they were on a known end-of-life pathway. The committee concluded that the 30-day mortality evidence for andexanet alfa compared with established clinical management using PCC had limitations.

The indirect treatment comparison predicts a reduced 30-day mortality with andexanet alfa compared with established clinical management including PCC, but the results are uncertain

3.7 The company did a propensity score matching analysis to compare 30-day mortality rates from ANNEXA-4 and ORANGE. The results showed a reduced 30-day mortality with andexanet alfa compared with PCC for the gastrointestinal cohort and the ICH cohort but not for the 'other major bleeds' cohort (pericardial, retroperitoneal, intraspinal and intraocular bleeds), where the 30-day mortality was higher. The committee understood that important prognostic factors such as severity and volume of the bleed could not be included as covariates, because these were not collected in ORANGE. It also noted that 30-day mortality was a key driver of the economic model. The company explained that only patients from ORANGE who had PCC were matched to patients in ANNEXA-4. The company assumed that patients who had PCC in ORANGE were a good proxy for those with more severe bleeds, because PCC is used off-label and would be reserved for more severely affected patients. The clinical experts explained that severity and volume of bleeds are the primary prognostic factors for bleed-related mortality. The committee considered that without key prognostic factors accounted for, the results of the propensity score matching analysis were uncertain. The committee also noted that for gastrointestinal bleeds, no comparative data were available on what other treatments people had in the 2 studies, particularly endoscopic therapy. The clinical experts explained that in the absence of a randomised controlled trial it was very difficult to reach any conclusion about the clinical benefit of andexanet alfa compared with established management, including PCC. The committee considered that the propensity score matching analysis predicted a reduced 30-day mortality for the gastrointestinal cohort and the ICH cohort, but the results were uncertain.

Andexanet alfa is likely to reduce 30-day mortality for people with gastrointestinal bleeds

3.8 The committee had concerns about the effect of andexanet alfa on 30-day mortality for gastrointestinal bleeds, because the ANNEXA-4 trial excluded patients with an expected survival of less than 1 month. In its response to the first appraisal consultation document, the company submitted an analysis of in-hospital mortality results from a US multicentre real-world study of patients who had andexanet alfa within its licensed indication. The study did not exclude patients with an expected survival of less than 1 month, unlike ANNEXA-4. However, the criteria for who had treatment in the study and what other treatments the patients had were not clear. The committee noted that in-hospital mortality in the real-world study was lower than in ANNEXA-4, even though an exclusion criterion based on expected survival was not applied. The committee considered that this potentially supported the generalisability of the trial outcomes to a broader population. The committee also considered the Rockall score submitted by the company for patients with gastrointestinal bleeds in ANNEXA-4. The clinical expert explained that the Rockall score is a validated predictor of mortality. In ANNEXA-4, patients had a lower mortality rate than predicted by the Rockall score, suggesting that andexanet alfa reduces mortality. The clinical expert noted that this data increased confidence about the benefit of andexanet alfa. The committee noted that the Rockall score was not developed in an anticoagulated population. However, it considered that the Rockall score submitted by the company was broadly supportive of andexanet alfa reducing 30-day mortality in patients with gastrointestinal bleeds. Nevertheless, in the absence of any direct evidence, there were still some uncertainties around the efficacy of andexanet alfa in gastrointestinal bleeds. This is particularly because other treatments are available and andexanet alfa itself carries a risk of thrombosis. The clinical expert noted that andexanet alfa would be best used as part of a major gastrointestinal bleed protocol, in line with its use in ANNEXA-4. The committee concluded that andexanet alfa is likely to reduce 30-day mortality for people with life-threatening or uncontrolled gastrointestinal bleeds.

The extent that andexanet alfa reduces mortality in ICH is unclear

3.9 The indirect treatment comparison predicted that andexanet alfa reduces mortality in people with ICH. The committee considered this to be plausible but

recalled its concern that the 30-day mortality data for andexanet alfa came from a trial that excluded people with a predicted life expectancy of less than 30 days, and also excluded people with the largest bleed volumes. The Delphi panel reached consensus that for intracerebral bleeds, the population that would be offered treatment should be similar to the clinical trial population. This means that some people with major intracranial bleeds would not be treated in clinical practice, based on a projected life expectancy, bleed volume and clinical judgements about their prognosis, even though the marketing authorisation did not exclude these people. However, the clinical experts emphasised the difficulty in deciding when not to use andexanet alfa in clinical practice, because treatment should be given as soon as possible, and the decision may fall to relatively inexperienced doctors. For this reason, it is likely that all people would be treated in the NHS, rather than the selected group in ANNEXA-4 which excluded people with a life expectancy under 1 month, larger bleed volumes and a Glasgow Coma Score below 7. The committee noted that, by excluding these people, a lower 30-day mortality would have been expected in ANNEXA-4 compared with the population seen in clinical practice. Therefore, the generalisability of the ANNEXA-4 results, and the size of any mortality benefit for andexanet alfa when used in routine clinical practice is unclear. The committee concluded that it is uncertain whether or to what extent andexanet alfa would reduce mortality in ICH.

The benefit of andexanet alfa on disability after an ICH is unproven

3.10 The company assumed that andexanet alfa would reduce the severity of long-term disability in people who had had an ICH, compared with conventional treatment including PCC. This assumption had a large effect on the incremental cost-effectiveness ratio (ICER). However, the committee was concerned by comments received at consultation from the British Association of Stroke Physicians, stating that it was unclear if andexanet alfa improves 'very disabled survival in people who would otherwise die, or is improving the number of people with excellent recovery'. This uncertainty would make treatment decisions difficult and might involve discussions with relatives about whether to use andexanet alfa for ICH. The British Association of Stroke Physicians commented at consultation that it was 'difficult to estimate any effect of this treatment on quality of life or recovery as the size of any beneficial treatment effect is unclear'. Disability after ICH is assessed using the modified Rankin scale

(mRS) score, and in the economic model these affected mortality risk, costs and utilities. The company used 2 different sources for mRS scores. For andexanet alfa, it used data from ANNEXA-4. For established management with PCC it used data from Øie et al. (2018), a study that included patients with ICH only and excluded those with other intracranial bleeds. The ERG and the clinical experts explained that ICH is the most severe type of ICH and therefore the company's comparison potentially overestimated the severity of disability and mRS scores for established management, including PCC. The committee also recalled that ANNEXA-4 excluded people with the worst prognoses. The committee noted that there was no direct evidence that people would have better mRS scores and less disability after andexanet alfa than other treatments including PCC, and that the company's assumption was based on a naive comparison of data from ANNEXA-4 and Øie et al. The clinical experts noted that without evidence from a study, it was impossible to predict a benefit in long-term disability. One clinical expert explained that around 80% of people who survive an ICH are on the dependent scale of mRS (scores of 3 or higher) and that evidence would need to show a clear shift in mRS scores to prove an improvement in disability. Another clinical expert stated that for an effective intervention that improves mortality, all people with an ICH would be expected to have an improved level of disability on their baseline. Consensus statements from the Delphi panel also supported an improvement in long-term morbidity after treatment with andexanet alfa. However the committee recalled its earlier conclusions that any mortality benefit with andexanet alfa was uncertain and that the Delphi panel results were based on clinical assumptions. The committee concluded that a benefit from andexanet alfa on long-term disability is unproven.

Additional data collection is needed on neurological outcomes compared with established clinical management

3.11 The committee noted that the marketing authorisation for andexanet alfa was on a conditional basis, with a need for a randomised controlled trial being completed in people with ICH to further explore the benefits and risks in this indication. The committee noted that the clinical outcome in this randomised controlled trial is neurological disability measured up to 24 hours from baseline, comparing andexanet alfa with standard care. The committee recognised that data from the randomised controlled trial will provide stronger evidence of haemostatic efficacy and short-term mortality and neurological outcomes, and

it has been mandated by the regulator. It acknowledged that the trial will not resolve the uncertainty about long-term morbidity or mortality. However, it will address the key clinical question of whether having had the infusion, people were more likely to be alive and in a better neurological state than if they had not had it. The committee concluded that additional data collection is needed on neurological outcomes compared with established clinical management.

The evidence in 'other major bleeds' is too unreliable for decision making

3.12 The committee noted that the indirect treatment comparison results for 'other major bleeds' showed that 30-day mortality was worse with andexanet alfa than established care in combination with PCC. The committee appreciated that the analysis was done with a very small sample size, however it considered it would be unreasonable to ignore these results. The company stated that it expected andexanet alfa treatment to be beneficial in this population. However, the committee concluded that andexanet alfa reducing mortality in 'other major bleeds' had not been shown or quantified.

Cost effectiveness

The company's economic model is suitable for decision making

3.13 The company submitted a decision tree followed by a Markov model to estimate the cost effectiveness of andexanet alfa compared with PCC. The committee considered that the model was suitable for decision making.

The company's assumptions about 'other major bleeds' are not well justified

3.14 The propensity score matching analysis was based on a small number of patients for bleeds classified as 'other major bleeds' (pericardial, retroperitoneal, intraspinal and intraocular bleeds). The analysis results for these bleeds did not favour andexanet alfa compared with established clinical management with PCC, so the company considered it was counterintuitive and several assumptions were made to model these bleeds. The company assumed that andexanet alfa would lead to a 25% relative reduction in mortality for pericardial and retroperitoneal bleeds, and it set the mortality to 0 for

intraspinal and intraocular bleeds. The company also assumed that andexanet alfa would reduce paralysis and blindness by 25% after intraspinal and intraocular bleeds, which reduced the long-term management costs and improved the long-term utilities. These assumptions were based on clinical opinion only. The clinical experts explained that the evidence was too scarce to make assumptions of 25% relative reduction in mortality, paralysis and blindness and that the ERG's assumption of 0% relative reduction was more reasonable in the absence of robust evidence. At consultation, the company agreed that its assumptions were uncertain because of the limited evidence available. The committee concluded that the company's assumptions were not supported by evidence.

The long-term outcomes and utilities after ICH are highly uncertain

3.15 The committee noted that there was no direct evidence that people who had an ICH had better long-term outcomes with andexanet alfa than if they had PCC (see section 3.10). Differences in mRS scores affected the long-term mortality risk, costs and utilities in the model. The long-term utility value for people who had an ICH in the established clinical management arm (using PCC as a proxy) in the company's model was 0.61. This was obtained from a 3-month post-acute care utility value for people who had an ICH, which was used in NICE's guidance on apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. The company calculated that andexanet alfa increased the long-term utility of people who had an ICH by 0.11 compared with PCC, based on the difference in mRS scores between ANNEXA-4 and Øie et al. (2018). This resulted in a long-term utility of 0.72 after an ICH for people who had andexanet alfa. The ERG was concerned that a utility of 0.72 is not plausible because it is only 0.01 lower than the UK general population aged 75 and over. Also, the differences in long-term outcomes were driven by the naive comparison of mRS scores from ANNEXA-4 and Øie et al. The ERG's preferred scenario was to use the mRS scores from Øie et al. only in people who had an ICH in ANNEXA-4, or alternatively to use the ANNEXA-4 mRS scores for both treatments (assuming no benefit in mRS scores). In its updated base case, the ERG's preferred scenario was to assume no benefit in morbidity and to use the same mRS scores from the trial. At the second consultation, the company provided scenarios with varying utility benefits for andexanet alfa compared with PCC. It presented results using baseline utility

values mapped from ANNEXA-4 and results using baseline utility values from NICE's guidance on apixaban. The committee recalled that the Delphi panel consensus supported an improvement in morbidity after treatment with andexanet alfa. However, it was concerned that any increase in benefit was uncertain, as was the size of the benefit. It noted the company had included a utility benefit in its base case that was higher than any predicted by individual experts or in the consensus statement from the Delphi panel. One clinical expert advised that a specific recommendation should be made for people having surgery, in which there is an unmet need. The committee recognised that theoretically a specific reversal agent would be useful. But it agreed there was as yet no evidence that in the situation of surgery andexanet alfa would be better than established clinical management including PCC, so it could not justify a specific recommendation for this situation. The committee concluded that differences in the long-term outcomes and utilities for people after an ICH, depending on the treatment they had, are highly uncertain.

Cost-effectiveness estimates

Andexanet alfa is likely to be cost effective compared with established clinical management including PCC in gastrointestinal bleeds

3.16 The committee considered the company's and the ERG's ICERs for the gastrointestinal cohort, which were very similar. Although associated with some uncertainty, the ICERs from the company and ERG were at a level that included a margin to accommodate uncertainty about mortality benefit. The committee concluded that the ICERs for the gastrointestinal cohort are likely to be within what NICE considers a cost-effective use of NHS resources.

Andexanet alfa has not been shown to be cost effective compared with established clinical management including PCC in ICH

3.17 The committee noted that the extent of the clinical benefit for ICH was uncertain. Therefore, the most plausible ICER for ICH was uncertain. One company scenario included the mortality benefit from the indirect comparison and the modal utility benefit predicted by the Delphi panel in their individual responses. This was within the range NICE normally considers a cost-effective use of NHS resources. However, the committee was concerned that the 30-day

mortality benefit from andexanet alpha in this population is highly uncertain because ANNEXA-4 excluded both those with a life expectancy of less than 30 days, and those with the most severe intracranial bleeds, and clinical experts explained that these people would not be excluded from treatment in an emergency situation in clinical practice. The committee also had concerns about the assumption of a benefit from andexanet alfa on long-term disability. The committee further considered the ERG's updated base case and scenarios modelling different utility benefits for andexanet alfa for the ICH cohort, all of which used baseline utility values mapped from ANNEXA-4, which the committee considered was appropriate, because it came directly from the trial in question. The ICERs which all included the 30-day mortality benefit from the indirect comparison, either with no utility benefit, as preferred by the ERG, or the modal benefit as suggested by the Delphi panel, were above what NICE normally considers a cost-effective use of NHS resources. The committee recalled that the extent to which andexanet alfa reduces mortality is uncertain and that reducing the 30-day mortality benefit for andexanet alfa compared with established clinical management including PCC would further increase the ICER. Therefore, the committee was not confident that any of the ICERs for ICH were robust, and those presented may well be underestimates. It recognised the need for an effective reversal agent for direct factor Xa inhibitors, such as apixaban and rivaroxaban, in people with uncontrolled or life-threatening ICH. However, it concluded that andexanet alfa had not been shown to be a cost-effective use of NHS resources for ICH. Therefore it could not recommend it for routine use in the NHS, pending further research as mandated by the regulator.

Andexanet alfa has not been shown to be cost effective compared with established clinical management for 'other major bleeds'

3.18 The committee noted that the indirect treatment comparison for 'other major bleeds' showed that mortality was worse with andexanet alfa than PCC. Also, the company's assumptions on a potential morbidity benefit were not supported by evidence. Therefore, the committee considered that the ICERs for 'other major bleeds' were very uncertain and that andexanet alfa had not been shown to be a cost-effective use of NHS resources for 'other major bleeds'.

Other considerations

Equalities

3.19 The committee noted an equality concern. Some people do not accept blood products, so would be unable to have PCC as part of their standard care. The committee noted that PCC is not an established treatment for reversing anticoagulation with apixaban or rivaroxaban and is used outside of its marketing authorisation. The committee was aware that people who would not be able to have PCC would have alternative clinical management. In the ORANGE study, 39% of patients had PCC, 41% had a blood transfusion and 28% had tranexamic acid. It noted that no data had been presented that compared established clinical management outcomes with and without blood products. The committee noted that data from the ongoing randomised controlled trial might reduce this uncertainty in ICH, because it compares andexanet alfa with standard care, which is not limited to PCC. However, the committee concluded that the effectiveness of andexanet alfa in ICH and other bleeds was still highly uncertain for people who could and could not have blood products. Therefore, there was no need to alter its recommendation. During the second consultation, stakeholders and clinical experts noted a further equality concern that there would be national variation in access to andexanet alfa if recommended only in research. However, the committee understood that any variation in access is governed by entry to a randomised controlled trial which had been mandated by the regulator. It concluded that the ability to take part in this research was not an issue that needed its recommendation to be altered.

Conclusion

Andexanet alfa is recommended for reversing anticoagulation in life-threatening or uncontrolled bleeding in gastrointestinal bleeds

3.20 Andexanet alfa is likely to reduce 30-day mortality for people with gastrointestinal bleeds. Despite the uncertainty, the committee concluded that the ICER for the gastrointestinal cohort is likely to be within what NICE considers a cost-effective use of NHS resources. Therefore, it concluded that andexanet alfa is recommended in gastrointestinal bleeds as defined in the ANNEXA-4 trial and used as part of a major gastrointestinal bleed protocol.

Andexanet alfa is recommended only in research for reversing anticoagulation in life-threatening or uncontrolled bleeding in ICH bleeds

3.21 The extent of benefits in terms of mortality and long-term disability from andexanet alfa in ICH are unclear and the committee was not confident that the cost-effectiveness results for ICH were robust. There is a need for an effective reversal agent for direct factor Xa inhibitors, such as apixaban and rivaroxaban, in people with uncontrolled or life-threatening bleeding in ICH. However, the committee was not convinced that andexanet alfa had been shown to be a cost-effective use of NHS resources in ICH. Therefore, andexanet alfa should be used only in research in ICH as part of the trial mandated by the regulator.

Andexanet alfa is not recommended for reversing anticoagulation in life-threatening or uncontrolled bleeding in 'other major bleeds'

3.22 The potential benefits of andexanet alfa in the 'other major bleeds' cohort were not supported by evidence and the cost-effectiveness estimates were very uncertain. Therefore, andexanet alfa is not recommended for reversing anticoagulation in life-threatening or uncontrolled bleeding in 'other major bleeds'.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has a life-threatening or uncontrolled gastrointestinal bleed and the doctor responsible for their care thinks that andexanet alfa is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Recommendations for research

5.1 The committee noted an ongoing randomised controlled trial of the effectiveness of andexanet alfa compared with standard care in people with intracranial haemorrhage. The main outcomes of interest are haemostatic efficacy and short-term mortality and neurological outcomes.

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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ISBN: 978-1-4731-4083-7

Accreditation

NICE National Institute for Health and Care Excellence

NICE guidance

Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia

Technology appraisal guidance
Published: 28 April 2021
www.nice.org.uk/guidance/ta694

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so 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.

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.

Contents

1 Recommendations

1.1 Bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:

- statins are contraindicated or not tolerated
- ezetimibe alone does not control low-density lipoprotein cholesterol well enough and
- the company provides bempedoic acid and bempedoic acid with ezetimibe according to the commercial arrangement.

  Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination.

1.2 This recommendation is not intended to affect treatment with bempedoic acid with ezetimibe that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia includes statins for lowering low-density lipoprotein cholesterol (LDL-C) levels. Ezetimibe and either alirocumab or evolocumab may be added when patients' LDL-C levels are not lowered enough with the maximally tolerated dose of statins. Bempedoic acid with ezetimibe would be used when statins are contraindicated or not tolerated, and when ezetimibe alone does not control LDL-C well enough. NICE was not able to evaluate the use of bempedoic acid plus ezetimibe with low intensity statins when higher intensity statins are not tolerated.

Clinical trial evidence suggests that bempedoic acid with ezetimibe may help lower LDL-C levels when other lipid-lowering therapies have not reduced them enough. But, there is no data directly comparing bempedoic acid with ezetimibe with either alirocumab or evolocumab. An indirect comparison of trials suggests that bempedoic acid with ezetimibe may not be as effective at reducing LDL-C levels as alirocumab or evolocumab.

Despite the uncertainty, the cost-effectiveness estimates for bempedoic acid with ezetimibe, when statins are contraindicated or not tolerated, are within what NICE normally considers an acceptable use of NHS resources. So, bempedoic acid with ezetimibe is recommended.

2 Information about bempedoic acid

Marketing authorisation indication

Bempedoic acid

2.1 Bempedoic acid (Nilemdo, Daiichi Sankyo) is 'indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated'.

Bempedoic acid–ezetimibe

2.2 Bempedoic acid–ezetimibe (Nustendi, Daiichi Sankyo) is 'indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe,
- alone in patients who are either statin intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone,
- in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin'.

Dosage in the marketing authorisation

2.3 The dosage schedule for bempedoic acid is available in the summary of product characteristics.

2.4 The dosage schedule for bempedoic acid–ezetimibe is available in the summary of product characteristics.

Price

2.5 Bempedoic acid and bempedoic acid–ezetimibe costs £55.44 per 28-pack, excluding VAT.

2.6 The company has a commercial arrangement (commercial access agreement). This makes bempedoic acid and bempedoic acid–ezetimibe available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Daiichi Sankyo, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical pathway

People with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia will welcome a new treatment option

3.1 People with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia would welcome a new treatment option. The clinical expert explained that the main aim of treatment is to lower low-density lipoprotein cholesterol (LDL-C) with a statin. People may also have ezetimibe if the maximum dose of statin is not lowering LDL-C enough. If LDL-C levels stay higher than normal and the person has cardiovascular disease or primary heterozygous familial hypercholesterolaemia, evolocumab or alirocumab are offered. The clinical expert explained that some people experience intolerance to statins. Statin intolerance can be difficult to define in clinical practice however some people experience muscle pains and in rare cases muscle breakdown. The patient expert explained the difficulty in appropriately identifying and offering treatment to people with increased levels of LDL-C because often they have no symptoms. In some people with increased LDL-C but who have not had a cardiovascular event (primary prevention), there can be reluctance to continue treatment with a statin. In people who have had a cardiovascular event (secondary prevention) treatment adherence is usually improved. The patient and clinical expert and responses to the appraisal consultation document noted that uptake of alirocumab and evolocumab in clinical practice is between 65% and 72% lower than expected. The clinical expert suggested this was because people who are eligible are not navigated through the lipid management pathway appropriately. The patient and clinical expert noted that bempedoic acid is an inexpensive, oral preparation that is easy to use and suitable for people who cannot tolerate statins. The committee concluded that a new treatment option for managing cholesterol would be

welcomed.

The company's proposed position of bempedoic acid with ezetimibe in the treatment pathway reflects NHS clinical practice

3.2 At the first committee meeting, the company had positioned bempedoic acid with ezetimibe for people when:

- statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough and
  - alirocumab or evolocumab are not appropriate (population 2a)
  - alirocumab or evolocumab are appropriate (population 2b).
- the maximally tolerated statin dose with ezetimibe alone does not control LDL-C well enough and
  - alirocumab or evolocumab are not appropriate (population 4a)
  - alirocumab or evolocumab are appropriate (population 4b).

The company's proposed position is narrower than the marketing authorisation (which allows bempedoic acid alone or in combination with a statin without ezetimibe), because they did not anticipate bempedoic acid would be used before ezetimibe in the treatment pathway in the NHS.

During the appraisal, the company decided that it was no longer seeking a recommendation in the maximally tolerated statin population (populations 4a and 4b), because the incremental cost-effectiveness ratio (ICER) estimates were too high to be recommended for routine use in the NHS.

The clinical and patient experts agreed with the position of bempedoic acid proposed by the company and noted it would likely not be used before ezetimibe in NHS clinical practice. The committee concluded that the company's proposed position of bempedoic acid in the treatment pathway reflects NHS clinical practice.

Previous treatment with ezetimibe

The network meta-analyses should include only trials in which all patients were having ezetimibe at baseline

3.3 The company's pivotal trial evidence for the effectiveness of bempedoic acid included 7 randomised controlled trials comprising 4 trials of bempedoic acid alone, 1 of bempedoic acid with ezetimibe, 1 of bempedoic acid alone or bempedoic acid with ezetimibe, and 1 trial of bempedoic acid–ezetimibe or bempedoic acid alone. Except for CLEAR Tranquility, the bempedoic acid trials included patients who had not previously had treatment with ezetimibe at baseline or who have had a washout period of lipid-lowering therapies. The ERG noted that this is not reflective of clinical practice because patients would be expected to have previously had ezetimibe according to the treatment pathway (see section 3.2). The clinical expert explained that generalising the clinical effectiveness of previous ezetimibe on improving cardiovascular outcomes and lipid levels depends on the length of time that a patient was having ezetimibe and the time since stopping. The clinical expert noted that the length of time that a patient was having ezetimibe will have an effect on cardiovascular outcomes for patients, and the time from stopping will affect the patients lipid profile. Furthermore, a washout period before bempedoic acid therapy may mitigate the effect of previous ezetimibe treatment. At the second committee meeting, the company updated its analysis to include a restricted network of trials, in which all patients were having ezetimibe at baseline (see section 3.8). The updated analysis included all the appropriate data from the CLEAR trials. The company noted that it was not feasible to include a network in which all trials had high background ezetimibe use (80% or more of patients in the trial had previously had ezetimibe). However, if the threshold were relaxed to 60%, 1 trial could be added to populations 2a and 2b (people who were intolerant to statins) network. The committee concluded that, given the proposed positioning of bempedoic acid in the treatment pathway, the network meta-analyses should be restricted to include only patients having ezetimibe at baseline.

Baseline LDL-C levels in subpopulations not eligible for alirocumab or evolocumab

Scenario analyses for adjusted baseline LDL-C levels were sufficient for decision making

3.4 The company used different mean baseline LDL-C levels in its economic model depending on the position of bempedoic acid in the treatment pathway. In patients who could have alirocumab and evolocumab, the company used mean baseline LDL-C levels from patients having alirocumab and evolocumab treatment in the CLEAR trials. However, in patients who could not have alirocumab and evolocumab, baseline LDL-C levels were taken from all patients in the CLEAR trials and did not distinguish between those who could have alirocumab or evolocumab and those who could not. NICE's technology appraisal guidance on alirocumab and evolocumab recommend treatment for:

- primary prevention patients with heterozygous familial hypercholesterolaemia only if LDL-C levels persistently above 5 mmol/L
- secondary prevention patients only if high risk for cardiovascular disease and LDL-C persistently above 4 mmol/L

- secondary prevention patients only if very high risk for cardiovascular disease and LDL-C persistently above 3.5 mmol/L.

The ERG preferred to use LDL-C levels separated by alirocumab or evolocumab eligibility because the baseline LDL-C levels in people not eligible were lower than the levels for those who were eligible. The clinical expert agreed that the baseline LDL-C levels will differ across the subpopulations. The committee agreed with the ERG, and wanted to see results based on the appropriate mean baseline LDL-C levels for the appropriate subpopulations. After the first committee meeting, NICE requested that the company provide results where baseline LDL-C levels reflect the intended positioning for bempedoic acid (that is, from patients who had already had ezetimibe and according to alirocumab or evolocumab eligibility). In response, the company provided an updated analysis which removed 2 trials from the network for populations 2a and 2b to improve similarity and comparability of baseline LDL-C, but made no adjustment for baseline LDL-C in patients who could not have alirocumab or evolocumab. The ERG presented results for adjusted baseline LDL-C levels in population 2a, according to alirocumab and evolocumab eligibility. The company did provide mean baseline LDL-C levels for patients in the CLEAR trials with and without ezetimibe at baseline, however no statistical tests for differences between patients who had previously had ezetimibe and all patients (that is, patients who had and did not have previous ezetimibe) were done. The company also noted that across the bempedoic acid trials, the percentage reduction in LDL-C at 12 weeks was similar for all patients regardless of whether they could have alirocumab or evolocumab or not. The ERG modelled the baseline LDL-C levels to reflect the intended positioning for bempedoic acid (that is, patients who had already had ezetimibe and according to alirocumab and evolocumab eligibility). However, it noted that because of small patient numbers having already had ezetimibe and limited data to determine eligibility to alirocumab or evolocumab, these results are not reliable for decision making. The committee understood the added uncertainty around the results given the limitations of the CLEAR trial informing baseline LDL-C levels. It concluded that cost-effectiveness results from scenario analyses were sufficient for decision making.

Subgroup analyses

Because of trial limitations, subgroup analyses could not be provided by heterozygous familial hypercholesterolaemia and cardiovascular risk status

3.5 The final NICE scope specified that subgroup analysis by cardiovascular risk and presence of heterozygous familial hypercholesterolaemia should be considered for the subgroups who were eligible for alirocumab or evolocumab. NICE's technology appraisals guidance for evolocumab and alirocumab made recommendations for these different subgroups (see section 3.4). The company noted that the proportion of patients with heterozygous familial hypercholesterolaemia in its trials were small. It noted that CLEAR Wisdom included the largest group of patients with heterozygous familial hypercholesterolaemia, and subgroup analysis suggested that the treatment effect is consistent with the non-heterozygous familial hypercholesterolaemia population. At technical engagement, the company presented cost-effectiveness results in 7 subgroups according to cardiovascular risk and heterozygous familial hypercholesterolaemia. The same treatment effect for bempedoic acid was used in each subgroup based on the assumption that the treatment effect would be similar in patients with and without heterozygous familial hypercholesterolaemia and with and without previous cardiovascular disease. The clinical expert explained that a common treatment effect should not be assumed across subgroups of heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia and mixed dyslipidaemia because they each have distinct lipid profiles. The ERG considered that the company's subgroup analyses show the cost effectiveness of bempedoic acid is correlated with the baseline LDL-C level rather than with alirocumab or evolocumab eligibility. Further, the ERG noted that the company's trials had not been designed to detect statistical differences across cardiovascular risk and heterozygous familial hypercholesterolaemia. Also, the subgroup analysis had low patient numbers and was underpowered. The company did not update their subgroup analyses for heterozygous familial hypercholesterolaemia and cardiovascular risk status using their latest network meta-analysis (see section 3.8). The committee acknowledged that because the data needed were not collected in the CLEAR trials, it is not possible to do the appropriate subgroup analyses for heterozygous familial hypercholesterolaemia and cardiovascular risk status. The committee

concluded that the company's subgroup analyses for these subgroups were not sufficient for decision making, because a treatment effect was assumed to be the same across patients with and without heterozygous familial hypercholesterolaemia, and with and without previous cardiovascular disease.

Analyses by primary and secondary prevention population

Because of trial limitations, analyses based on efficacy data directly related to the primary and secondary prevention populations could not be done

3.6 At technical engagement, the ERG noted that efficacy data for bempedoic acid are limited in primary prevention and patients with heterozygous familial hypercholesterolaemia. The clinical expert noted that it is possible to assume a similar treatment effect of bempedoic acid on lipid reduction across primary and secondary prevention status. However, it is not reasonable to assume a similar treatment effect on cardiovascular prevention, because cardiovascular risk is higher in secondary prevention patients. To avoid modelling a mixed prevention cohort, the company accepted the ERG's suggestion to model the subpopulations according to most of the population in the CLEAR trials. The populations were modelled as follows:

- subpopulation 2a, primary prevention without heterozygous familial hypercholesterolaemia;

- subpopulation 2b, secondary prevention without heterozygous familial hypercholesterolaemia.

However, the ERG noted that not all patients in the trials included in the company's original network meta-analysis supporting the data for subpopulation 2b come from trial populations without heterozygous familial hypercholesterolaemia in secondary prevention. Also, not all patients in the network meta-analysis supporting the data for subpopulation 2a come from trial populations without heterozygous familial hypercholesterolaemia in primary prevention. At the second appraisal meeting, NICE requested analyses based on efficacy data directly relevant to the intended subpopulation should be done to provide reliable cost-effectiveness estimates. The company noted that limiting to primary prevention and secondary prevention trials is challenging, because trials had mixed populations, and reporting of cardiovascular risk and previous cardiovascular events was unclear. As such, the company did not present updated results in response to this request. The committee concluded that the clinical heterogeneity resulting from generalised subgroup efficacy data is unlikely to be resolvable because of the limitations in the data from the CLEAR trials.

Primary cardiovascular risk and cardiovascular event risk could not be collected from the company's CLEAR trials data

3.7 The company's model calculated background cardiovascular risks by converting the SCORE risk algorithm in European Society of Cardiology guidelines for a high-risk population into a QRISK3 risk. The subsequent annual risk was then used to estimate annual risk for the different cardiovascular events based on the relative rates of first events in Ward et al., 2007. The company noted that this approach is consistent with the approach in NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification. The ERG considered that primary cardiovascular risks and cardiovascular event history in the CLEAR trials may be more appropriate to use than other sources. The ERG considered that the true risk for primary cardiovascular events would lie somewhere between the company's base-case analysis (a 10-year risk of around 30% for myocardial infarction, ischemic stroke or cardiovascular death estimated using the SCORE risk) and the company's scenario analysis provided during the clarification stage (a 10-year risk of 20% for myocardial infarction, ischemic stroke or cardiovascular death). After the first committee meeting, NICE requested that the analyses use data from the CLEAR trials to inform baseline cardiovascular risk and event history in the model. The company reiterated that the parameters needed to reliably calculate

cardiovascular risks using the QRISK3 algorithm had not been captured in the CLEAR trial datasets and cannot be obtained from published data. Additionally, the company noted that they were unable to use previous cardiovascular events from the CLEAR trials to estimate what previous events would have happened in the model, because these data were also not available from the CLEAR trials. The ERG reported, that in absence of the CLEAR trial data, using Ward et al., to inform the distribution of previous cardiovascular events is a reasonable alternative. At the second committee meeting, the ERG presented the updated scenario analysis from the first committee meeting using the ERG preferred network meta-analysis (see section 3.8) for population 2a (that is, patients who were statin intolerant and not eligible for alirocumab or evolocumab). The committee understood that data on primary cardiovascular risks and cardiovascular event history could not be obtained from the CLEAR trials. They concluded that using data from Ward et al., was a reasonable alternative, and the resulting uncertainty in the cost-effectiveness results could not be resolved.

Methodological uncertainty

The ERG's updated network meta-analysis is the most suitable for decision making

3.8 The ERG noted that the company's network meta-analysis submitted at technical engagement had high levels of statistical and clinical heterogeneity present. This included differences between trials in terms of baseline cardiovascular risk, statin intensity, proportion of patients having lipid-lowering therapy for primary prevention, and proportions of patients with heterozygous familial hypercholesterolaemia. It also noted that the high residual deviance implied that the company's network meta-analysis would poorly predict the data from the trials used in the analysis. At the first appraisal meeting, the committee considered the high levels of statistical and clinical heterogeneity present in the company network meta-analysis to be unreliable for decision making. The committee noted that neither the ERG's or company's network meta-analysis were suitable, and preferred to see network meta-analyses with improved statistical fit and reduced clinical heterogeneity. After the first appraisal committee meeting, NICE requested that the company do an analysis which builds upon the network meta-analyses done by the ERG and presented in the first appraisal meeting to reduce statistical and clinical heterogeneity. As part of the analysis, NICE also asked the company to identify any additional

trials that meet the following:

- People in the trial have had treatment with ezetimibe before randomisation (see section 3.3).
- People in the trials have similar unadjusted baseline LDL-C levels (see section 3.4).
- Use appropriate trials to inform treatment efficacy for primary prevention (population 2a) and secondary prevention (population 2b) (see section 3.6 and section 3.7).
- Trials that have other similar baseline characteristics such as cardiovascular disease risk, heterozygous familial hypercholesterolaemia, type of statin, sex, and ethnicity (see section 3.5).

In response, the company presented 2 further network meta-analyses:

- An additional network meta-analysis, which included several changes in line with the requests by NICE (see sections 3.3 to 3.7). The committee agreed with the ERG and remained concerned that there was substantial unresolved clinical heterogeneity between the trials included in the company's additional network meta-analysis, and the results were not suitable for decision making.
- An update of the ERG preferred network meta-analysis to include all available data for bempedoic acid in patients having ezetimibe at baseline from the CLEAR trials, to which the ERG did not previously have access to. The ERG considered that the updated ERG analysis met the requests from NICE.

The committee concluded that the company's updated ERG network meta-analysis was preferred and the most suitable for decision making. In response to the appraisal consultation document, the company provided updated cost-effectiveness results using the committee's preferred network meta-analysis.

Long-term treatment effect of bempedoic acid

There is uncertainty with the evidence informing the long-term treatment effect of bempedoic acid

3.9 The primary efficacy outcome of all relevant bempedoic acid trials was percentage change from baseline LDL-C at 12 weeks. The company model

assumed that results achieved at 12 weeks were maintained for the duration of the model's time horizon, or until treatment is stopped. The ERG noted that there may be a slight waning of treatment effect with bempedoic acid beyond 12 weeks in the data for CLEAR Tranquility and CLEAR Serenity. In response to the appraisal consultation document, the company highlighted evidence from the CLEAR Harmony open-label extension study which showed a mean LDL-C reduction from baseline in CLEAR Harmony of -14.9% and -14.4% at 12 and 78 weeks. The ERG noted that the data relate to people who have maximally tolerated statin levels, which is a population that the company is no longer seeking recommendation for, and it also includes people who have not previously had ezetimibe. The ERG considered that there may be a slight waning of treatment effect with bempedoic acid beyond 12 weeks but it did not know if a similar waning would be seen with the comparators. Therefore, the ERG explored 2 scenarios to show what effect a treatment waning effect on LDL-C could have on the cost-effectiveness results using data from CLEAR Serenity (study data directly relating to the statin intolerant population). Clinical experts could not comment on the potential waning effect of bempedoic acid. The company and the ERG noted that treatment waning effects could be because of other factors (for example when people stop following advice on diet and exercise improvements) and not just lipid-lowering drug efficacy. The committee concluded that there is uncertainty in the evidence informing the long-term treatment effect of bempedoic acid.

Evidence of the direct effect on cardiovascular outcomes is not available

3.10 The company noted that it modelled the relationship between LDL-C reduction and cardiovascular risk based on the Cholesterol Treatment Trialist Collaboration meta-analyses of statin studies. The company noted that although bempedoic acid and statins both inhibit cholesterol synthesis in the liver, a differentiating factor is that, unlike statins, bempedoic acid is inactive in skeletal muscle. At the second appraisal meeting, the committee expressed a concern that the link between changes in LDL-C levels and cardiovascular outcomes used in the company model, may not be appropriate for bempedoic acid because the mechanism of action of bempedoic acid is different to that of statins. In response to the appraisal consultation document, the company provided additional information reinforcing that the cardiovascular benefits of LDL-C lowering are independent of the methods by which it is achieved. The

committee accepted the association between LDL-C lowering and cardiovascular benefits, but concluded that it would have liked to have seen evidence of the direct impact of bempedoic acid on cardiovascular outcomes.

Cost-effectiveness results

The ERG's updated base case includes the committee's preferences

3.11 The ERG's revised base case (which is the same as the company's updated ERG preferred network meta-analysis) provided at the second appraisal meeting included the committee's preferred network meta-analysis. The ERG network meta-analysis comprised of restricted networks of trials for populations 2a and 2b (people who were intolerant to statins) in which all patients were having ezetimibe at baseline (see section 3.3), and thus were aligned with the company's proposed positioning of bempedoic acid in the treatment pathway. The results of the ERG's revised base case included the cost of the bempedoic acid–ezetimibe fixed-dose combination tablet only. The committee was aware that this was cheaper than separate tablets for bempedoic acid and ezetimibe. The committee concluded that the revised ERG base case was the most suitable for decision making. In response to the appraisal consultation document, the company provided updated cost-effectiveness results based on the committee's preferred modelling assumptions with a commercial arrangement for bempedoic acid and bempedoic acid–ezetimibe.

Because of the uncertainty, an acceptable ICER is below £20,000 per quality-adjusted life year (QALY) gained and above £30,000 per QALY lost

3.12 The committee recalled that the company was no longer seeking a recommendation in the maximally tolerated statin population (population 4a and 4b) (see section 3.2). For population 2a, the ICER resulted in additional costs and a gain of QALYs. For population 2b, the ICER resulted in cost savings and a loss of QALYs. NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.

The committee noted the high level of uncertainty. In particular:

- the committee remained uncertain that the results appropriately reflect the intended positioning of bempedoic acid given the limitations of the CLEAR trial informing baseline LDL-C levels (see section 3.4)
- subgroup analyses by cardiovascular risk and heterozygous familial hypercholesterolaemia could not be appropriately done (see section 3.5)
- the appropriate analyses based on efficacy data directly related to the primary and secondary prevention populations could not be done (see section 3.6)
- that primary cardiovascular risks and cardiovascular event history could not be informed by the CLEAR trial (see section 3.7)
- the committee remain uncertain about the evidence provided on the long-term impact of bempedoic acid on cardiovascular outcomes (see section 3.10)

Therefore, the committee agreed that conservative thresholds for populations 2a and 2b should be adopted. The committee concluded that an acceptable ICER for population 2a would be below £20,000 per QALY gained, and an acceptable ICER for population 2b would be above £30,000 per QALY lost.

Bempedoic acid with ezetimibe is recommended as a cost-effective use of NHS resources

3.13 Using the committee's preferred assumptions (see section 3.11) the most plausible ICER for population 2a (statins are contraindicated or not tolerated and not eligible for alirocumab or evolocumab) was less than £20,000 per QALY gained for bempedoic acid and bempedoic acid–ezetimibe. Because of the confidential discount for bempedoic acid and bempedoic acid–ezetimibe, the exact ICER for population 2a cannot be reported here.

3.14 Using the committee's preferred assumptions (see section 3.11) the most plausible ICER for population 2b (statins are contraindicated or not tolerated and eligible for alirocumab or evolocumab) was more than £30,000 saved per QALY lost for bempedoic acid and bempedoic acid–ezetimibe. Because of the confidential discount for bempedoic acid and bempedoic acid–ezetimibe, the exact ICER for population 2b cannot be reported here.

3.15 The committee concluded that bempedoic acid with ezetimibe (both as separate tablets and in a fixed-dose combination) is cost effective for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough.

Other factors

There are no equalities issues

3.16 No equality or social value judgement issues were identified.

There are no additional benefits not already captured in the economic analysis

3.17 The committee understood that there is an unmet need for patients who cannot tolerate statins. The committee was aware that bempedoic acid is an oral preparation compared with alirocumab and evolocumab which are administered subcutaneously and took this into account in its decision making. The committee concluded that there were no additional benefits associated with this treatment that had not been captured in the economic analysis.

Conclusion

Bempedoic acid with ezetimibe is recommended

3.18 The committee concluded that bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough. The committee was concerned about the clinical effectiveness of bempedoic acid because of the lack of long-term data on cardiovascular outcomes in the pivotal trials, and that appropriate subgroup analyses relating to cardiovascular risk and heterozygous familial hypercholesterolaemia could not be provided. However, it noted that further data were unlikely to become available. The cost-effectiveness results based on the committee's preferred modelling assumptions with a commercial arrangement for bempedoic acid and bempedoic acid–ezetimibe represent a

cost-effective use of NHS resources. The committee therefore concluded that bempedoic acid with ezetimibe be recommended for routine use in the NHS in people for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has primary hypercholesterolaemia or mixed dyslipidaemia and the doctor responsible for their care thinks that bempedoic acid with ezetimibe is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Cameron Collins
Technical lead

Victoria Kelly and Sally Doss
Technical adviser(s)

Gavin Kenny
Project manager

Update information

Minor changes since publication

September 2021: We added a clarification to 'Why the committee made these recommendations' to say that NICE was not able to evaluate bempedoic acid plus ezetimibe with low intensity statins when higher intensity statins are not tolerated. We also clarified that the cost-effectiveness estimates were for bempedoic acid plus ezetimibe when statins are contraindicated or not tolerated.

ISBN: 978-1-4731-4099-8

Accreditation

NICE National Institute for Health and Care Excellence

NICE guidance

Dapagliflozin for treating chronic heart failure with reduced ejection fraction

Technology appraisal guidance
Published: 24 February 2021
www.nice.org.uk/guidance/ta679

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so 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.

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.

Contents

1 Recommendations

1.1 Dapagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it is used as an add-on to optimised standard care with:

- angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), with beta blockers, and, if tolerated, mineralocorticoid receptor antagonists (MRAs), or
- sacubitril valsartan, with beta blockers, and, if tolerated, MRAs.

1.2 Start treatment of symptomatic heart failure with reduced ejection fraction with dapagliflozin on the advice of a heart failure specialist. Monitoring should be done by the most appropriate healthcare professional.

1.3 These recommendations are not intended to affect treatment with dapagliflozin that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with heart failure with reduced ejection fraction may have symptoms that are not controlled well enough despite being on the most appropriate (optimised) treatment. Standard care includes an ACE inhibitor or an ARB, with beta blockers and, if tolerated, an MRA. Alternatively, people may be offered sacubitril valsartan, with beta blockers and, if tolerated, MRAs, if symptoms continue on ACE inhibitors or ARBs.

A clinical trial compared dapagliflozin as an add-on treatment to standard care (based on an ACE inhibitor, ARB or sacubitril valsartan) with standard care alone. Evidence from the trial shows that dapagliflozin lowers the risk of dying from cardiovascular causes, and reduces the likelihood of hospitalisation or an urgent outpatient visit because of heart failure.

There are no trials directly comparing dapagliflozin with sacubitril valsartan. An indirect comparison shows dapagliflozin is likely to be as effective at reducing the risk of death from

cardiovascular causes.

The cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources. So dapagliflozin is recommended as an add-on to optimised standard care for symptomatic chronic heart failure with reduced ejection fraction.

People whose symptoms continue or worsen on optimised doses of standard care based on ACE inhibitors or ARBs can only start sacubitril valsartan under the supervision of a specialist with access to a multidisciplinary team. So dapagliflozin should only be started on advice from a heart failure specialist in primary, secondary or community care.

2 Information about dapagliflozin

Marketing authorisation indication

2.1 Dapagliflozin (Forxiga, AstraZeneca) has a marketing authorisation 'for the treatment of symptomatic chronic heart failure with reduced ejection fraction'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of dapagliflozin is £36.59 per 28-tablet pack (excluding VAT; BNF online, accessed November 2020). The annual treatment cost is £476.98. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware of 1 issue that was resolved during the technical engagement stage. It agreed that the probabilistic sensitivity analysis provided at technical engagement should inform the comparison with sacubitril valsartan (issue 5, see technical report page 7).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 1, pages 3 to 10), and took these into account in its decision making. It discussed issues 1, 2, 3, 4, 6 and 7, which were outstanding after the technical engagement stage.

The condition

People with chronic heart failure with reduced ejection fraction would welcome a new treatment option

3.1 Heart failure with reduced ejection fraction (HFrEF) is a chronic condition that affects survival and quality of life. The patient experts highlighted the psychological effects of a diagnosis and explained that breathlessness, extreme fatigue and fluid accumulation in particular can be debilitating. Clinical expert submissions to NICE confirmed that HFrEF is associated with high rates of death and hospitalisation and that there is an unmet need for new treatment options. Current treatments aim to manage symptoms and stabilise the disease to prevent further decline in quality of life and to keep people alive longer. The committee heard from clinical experts that despite optimising therapies, many people still have symptoms, including breathlessness. The patient experts said that they would welcome a new option, especially if it could be used early in the treatment pathway. The committee concluded that there is an unmet need for a new treatment option for symptomatic HFrEF and that patients and healthcare professionals would welcome a new treatment option.

The treatment pathway

If symptoms worsen or continue on optimised standard care specialist advice is needed

3.2 NICE's guideline on chronic heart failure in adults: diagnosis and management recommends that a specialist heart failure multidisciplinary team work collaboratively with the primary care team. It recommends that the specialist multidisciplinary team diagnose heart failure, optimise treatment and manage heart failure not responding to treatment. Recommended drug treatments for newly diagnosed HFrEF include diuretics for congestive symptoms and fluid retention, and an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-2 receptor blocker (ARB) when an ACE inhibitor is not tolerated, aiming for maximum tolerated doses. A beta blocker and a mineralocorticoid receptor antagonist (MRA) should also be offered if appropriate and tolerated. The clinical experts said that current clinical practice is to get specialist advice, or refer a patient to specialist care, if symptoms worsen or continue after optimising standard care with ACE inhibitors or ARBs, beta blockers and, if tolerated, MRAs. NICE's guidance says that subsequent treatment with sacubitril valsartan or ivabradine should be started under the supervision of a specialist with access to a multidisciplinary team (see NICE's technology appraisal guidance on sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction and ivabradine for treating chronic heart failure). Treatment with hydralazine plus nitrate or digoxin also requires specialist advice. The clinical experts said that specialist care might include heart failure teams based in the community or GPs with a special interest in heart failure. The committee concluded that current clinical practice involved specialist advice or referral to specialist care if symptoms worsen or continue on optimised standard care based on ACE inhibitors or ARBs.

Clinical evidence

The DAPA-HF trial is the key trial for dapagliflozin and is broadly generalisable to NHS clinical practice

3.3 DAPA-HF was a double-blind randomised clinical trial comparing dapagliflozin (a sodium-glucose cotransporter-2 inhibitor) plus standard care with placebo plus standard care. Standard care was defined by the company as:

- ACE inhibitors or ARBs, beta blockers and, if tolerated, MRAs (referred to in this guidance as standard care based on ACE inhibitors or ARBs), or
- sacubitril valsartan, plus beta blockers, and, if tolerated, MRAs (referred to in this guidance as standard care based on sacubitril valsartan).

People in the trial had HFrEF defined by an ejection fraction of 40% or less who despite being 'optimally treated with pharmacological and/or device therapy' remain symptomatic. Symptomatic HFrEF was defined as New York Heart Association (NYHA) functional class 2 to 4 present for at least 2 months. Eleven per cent of people in the trial had sacubitril valsartan at baseline. Nineteen per cent of patients had digoxin and 5% had ivabradine. Thirty-eight per cent of patients had co-existing atrial fibrillation, 42% had diabetes and 41% had chronic kidney disease. The clinical experts said that the trial findings were generalisable to NHS clinical practice but highlighted several differences between the population in DAPA-HF and the population in the NHS:

- The average age in the full population was 66, which is younger than in the NHS where the average age at diagnosis is 77.
- The proportion of men was higher in the trial than in the NHS.
- Not all people in the trial were taking NICE guideline-recommended doses of standard care.
- More people were taking diuretics in the trial than in the NHS.

The ERG said that the characteristics of people in DAPA-HF, which is a multinational trial, may not reflect that of the population in the NHS. It noted the differences in healthcare systems in different countries. The ERG preferred the European subgroup of the trial, which had an older population (mean age 68) with more severe disease whose background therapies better reflected those in the NHS. However, the European subgroup was over 99% white and was only 45% of the full DAPA-HF population. The clinical experts explained that the relative clinical effectiveness results were not expected to change as a result of these differences in baseline characteristics. The committee recognised that the absolute risk of complications might differ between the European subgroup and the patients from the rest of the world. It also recognised that larger populations are associated with less uncertainty. The committee concluded that data from the overall DAPA-HF population were acceptable for decision making, and it was therefore appropriate to use these for the clinical effectiveness analyses.

The DAPA-HF trial is generalisable to people whose standard care has been optimised

3.4 People in the DAPA-HF trial were clinically stable and optimised on heart failure therapies according to local guidelines. The trial protocol inclusion criteria listed that therapy should have been individually optimised and stable for 4 weeks or more. It also noted that participants should 'be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual'. The clinical experts confirmed that if dapagliflozin were available, clinicians would start dapagliflozin only in people stable on standard heart failure treatments available in the NHS. The company confirmed that this included loop diuretics, which are used together with ACE inhibitors and ARBs based on patient symptoms and clinical presentation. The committee agreed that, in line with the clinical evidence, in the NHS dapagliflozin would be offered to people taking optimised doses of standard care based either on an ACE inhibitor or ARB, or on sacubitril valsartan, and that the DAPA-HF trial results are generalisable to people whose standard care has been optimised.

Dapagliflozin plus standard care compared with placebo plus standard care is clinically effective

3.5 The primary efficacy outcome in the DAPA-HF trial was a composite of cardiovascular death, hospitalisation for heart failure or an urgent heart failure visit. Intention-to-treat analyses showed that dapagliflozin plus standard care reduced the incidence of the primary endpoint of composite cardiovascular events by 26% compared with placebo plus standard care (hazard ratio 0.74, 95% confidence interval 0.65 to 0.85; $p<0.001$). It also reduced the incidence of all the individual components of the composite endpoint. Secondary endpoints included change in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) at 8 months and death from any cause. Among people randomised to dapagliflozin, 12% of people died compared with 14% of people randomised to placebo. Cox survival modelling estimated a hazard ratio of 0.83 (95% confidence interval 0.71 to 0.97) in favour of dapagliflozin. The committee concluded that dapagliflozin is clinically effective compared with placebo and reduces the risk of cardiovascular events and all-cause mortality when added to standard care.

Risk factors for adverse effects should be identified, and

increased monitoring may be needed with dapagliflozin

3.6 The frequency and type of most adverse events were broadly similar for people on the dapagliflozin and placebo arms of DAPA-HF. However, in the DAPA-HF trial, more people on dapagliflozin had diabetic ketoacidosis and volume depletion, and fewer people had acute kidney injury. The marketing authorisation for dapagliflozin says: 'Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.' Dapagliflozin has a separate marketing authorisation as a glucose-lowering agent for type 1 and type 2 diabetes, but the marketing authorisation for HFrEF prohibits prescribing dapagliflozin to people with type 1 diabetes at the dose used for HFrEF. One clinical expert said that additional kidney function monitoring may be needed for dapagliflozin based on its mechanism of action. The marketing authorisation for dapagliflozin also says that for people treated with dapagliflozin for heart failure and type 2 diabetes, a lower dose of insulin or an insulin secretagogue may be needed to reduce the risk of hypoglycaemia. The committee was aware that at times increased monitoring may be needed in people taking dapagliflozin for heart failure, for example, with intercurrent illness to monitor for volume depletion. Non-severe genital infections, a common adverse effect for dapagliflozin in diabetes, were not collected in the DAPA-HF trial, but all severe adverse events, including severe genital infections, were collected. The company included incidence rates for genital infections in the cost-effectiveness modelling taken from the DECLARE-TIMI 58 trial, a placebo-controlled cardiovascular outcomes safety trial of dapagliflozin in people with type 2 diabetes. The committee concluded that the safety data from the DAPA-HF trial with the genital infections data from the DECLARE-TIMI 58 trial accurately capture the adverse effects of dapagliflozin, but that risk factors for adverse effects should be identified and increased monitoring may be needed.

Comparators

ACE inhibitors, ARBs, diuretics, beta blockers and MRAs are not direct comparators alone, but are comparators when used in combination as standard care

3.7 The committee heard from a patient expert that they wished dapagliflozin to be used as early as possible in treating heart failure (see section 3.1). But the

committee recalled its earlier conclusion, based on the trial evidence presented, that dapagliflozin would be used after standard care is optimised. For this reason, the committee concluded that optimised standard care, rather than the individual components, reflected what patients would otherwise be offered. It agreed that ACE inhibitors, ARBs, diuretics, beta blockers and MRAs were not direct comparators alone but are comparators when used in combination as standard care.

Ivabradine, digoxin and hydralazine with nitrate are not relevant comparators

3.8 NICE's guideline on chronic heart failure in adults: diagnosis and management recommends sacubitril valsartan, ivabradine and hydralazine with nitrate or digoxin as specialist treatments for HFrEF. The final scope for this guidance did not include ivabradine, digoxin and hydralazine with nitrate as relevant comparators for dapagliflozin. The clinical experts explained that these drugs are rarely prescribed in clinical practice for HFrEF. They said that ivabradine is primarily a heart-rate-lowering medicine for people with left ventricular systolic disfunction who are in sinus rhythm and have a resting heart rate of over 75 beats per minute. One clinical expert noted that hydralazine with nitrate is used in people with poor kidney function or for whom ACE inhibitors are not suitable. A clinical expert said that digoxin is used in atrial fibrillation and in worsening or severe heart failure with sinus rhythm when reduced kidney function means no other treatments are an option. A clinical expert explained that hydralazine with nitrate and digoxin are generally used in different populations and would not be relevant at this point in the pathway. The company provided pharmacoepidemiologic data from the Clinical Practice Research Datalink which suggests that around 2%, 1% and 11% of people with heart failure have ivabradine, hydralazine with nitrate and digoxin in NHS practice, respectively. However, the committee recognised that these data included people with preserved ejection fraction and that all 3 technologies are licensed for other indications, so the proportion of people taking these medicines in England to treat HFrEF was likely to be lower. The committee concluded that ivabradine, digoxin and hydralazine with nitrate are not relevant comparators for dapagliflozin.

Sacubitril valsartan is an appropriate comparator

3.9 The clinical experts explained that currently they would consider sacubitril valsartan as an option for people whose symptoms continue on optimised standard care based on ACE inhibitors or ARBs. If dapagliflozin were available, the clinical experts noted that specialist teams considering sacubitril valsartan would take into account which treatment was more appropriate based on a person's symptoms and comorbidities. The committee agreed that sacubitril valsartan was an appropriate comparator.

Optimised standard care based on sacubitril valsartan is also an appropriate comparator

3.10 The clinical experts explained that it was likely that for many people symptoms would continue on sacubitril valsartan, so it was reasonable to consider dapagliflozin as an add-on to standard care at this point in the pathway. The committee concluded that, for people who remain symptomatic on sacubitril valsartan, standard care based on sacubitril valsartan is the relevant comparator.

Optimised standard care based on ACE inhibitors or ARBs is the appropriate comparator for people who cannot take sacubitril valsartan

3.11 The committee then considered a population proposed by the company who could not take sacubitril valsartan but could take dapagliflozin. One clinical expert confirmed that they would include people with hypotension or with poor kidney function in the population that cannot have sacubitril valsartan. However, for both sacubitril valsartan and dapagliflozin, there is very limited clinical experience in people with severe kidney impairment (estimated glomerular filtration rate [GFR] less than 30 ml/min/1.73 m^2). The committee noted that people with a left ventricular ejection fraction between 36% and 40% would not be offered sacubitril valsartan, in line with NICE guidance, but could be offered dapagliflozin. The GP committee members said that they would not determine who could and could not take sacubitril valsartan. They said they would refer anyone who continued to have symptoms despite being optimised on standard care based on ACE inhibitors or ARBs to heart failure specialist care. The committee agreed that members of specialist heart failure teams are

able to define and identify people who cannot or should not take sacubitril valsartan. It concluded that the appropriate comparator for these people is optimised standard care based on ACE inhibitors or ARBs (see section 3.7).

Indirect treatment comparison

The Bucher method is appropriate for an indirect comparison of dapagliflozin with sacubitril valsartan

3.12 There were no trials directly comparing dapagliflozin with sacubitril valsartan. To estimate the relative efficacy of dapagliflozin plus standard care based on ACE inhibitors or sacubitril valsartan with beta blockers and, if tolerated, MRAs, the company used a matching-adjusted indirect comparison. This adjusted patient-level data from the subgroup of people in DAPA-HF who received standard care based on ACE inhibitors, to match study-level baseline patient characteristics from PARADIGM-HF, a randomised controlled trial comparing sacubitril valsartan with enalapril (an ACE inhibitor). The ERG explained that the results of the matching-adjusted indirect comparison were uncertain because the company excluded a large proportion of the DAPA-HF population when adjusting it to match the baseline characteristics of participants in the PARADIGM-HF trial. The ERG said that the company had not justified why it had chosen a matching-adjusted indirect comparison. The company also presented an analysis using the alternative Bucher method, which compares treatments without matching baseline characteristics across trials and used the whole subgroup of people in DAPA-HF who had standard care based on ACE inhibitors. The ERG noted that results using both methods were similar, which suggested it was unlikely that the baseline characteristics of participants in the PARADIGM-HF and DAPA-HF trial were substantially different and required matching. Because of this, the ERG preferred the Bucher method, which gives more precise estimates, for its analyses. The committee concluded that results from the matching-adjusted indirect comparison were associated with higher uncertainty and that the Bucher method should be used to compare effectiveness of dapagliflozin with sacubitril valsartan.

Dapagliflozin may be more effective than sacubitril valsartan, but the results are uncertain

3.13 The primary endpoint in the indirect comparison was time to first

hospitalisation for heart failure or cardiovascular death because these data were available from both the DAPA-HF and the PARADIGM-HF trials. The results from the indirect treatment comparison indicated that dapagliflozin was more effective than sacubitril valsartan at delaying cardiovascular events and all-cause mortality. However, the committee noted that the results were uncertain and included the possibility of no benefit for dapagliflozin compared with sacubitril valsartan (a relative risk of 1.0). The committee was aware that the company originally modelled dapagliflozin as equally effective as sacubitril valsartan in its submission. The committee concluded it would consider both the relative effectiveness results from the Bucher method and the results from assuming equal effectiveness with sacubitril valsartan in its decision making.

The company's economic model

The company's model is appropriate for decision making

3.14 The company modelled cost effectiveness using a Markov model with 9 states (4 based on symptom severity, split by presence of type 2 diabetes, plus 1 for death). It captured disease severity using the KCCQ-TSS, which is a disease-specific measure of quality of life. People transitioned through quartiles based on KCCQ-TSS (0 to 100, with high scores denoting lower symptom burden) and a specific utility and cost was associated with each state. The ERG noted that cut offs for the quartiles chosen by the company to measure KCCQ-TSS in the model were arbitrary. But it said it expected that using other cut offs or approaches to grouping would minimally affect the cost-effectiveness results. The company also modelled hospitalisation for heart failure, urgent heart failure visits and adverse events based on the incidence in each quartile, and stratified people by whether they had type 2 diabetes at baseline. The model included a treatment effect (relative effectiveness from DAPA-HF and Bucher indirect treatment comparison) using survival equations. The committee concluded that the company's model structure was appropriate for decision making.

The KCCQ tool is a reasonable way to measure disease severity

3.15 The company's model structure differed from those used in NICE's technology appraisal guidance on sacubitril valsartan and ivabradine. These used a 2-state dead and alive Markov model and indirectly measured disease severity using the NYHA classification (in survival equations and baseline characteristics). The company said it considered that scores from patient questionnaires, like the

KCCQ tool, were more accurate for measuring symptom severity than the NYHA classification, which was based on healthcare professionals' assessments. The clinical experts confirmed that, although NYHA classification is more commonly used in clinical practice, it is more subjective and less sensitive to changes in patient symptoms than the KCCQ tool. The results of a subgroup analysis from DAPA-HF showed a difference in treatment effect by NYHA classification. The company explained that there was no plausible biological explanation for this finding and results of subgroup analyses in other markers of disease severity (such as prior hospitalisation for heart failure and left ventricular ejection fraction) did not find a difference. In response to technical engagement, the company presented data on health state occupancy over time using the NYHA class for disease severity. This placed most people from the DAPA-HF control arm in the NYHA class 1 or 2 health state (zero to mild symptoms) over the model time horizon. One clinical expert confirmed that this did not reflect the chronic nature of HFrEF. The company explained that health state occupancy using KCCQ-TSS better aligned with the expected symptom changes for standard care: initial improvement for 4 to 8 months then stabilisation. The company also said that few people were NYHA class 1 or 4 at baseline so the transition probabilities in these health states would be uncertain. The committee concluded that the KCCQ tool is a reasonable way to classify disease severity and is appropriate for decision making.

Survival extrapolations for cardiovascular and all-cause mortality

A Gompertz distribution produces the most plausible survival extrapolations, but the distribution used has limited impact on cost-effectiveness results

3.16 The mortality data from the DAPA-HF trial were relatively immature because only 12% and 14% of people had died in the dapagliflozin and placebo arms respectively (median follow up was 18 months). The company used a Weibull distribution to extrapolate cardiovascular and all-cause mortality beyond the end of the trial for the entire duration of the model in its base-case analysis. A clinical expert said that the Weibull curve predicted survival estimates that were aligned with those in NICE's technology appraisal guidance on sacubitril valsartan and their own audit. The ERG confirmed that, based on the observed data, it was plausible to use the Weibull distribution and to assume proportional

hazards. However, the Taylor et al. 2019 study of trends in overall heart failure survival in the UK (for reduced and preserved ejection fraction) predicted fewer people would be alive at 1 year, 5 years and 10 years than estimated by the Weibull distribution. The committee noted these data aligned better with the survival estimates predicted using the Gompertz curve, although they may still overestimate survival given the poor prognosis for HFrEF. The company did not validate its survival estimates using epidemiological data. The committee noted that the incremental proportional hazards and treatment effect appeared to be maintained across the different extrapolation methods. Because of this, the choice of distribution to extrapolate survival had little impact on the cost effectiveness of dapagliflozin. The committee concluded that extrapolating survival with a Gompertz distribution is the most plausible for decision making, but that the distribution used has limited impact on cost-effectiveness results.

Treatment waning

Excluding waning of the treatment effect from the model is appropriate

3.17 The company modelled the relative survival benefit for dapagliflozin plus standard care as being maintained at the same level for the rest of the person's life. It justified this by noting that the DAPA-HF trial had no stopping rule for dapagliflozin and NICE's technology appraisal guidance on sacubitril valsartan assumed no waning of effect. Also, the treatment effect for dapagliflozin was stable in DAPA-HF and the DECLARE-TIMI 58 trial, the latter of which had a median follow up of 4.2 years. The committee questioned whether it was possible that treatment effect may not be continued over a lifetime, as seen for some diuretic treatments. It noted there was no evidence for or against treatment waning in the long term. Clinical experts and stakeholders confirmed that treatment with dapagliflozin would likely be lifelong. Because the maximum follow-up in the DAPA-HF trial was 2.3 years, the committee considered the company's scenarios in which the treatment effect of dapagliflozin stopped at 3 years, 5 years and 10 years from starting treatment. However, it noted that cost-effectiveness results were robust to these scenarios. The committee concluded that it is appropriate that the model does not include waning of the treatment effect, and that incorporating this assumption has limited impact on the cost-effectiveness results.

Utilities

Utility values from the DAPA-HF trial and the literature should both be considered in decision making

3.18 In its initial base case, the company used utilities derived directly from EQ-5D-5L questionnaires collected in the DAPA-HF trial. The company mapped the EQ-5D-5L data to EQ-5D-3L to estimate mean utility values for all health states, in line with NICE's guide to the methods of technology appraisal. The ERG noted that the company's utility value for KCCQ-TSS quartile 4 (people with the lowest reported symptom burden) was 0.833. The committee noted that this was higher than the 0.774 utility value for the general population aged 60 to 69 calculated by Sullivan et al. (2011). The clinical experts pointed out that people with heart failure are unlikely to have a better quality of life than the general public for the same age range. For this reason, the ERG preferred a scenario that used the utility value from Sullivan et al. for KCCQ-TSS quartile 4 and applied the relative differences between quartiles that was observed in the DAPA-HF study to calculate utilities for quartiles 1 to 3. The committee noted that utility values taken directly from the clinical trial are often preferred but considered the high values from the unadjusted DAPA-HF utilities to lack face validity. It concluded that it would consider utility values from the DAPA-HF trial and the literature in its decision making.

Costs

Costs used in the company's model are appropriate for decision making

3.19 The company's model included costs of treatment with dapagliflozin and sacubitril valsartan at list price, but the committee was aware that the cost of sacubitril valsartan may vary in different settings because of negotiated procurement discounts. The company assumed that treatment costs accrued over a person's lifetime until that person stopped treatment because of adverse events or by choice. The committee was aware that because standard care costs were included in both arms of the DAPA-HF trial they had limited impact on the overall cost-effectiveness results. Costs were associated with hospitalisation for heart failure, an urgent heart failure visit, death from cardiovascular causes, and having type 2 diabetes at baseline. The company included costs for adverse

events including hypoglycaemia, volume depletion, fractures, kidney adverse events and diabetic ketoacidosis as well as genital and urinary tract infections. The committee concluded that the costs used in the company's model were appropriate for decision making.

Cost-effectiveness estimates

Dapagliflozin dominates sacubitril valsartan in all scenarios

3.20 Dapagliflozin dominated sacubitril valsartan in the company and ERG's base cases (that is, it was less costly and at least equally effective). This was true for all scenarios, including when the company used alternative methods of indirect comparison or if equal clinical effectiveness between dapagliflozin and sacubitril valsartan was assumed. Exact costs for the comparison with sacubitril valsartan are not reported because of varying procurement discounts associated with sacubitril valsartan in different settings. The committee concluded that dapagliflozin added on to optimised standard care based on ACE inhibitors or ARBs is less costly and at least equally effective as optimised sacubitril valsartan with beta blockers and, if tolerated, MRAs.

Dapagliflozin is cost effective as an add-on to optimised standard care

3.21 The committee first considered the population taking dapagliflozin as an add-on to optimised standard care based on ACE inhibitors or ARBs. The company's base-case incremental cost-effectiveness ratio (ICER; updated at technical engagement) was £6,939 per quality-adjusted life year (QALY) gained. The ICERs for company scenarios ranged from £5,435 to £17,087 per QALY gained. The ERG's preferred assumptions, which used baseline characteristics and the treatment effect from the European subgroup, increased the ICER to around £18,000 per QALY gained. However, the committee recalled that it did not consider the European subgroup the most appropriate for decision making (see section 3.3). The committee agreed that its preferred assumptions to compare dapagliflozin added to optimised standard care (based on ACE inhibitors or ARBs) with optimised standard care (based on ACE inhibitors or ARBs) without dapagliflozin included:

- the Gompertz distribution to calculate overall and cardiovascular mortality

- the whole DAPA-HF population for baseline characteristics and treatment effect
- no waning of treatment effect
- utility values from the DAPA-HF trial and the literature.

Using the above assumptions with utility values from the DAPA-HF trial, the committee's preferred ICER for dapagliflozin was £7,264 per QALY gained as an add-on to optimised standard care based on ACE inhibitors or ARBs. The committee understood that the ICER would be higher if utility values from the literature were used but that this increase would be minimal.

The committee then considered the population taking dapagliflozin as an add-on to optimised standard care based on sacubitril valsartan. The cost-effectiveness results are not reported here because of varying procurement discounts associated with sacubitril valsartan in different settings. However, the committee noted that its preferred ICER for this population would be under £10,000 per QALY gained. It concluded that the most plausible ICERs were within what NICE normally considers to be a cost-effective use of NHS resources and that dapagliflozin is cost effective when compared with optimised standard care based on ACE inhibitors or ARBs, or optimised standard care based on sacubitril valsartan.

Other factors

Dapagliflozin is innovative and the benefits for people with diabetes and heart failure may not be fully captured in the model

3.22 The committee recalled that people with HFrEF have a poor prognosis and that there is an unmet need for treatment options (see section 3.1). The committee noted that it is the first drug of its class to gain regulatory approval for use in heart failure. It also considered that dapagliflozin has a marketing authorisation for the treatment of glycaemic control in people with diabetes, who comprised a large proportion of the DAPA-HF trial (see section 3.3). The committee recalled that the company had not included additional benefits (for example, prevention of diabetic eye disease) associated with improved glycaemic control for diabetes. The committee concluded that dapagliflozin is innovative and is a step-change in the treatment of HFrEF, and that the benefits for people who also have diabetes may not be fully captured in the model.

A heart failure specialist should advise on starting dapagliflozin

3.23 The committee recalled its earlier conclusion that current clinical practice involved specialist advice or referral to specialist care if symptoms worsen or continue on optimised doses of standard care based on ACE inhibitors or ARBs, to determine the appropriate next treatment. It recalled that regulatory advice for dapagliflozin as a treatment for heart failure is to identify people at high risk of adverse effects before starting treatment (see section 3.6). The company positioned dapagliflozin as an add-on treatment to standard care, highlighting that dapagliflozin could be started before consulting specialist care while people awaited referral. The GPs on the committee said they would not start dapagliflozin without consulting a specialist or heart failure team. The patient expert said that primary care clinicians are familiar with prescribing the drug for type 2 diabetes. However, the committee was aware that the population in the current marketing authorisation for dapagliflozin for heart failure differed from the population for dapagliflozin for diabetes and included people with worse kidney function (with estimated GFR values down to 30 ml/min/1.73 m^2). The committee noted that GPs would not be familiar in treating these people with dapagliflozin for diabetes. One clinical expert said that everyone with a new diagnosis of heart failure would see a specialist to start and manage treatment, so people who could have dapagliflozin would already be known to specialist care. The committee concluded that dapagliflozin should be started on advice from a heart failure specialist who can determine the most appropriate treatment.

Monitoring should be done by the most appropriate healthcare professional

3.24 NICE's guideline on chronic heart failure in adults: diagnosis and management recommends that a specialist heart failure multidisciplinary team should work in collaboration with the primary care team to start new medicines that need specialist supervision. NICE's technology appraisal guidance on sacubitril valsartan says that monitoring should be carried out by a heart failure specialist or in primary care by the most appropriate team member. A clinical expert said that people who were taking dapagliflozin for heart failure who also had diabetes might need adjustments in their diabetes medication for safety reasons (see section 3.6). The committee recalled its conclusion that risk factors should be identified and some increased monitoring may be needed for treating heart

failure with dapagliflozin. It concluded that monitoring of people who have dapagliflozin for heart failure should be done by the most appropriate healthcare professional from a specialist heart failure multidisciplinary team or primary care team.

No equalities considerations were identified for dapagliflozin

3.25 The committee recalled that dapagliflozin is currently offered to people with diabetes in primary and secondary care. A patient expert explained that, if dapagliflozin were limited to specialist care for heart failure, people with type 2 diabetes would have access to it in primary care, but people who had HFrEF without diabetes would not. The committee considered that the population who had HFrEF were likely to be older and have worse kidney function than people with diabetes alone. The committee recalled standard clinical practice is for a heart failure specialist and a multidisciplinary team to determine the most appropriate second-line treatment to offer. It noted that specialist advice could be given to a primary care healthcare professional, so people would not need to visit a hospital to start dapagliflozin. The committee noted its recommendation applied to all people included in the dapagliflozin for HFrEF marketing authorisation and not only those with comorbid diabetes. It therefore did not consider this an equalities issue.

Conclusion

Dapagliflozin is recommended for use in the NHS

3.26 The committee agreed that the most plausible ICERs for dapagliflozin compared with all relevant comparators were within what NICE normally considers to be an acceptable use of NHS resources. It therefore concluded that it could recommend dapagliflozin for routine commissioning as an option to treat symptomatic chronic HFrEF as an add-on in people who are already taking optimised standard care based on an ACE inhibitor or ARB, or on sacubitril valsartan.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has symptomatic chronic heart failure with reduced ejection fraction and the doctor responsible for their care thinks that dapagliflozin is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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ISBN: 978-1-4731-4060-8

Accreditation

NICE National Institute for Health and Care Excellence

NICE guidance

Mepolizumab for treating severe eosinophilic asthma

Technology appraisal guidance
Published: 3 February 2021
www.nice.org.uk/guidance/ta671

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so 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.

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.

Contents

This guidance replaces TA431.

1 Recommendations

1.1 Mepolizumab, as an add-on therapy, is recommended as an option for treating severe refractory eosinophilic asthma, only if:

- it is used for adults who have agreed to and followed the optimised standard treatment plan and
- the blood eosinophil count has been recorded as 300 cells per microlitre or more and the person has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months or
- the blood eosinophil count has been recorded as 400 cells per microlitre or more and the person has had at least 3 exacerbations needing systemic corticosteroids in the previous 12 months (so they are also eligible for either benralizumab or reslizumab).

  Mepolizumab is recommended only if the company provides it according to the commercial arrangement.

1.2 If mepolizumab, benralizumab or reslizumab are equally suitable, start treatment with the least expensive option (taking into account drug and administration costs).

1.3 At 12 months:

- stop mepolizumab if the asthma has not responded adequately or
- continue mepolizumab if the asthma has responded adequately and assess response each year.

  An adequate response is defined as:

- a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or

- a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control.

1.4 These recommendations are not intended to affect treatment with mepolizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

For severe refractory eosinophilic asthma, standard therapy alone does not work well enough. So people usually also have benralizumab or mepolizumab if:

- their blood eosinophil count is 300 cells per microlitre or more and
- they have had at least 4 severe exacerbations needing systemic corticosteroids in the previous 12 months or continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months.

People can have benralizumab or reslizumab if their blood eosinophil count is 400 cells per microlitre or more and they have had at least 3 severe exacerbations in the previous 12 months.

There is no evidence directly comparing mepolizumab with benralizumab and reslizumab. But an indirect comparison suggests that it works as well as benralizumab and reslizumab for people with a blood eosinophil count of 400 cells per microlitre or more.

Mepolizumab is cost saving compared with benralizumab and reslizumab. So it is now also recommended for people with a blood eosinophil count of 400 cells per microlitre or more and at least 3 severe exacerbations in the previous 12 months.

2 Information about mepolizumab

Marketing authorisation indication

2.1 Mepolizumab (Nucala, GlaxoSmithKline) has a marketing authorisation in the UK as an 'add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older'.

Dosage in the marketing authorisation

2.2 Mepolizumab is available as a powder for solution for injection in vials, or as a solution for injection in pre-filled syringes and pre-filled pens. The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of mepolizumab is £840 per 100 mg dose (excluding VAT; BNF online, accessed November 2020). The company has a commercial arrangement. This makes mepolizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by GlaxoSmithKline, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence. The company proposed that this technology be considered in a fast track appraisal using cost-comparison methodology.

New treatment option

People with severe eosinophilic asthma will welcome a new treatment option

3.1 Severe refractory eosinophilic asthma is a debilitating condition, which does not respond well enough to standard therapy and has many distressing symptoms. Asthma exacerbations can happen without warning, be life threatening, cause fear, and result in hospitalisation and intubation. People with uncontrolled severe eosinophilic asthma are often unable to work and may need help with day-to-day activities because of the symptoms. These physical and psychological pressures negatively affect quality of life. The patient experts highlighted an urgent need for more biological treatments for people who are not eligible for benralizumab or reslizumab or whose asthma does not respond to them. These people would otherwise need more intensive treatment with oral corticosteroids, which are associated with major side effects including diabetes, glaucoma, weight gain, loss of bone density and raised blood pressure. The clinical experts explained that the clinical community would welcome treatment criteria for biologicals to be standardised. The committee concluded that people with severe eosinophilic asthma with a blood eosinophil count of 400 cells per microlitre or more and at least 3 severe asthma exacerbations would welcome a new treatment option.

Clinical effectiveness

The indirect treatment comparison of mepolizumab, benralizumab and reslizumab is appropriate

3.2 NICE originally recommended mepolizumab for treating severe refractory eosinophilic asthma in adults with:

- a blood eosinophil count of 300 cells per microlitre or more and
- at least 4 severe exacerbations needing systemic corticosteroids in the past 12 months or if they have had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months.

The company proposed extending this recommendation, in line with NICE's technology appraisal guidance on benralizumab and reslizumab, to include people with:

- a blood eosinophil count of 400 cells per microlitre or more and
- at least 3 severe exacerbations needing systemic corticosteroids in the past 12 months.

The company's evidence submission did not include any head-to-head trials directly comparing mepolizumab with benralizumab and reslizumab. It presented an indirect treatment comparison (ITC) of mepolizumab, benralizumab and reslizumab in severe eosinophilic asthma. The ITC included 9 placebo-controlled studies. The primary outcomes included:

- exacerbation needing treatment with oral corticosteroids
- exacerbation needing an emergency department visit or hospitalisation
- Asthma Control Questionnaire score and change from baseline pre-bronchodilator forced expiratory volume in 1 second.

The committee noted the limitations of the company's ITC, namely that potentially relevant studies were omitted. The 75 mg treatment arms from DREAM and MENSA were omitted to ensure that the data reflected the licensed dose of 100 mg. The ERG was unable to fully assess the effect of excluding these on the final efficacy results. It considered that omitting ZONDA and SIRIUS from the ITC was appropriate because of their different primary outcomes. The ERG also noted variation between studies in length of follow up, dosing and administration, asthma severity, blood eosinophil counts and previous exacerbations. But it recognised that most of the pairwise meta-analyses had low heterogeneity. It also noted that corticosteroid reduction was among the outcomes missing from the ITC. However, its clinical advisers suggested that a reduction in exacerbations may also imply a reduction in corticosteroid use so the ERG did not consider this to be an issue. The committee concluded that the ITC of mepolizumab, benralizumab and reslizumab is appropriate.

There is sufficient evidence that mepolizumab has comparable efficacy to benralizumab and reslizumab

3.3 The results of the ITC for the primary outcomes broadly favoured mepolizumab over benralizumab and reslizumab for the subgroups in the trials with an eosinophil count of 400 cells per microlitre or more. But no evidence of a difference between treatments was found when the full trial populations were compared. The analysis for the comparison of mepolizumab with benralizumab and reslizumab was done for people with:

- a blood eosinophil count of 400 cells per microlitre or more and
- at least 1 severe exacerbation in the reslizumab arm or 2 severe exacerbations in the mepolizumab and benralizumab arms.

However, the ERG stated that although this broader subgroup was not exactly aligned to the population being considered, it was closer than any other analysis. The ERG confirmed that there was a low risk that mepolizumab was less effective than benralizumab and reslizumab for severe eosinophilic asthma. The committee concluded that there was sufficient evidence that mepolizumab has comparable efficacy to benralizumab and reslizumab.

Cost comparison

A 10-year time horizon is more appropriate for decision making

3.4 The company did a cost comparison of mepolizumab with benralizumab and reslizumab. The costs were presented over a 1-year time horizon and were not discounted. The analysis compared:

- mepolizumab 100 mg; a powdered vial for mixing, a pre-filled syringe and pre-filled pen, administered subcutaneously every 4 weeks
- benralizumab 30 mg; a pre-filled syringe and pre-filled pen, administered subcutaneously every 4 weeks for the first 3 doses, then every 8 weeks and

- reslizumab with a weight-dependent dose (assuming a mean weight of 78 kg for the UK adult population); concentrate for intravenous infusion administered every 4 weeks.

The analysis included drug, administration and monitoring costs. Oral corticosteroid costs were not included in the analysis. The analysis assumed that there were no differences in adverse event costs based on a Cochrane review that found no excess serious adverse events with any anti-interleukin-5 treatments (such as mepolizumab, benralizumab and reslizumab). It was uncertain whether a 1-year time horizon was sufficient to capture the key differences in costs between treatments. This was particularly because of the loading dose for benralizumab, and differences in dosing frequency and administration costs over time. However, an ERG scenario showed that mepolizumab remained cost saving over a 10-year time horizon. The ERG did not consider monitoring costs to be a key driver of the results. The committee concluded that a 10-year time horizon was more appropriate for decision making.

Self-administration has a small effect on the cost-comparison results

3.5 The committee questioned the proportion of people likely to self-administer the drug and the effect of this on savings with mepolizumab. The company explained that around 97% of people are currently self-administering and only 3% need mepolizumab to be given by a nurse. The clinical experts advised that the largest saving from those self-administering is in secondary care, with savings related to pharmacy and nurse time. However, people being set up for self-administration would need slightly longer appointments. The ERG explained that in the context of the drug costs, administration cost differences have little effect. The committee concluded that self-administration has a small effect on the cost-comparison results and the incremental savings with mepolizumab are mainly related to lower drug costs.

Mepolizumab results in cost savings when compared with benralizumab and reslizumab

3.6 The company's cost comparison included a range of assumptions for:

- administration and monitoring costs
- oral corticosteroid use

- the comparable safety profile of mepolizumab, benralizumab and reslizumab over a 1-year time horizon.

  Assuming equivalent effectiveness and based on the list price for all treatments, mepolizumab had incremental cost savings compared with benralizumab and reslizumab. Mepolizumab remained cost saving in the additional ERG scenario over a 10-year time horizon. The committee concluded that, at list price, mepolizumab was cost saving compared with benralizumab and reslizumab for people with an eosinophil count of 400 cells per microlitre or more, and at least 3 severe exacerbations per year. Mepolizumab, benralizumab and reslizumab are available to the NHS with confidential commercial arrangements. The ERG analysis including these commercial arrangements did not change the committee's conclusion.

Mepolizumab is recommended

3.7 The committee concluded that mepolizumab met the criteria to be recommended based on a cost comparison, because the overall health benefits are similar to those of benralizumab and reslizumab. The committee concluded that mepolizumab could be recommended as an option for treating severe refractory eosinophilic asthma in adults with:

- a blood eosinophil count of 300 cells per microlitre or more and at least 4 exacerbations needing systemic corticosteroids in the previous 12 months or continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months or
- a blood eosinophil count of 400 cells per microlitre or more and at least 3 exacerbations needing systemic corticosteroids in the previous 12 months.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Because mepolizumab has been recommended through the fast track appraisal process, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has severe eosinophilic asthma and the doctor responsible for their care thinks that mepolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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ISBN: 978-1-4731-3995-4

Accreditation

NICE National Institute for Health and Care Excellence

NICE guidance

Naldemedine for treating opioid-induced constipation

Technology appraisal guidance
Published: 30 September 2020
www.nice.org.uk/guidance/ta651

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so 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.

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.

Contents

1 Recommendations

1.1 Naldemedine is recommended, within its marketing authorisation, as an option for treating opioid-induced constipation in adults who have had laxative treatment.

Why the committee made these recommendations

The treatment of opioid-induced constipation depends on whether the opioid is the only cause of the constipation (pure opioid-induced constipation) or if there are other contributing factors (mixed aetiology constipation). Treatment may include a peripherally acting mu-opioid receptor antagonist (PAMORA) alone. But, commonly a PAMORA and a conventional laxative are used together. Naldemedine is an oral PAMORA for adults who have had laxative treatment.

The clinical evidence shows that naldemedine increases the frequency of bowel movements compared with no treatment and other PAMORAs.

The cost-effectiveness evidence includes naldemedine in several clinical scenarios, for both pure opioid-induced constipation and mixed aetiology constipation. In all scenarios, the most likely cost-effectiveness results are within what NICE normally considers an acceptable use of NHS resources. Therefore, naldemedine is recommended for opioid-induced constipation in adults who have had laxative treatment.

2 Information about naldemedine

Marketing authorisation indication

2.1 Naldemedine (Rizmoic, Shionogi) has a marketing authorisation in the UK for 'the treatment of opioid-induced constipation in adult patients who have previously been treated with a laxative'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of a 28-tablet pack of naldemedine is £41.72 (excluding VAT; BNF online, accessed March 2020). The cost of a course of treatment depends on the duration of opioid-induced constipation needing treatment. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Shionogi, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- Combination standard laxatives are recommended for mixed aetiology constipation, when initial laxative therapy has been tried (see technical report, issue 1, page 14).
- Opioid-induced constipation often happens at the same time as other causes of constipation (mixed aetiology constipation) in people with both non-cancer and cancer pain. In these circumstances, naldemedine is suitable for managing the opioid-induced component of mixed aetiology constipation (see technical report, issue 1, page 14).
- Laxative-inadequate response is an artificial definition not used in clinical practice and has been removed from the treatment pathway. The company positioning of naldemedine in the relevant subgroups in the treatment pathway is now clear (see technical report, issue 2, page 15).
- Rescue medication should be included in both the naldemedine and comparator groups. Cost-effectiveness analyses include the intention-to-treat (ITT) population and can be considered relevant for decision making (see technical report, issue 3, page 16).
- The results of the COMPOSE trials can be generalised to England. Naldemedine is likely to be equally effective in people with non-cancer and cancer pain who have opioid-induced constipation (see technical report, issue 5, page 19).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 11, page 25), and took these into account in its decision making. It discussed the following issues, including issues 4 and 6 from the technical report, which remained unresolved after the technical engagement stage.

New treatment option

People with opioid-induced constipation would welcome a new

treatment option

3.1 Opioid receptors are present in the gastrointestinal tract. When opioids bind to these receptors they can disrupt normal gastrointestinal function, usually resulting in opioid-induced constipation. Treatment for opioid-induced constipation could be a single treatment with a peripherally acting mu-opioid receptor antagonist (PAMORA) such as oral naloxegol or subcutaneous methylnaltrexone. But it commonly involves a combination of a PAMORA and a conventional laxative. Naldemedine is an alternative oral PAMORA taken as a single daily dose. The clinical expert explained that opioid-induced constipation is very common in people with non-cancer and cancer pain, and continues regardless of the type of opioid used. The expert estimated that over 80% of patients with cancer pain will have opioid-induced constipation, while the prevalence is likely to be lower in patients with non-cancer pain. The clinical expert also highlighted that in clinical practice, many patients taking a PAMORA have mixed aetiology constipation and so need a combination treatment to target the different causes of constipation. For some patients the burden of opioid-induced constipation on quality of life is greater than the pain that needs an opioid. This often means patients stop opioid treatment. The clinical expert said that a key benefit of a PAMORA is that patients can have a normal stool, while those taking conventional laxatives often experience a continual back and forth of being constipated and then having diarrhoea. This is a huge burden for both patients and carers in terms of continually managing bowel function. The committee concluded that people with opioid-induced constipation would welcome a new treatment that improves their constipation symptoms and quality of life.

Comparators

There are several relevant comparators including no treatment, laxatives, naloxegol and methylnaltrexone

3.2 The clinical expert confirmed that all relevant comparators had been included in the key subpopulations modelled by the company (see section 3.4, table 1). The clinical expert explained that the available PAMORAs are subcutaneous methylnaltrexone and oral naloxegol. The committee was informed that methylnaltrexone is primarily used to treat severe cases of constipation when a response is needed quickly, before switching to an oral treatment. The

comparators included:

- naloxegol for people with opioid-induced constipation
- methylnaltrexone for people with opioid-induced constipation and cancer pain
- laxatives for people with mixed aetiology constipation
- no treatment for people with opioid-induced constipation or mixed aetiology constipation.

The committee also discussed the value of conventional laxatives in managing opioid-induced constipation. The clinical expert explained that because of the way opioids cause constipation and the way conventional laxatives work, there is very little evidence to support the use of conventional laxatives for treating opioid-induced constipation. The committee concluded that all relevant comparators had been included in the correct subpopulations' analyses.

Response in the COMPOSE trials

Naldemedine is clinically effective compared with placebo and there are more clinical benefits for patients than considered in the trials

3.3 The company submission included 4 pivotal randomised trials (COMPOSE-1, -2 -3 and -4) and 3 supportive open-label safety studies (COMPOSE-5, -6 and -7). The primary outcome for COMPOSE-1, -2 and -4 was the proportion of people who had spontaneous bowel movements. For COMPOSE-3, the primary outcome was measures of treatment-emergent adverse events. The proportion of people who had spontaneous bowel movements was significantly greater in the naldemedine arm compared with placebo for COMPOSE-1, -2 and -4:

- COMPOSE-1: naldemedine 48%, placebo 35%, percentage change 13.0% (95% confidence interval [CI] 4.8 to 21.2).
- COMPOSE -2: naldemedine 53%, placebo 34%, percentage change 18.9% (95% CI 10.8 to 27.0).

- COMPOSE-4: naldemedine 71%, placebo 34%, percentage change 36.8% (95% CI 23.7 to 49.9).

The committee discussed the response rates in the COMPOSE trials and noted that there was response in both the naldemedine and placebo groups. The clinical expert explained that pure opioid-induced constipation should respond to a PAMORA (including naloxegol and methylnaltrexone). Because the response rates in the COMPOSE trials were not 100%, this suggests that patients having naldemedine had mixed aetiology constipation. The expert explained that many other factors other than opioid use can contribute to constipation. These include gastrointestinal pathology, other medications including antiemetics and painkillers, level of mobility and diet. These causes of constipation would not respond to a PAMORA and in some cases would not respond to a conventional laxative. The clinical expert also explained that the frequency of bowel motions is not as important to patients as other symptoms of opioid-induced constipation such as bloating, straining and incomplete evacuations, which affect the patient's quality of life. Opioids may also affect other functions in the gut, causing symptoms such as nausea and gastroparesis. The expert explained that PAMORAs not only increase the frequency of bowel movements but also help to manage these other side effects of opioids. The committee concluded that the increase in quality of life for people whose constipation had a response to naldemedine compared with placebo includes relief of other opioid-induced symptoms, which may be directly or indirectly related to constipation. It also concluded that naldemedine is more clinically effective compared with placebo and there are more clinical benefits for patients than considered in the trials.

Subpopulations included in the economic model

The key subpopulations (0 to 4) reflect the clinical pathway in NHS practice and were relevant for decision making

3.4 The committee considered several key subpopulations revised by the company after clarification stage and after technical engagement. The committee agreed that subpopulations 1 to 4 reflect the clinical pathway in NHS practice (see table 1 below).

Table 1: Key subpopulations modelled by the company

Subpopulation	Intervention	Comparator	Source
0: OIC, patients with non-cancer pain	Naldemedine with or without a rescue laxative	Placebo with or without a rescue laxative	COMPOSE-1 and COMPOSE-2 (ITT)
1: OIC and mixed aetiology constipation, patients with non-cancer pain	Naldemedine with or without a laxative and with or without a rescue laxative	Placebo with or without a laxative and with or without a rescue laxative	COMPOSE-3 (ITT)
2: mixed aetiology constipation, patients with non-cancer pain	Naldemedine plus stable laxative with or without a rescue laxative	Placebo plus stable laxative with or without a rescue laxative	COMPOSE-3 (ITT stable laxative subgroup)
3: OIC, patients with non-cancer pain	Naldemedine with or without a rescue laxative	Naloxegol with or without a rescue laxative	ITC from Luthra et al. 2018
4: OIC, patients with cancer pain	Naldemedine with or without a rescue laxative	Methylnaltrexone (SC) with or without a rescue laxative	ITC based on COMPOSE-4 and Bull et al. 2015

Abbreviations: ITC, indirect treatment comparison; ITT, intention-to-treat analysis; OIC, opioid-induced constipation; SC, subcutaneous injection.

The committee discussed the clinical plausibility of the various subpopulations modelled by the company. The clinical expert confirmed that the key subpopulations 0 to 4 reflected NHS practice. The clinical expert explained that standard practice in England often involves patients starting therapy with a conventional laxative, which will often remain as part of the treatment regimen in both pure opioid-induced constipation and mixed aetiology constipation. When there is a poor response, a PAMORA would be considered in addition to the conventional laxative, and response to therapy would be monitored. The experience of the clinical expert indicated varying NHS practice, and limited use of the NICE technology appraisal guidance on naloxegol for treating opioid-induced constipation. The committee agreed that subpopulations 0 to 4 reflected naldemedine in clinical practice and were relevant for decision making.

Indirect treatment comparisons

The indirect treatment comparisons for subpopulations 3 and 4 are relevant for decision making

3.5 The company submission did not include any direct evidence comparing naldemedine with any of the active comparators (naloxegol and methylnaltrexone). It included the results from an indirect treatment comparison comparing naloxegol with naldemedine (relative risk [RR] 0.79 [95% CI 0.63 to 0.99]) which informed subpopulation 3, based on an independent publication by Luthra et al. (2018). Also, the company included the results from an indirect treatment comparison comparing methylnaltrexone with naldemedine (RR 0.88 [95% CI 0.71, 1.06]). This informed subpopulation 4, based on the COMPOSE-4 trial and a randomised controlled trial by Bull et al. (2015). The company did not provide the methods used to combine the data from the trials in the indirect treatment comparison for subpopulation 4 after technical engagement. The company also highlighted that they did not have the input data for the indirect treatment comparison used to inform subpopulation 3. Therefore, the ERG was unable to assess the appropriateness of the indirect treatment comparison analyses or verify the results. After technical engagement, the ERG did several probabilistic sensitivity analyses and concluded that the uncertainty in the indirect treatment comparisons were unlikely to have a large effect on the cost-effectiveness results. For subpopulation 4, the ERG noted that methylnaltrexone is much more expensive than naldemedine. So, even if methylnaltrexone was much more effective, naldemedine would still be cost effective. The clinical expert noted that as subpopulations 3 and 4 did not include a direct comparison of these PAMORAs with naldemedine, it was difficult to determine whether there was a true difference between treatments. The committee concluded that any uncertainty was likely to have a small effect on the cost-effectiveness results for these subpopulations. It therefore considered that the indirect treatment comparisons for subpopulations 3 and 4 were relevant for decision making.

Assumptions in the economic model

Stopping treatment for constipation that does not respond is an appropriate assumption in the model

3.6 The company's economic model structure was based on the model considered in NICE's technology appraisal guidance on naloxegol. This consisted of a decision-tree structure for the first cycle followed by a Markov-structure from the second cycle onwards. Patients enter the Markov model at either opioid-induced constipation or non-opioid-induced constipation (when having treatment) health states, with a cycle length of 4 weeks and time horizon of up to 5 years. The company made several structural assumptions in their economic model, based on the NICE technology appraisal guidance, including for stopping treatment. Patients were assumed to stop treatment with naldemedine if their constipation had not responded by week 4 or had responded but they then experienced a reoccurrence of opioid-induced constipation. After stopping treatment, people whose constipation had not responded were assumed to not resume treatment across the 5-year time horizon of the economic model. The committee discussed loss of treatment response and the clinical likelihood of having only 1 possibility of response to naldemedine. The clinical expert explained that patients with pure opioid-induced constipation often develop mixed aetiology constipation, meaning response to a PAMORA may reduce. However, the clinical expert explained that for people with pure opioid-induced constipation, a PAMORA should not stop working and people should not develop a tolerance. Any loss of efficacy is normally because of a change in the patient's underlying condition rather than because of the PAMORA itself. The committee discussed the effect of assuming that treatment would be stopped on the estimates of cost effectiveness. It noted that the company had modelled naldemedine across various time horizons between 1 and 5 years. For most subpopulations, the incremental cost-effectiveness ratios (ICERs) increased slightly with a shorter time horizon. The ERG also noted that their clinical expert confirmed the appropriateness of assuming that treatment would be stopped for people whose constipation does not respond, or those who lost response. The committee recognised that stopping treatment for constipation that stops responding to naldemedine is plausible in clinical practice and is an appropriate assumption for the model.

Extrapolation of treatment response

Choice of survival distribution has a minimal effect on the ICERs for each subpopulation

3.7 The company submission included the probabilities for loss of treatment response to naldemedine, which were based on extrapolated time-to-event data from the relevant trials (see section 3.4, table 1). The company did not explore the clinical plausibility of their preferred parametric curves to model loss of treatment response at the clarification stage or after technical engagement. Instead, it highlighted that for all subpopulations, the choice of survival distribution has a minimal effect on the ICERs for each subpopulation. The ERG agreed with the choice of parametric curve in the company submission for subpopulations 1 to 4 but concluded that the Gompertz model was more appropriate for subpopulation 0. This was based on clinical opinion, which suggests that loss of response is likely to plateau at a certain level. The committee was aware that the choice of the curve has a minimal effect on the ICERs for all the subpopulations. It agreed that, while the clinical plausibility of the time-to-event curves is not known and that it would have been helpful for the company to provide this information, the effect on the ICERs is likely to be small.

Utility values in the economic model

The ICERs are sensitive to treatment-specific utility values and it is acceptable to include these in the economic model

3.8 The EQ-5D was not used in the COMPOSE trials, and so utility values from NICE's technology appraisal guidance on naloxegol were used. The company used treatment-specific utilities for the non-opioid-induced constipation (when having treatment) health state in the base case. The ERG noted that each health state should be homogeneous enough that the utility does not differ between different treatments. Therefore, it would have preferred a refined Markov model to which health state-specific utility values could be applied. The ERG's clinical expert did not expect differences in quality of life between people having naldemedine or naloxegol. The committee was aware that the ICER was sensitive to assuming treatment-specific utilities. Using health state-specific utilities increased the company's base case ICERs for subpopulations 0, 1 and 2

to £28,131, £27,484 and £15,020 per quality-adjusted life year (QALY) gained, respectively. The ERG noted that while it was not ideal to use treatment-specific utilities, the non-opioid-induced constipation (when having treatment) health state was probably quite heterogeneous in terms of spontaneous bowel movements. The committee agreed that using treatment-specific utilities was reasonable based on the approach in the technology appraisal guidance on naloxegol, and on the clinical expert opinion that naldemedine would improve a range of opioid-induced side effects, in addition to increases in spontaneous bowel movements seen in the COMPOSE trials. The committee noted that the company's model may not have captured these additional health benefits of naldemedine, and therefore accepted the use of treatment-specific utilities in the economic model.

Cost-effectiveness estimates

The most plausible ICER is likely to be below £20,000 per QALY gained for all subpopulations

3.9 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of the uncertainty in the indirect treatment comparisons and the impact on the choice of utility values, the committee agreed that an acceptable ICER would be below £20,000 per QALY gained. The committee recognised that the company's cost-effectiveness estimates for naldemedine using treatment-specific utility values were below £20,000 per QALY gained for all subpopulations (see table 2 below) and considered this to be a cost-effective use of NHS resources.

Table 2 Naldemedine cost-effectiveness results for key subpopulations

Subpopulation	Incremental costs	Incremental QALYs	ICER (per QALY gained)
Subpopulation 0	£275.11	0.022	£12,556

Subpopulation	Incremental costs	Incremental QALYs	ICER (per QALY gained)
Subpopulation 1	£838.46	0.067	£12,489
Subpopulation 2	£788.59	0.083	£9,462
Subpopulation 3	£73.72	0.02	£3,649
Subpopulation 4	-£3,356	0.014	Naldemedine is dominant (it is more effective and costs less than comparators)

The ICERs in table 2 have been calculated using incremental costs and QALYs from the company's economic model.

The committee noted that the use of health state-specific utilities increased the ICERs for some of the subpopulations above this range, but that these were still under £30,000 per QALY gained. The committee was also persuaded that using health state-specific utilities did not capture all the broader benefits of treatment with naldemedine as highlighted by the clinical expert. If these were taken into account, the ICERs were likely to be under £20,000 per QALY gained. The committee was reassured by the results of the ERG's probabilistic sensitivity analysis for subpopulation 1. This indicated that naldemedine had probabilities of being cost effective of 74.8% and 86.3% at £20,000 and £30,000 per QALY gained, respectively. The committee agreed that treatment with naldemedine will likely result in an ICER below £20,000 per QALY gained compared with the relevant comparators for all the subpopulations.

Other factors

There are no equality issues relevant to the recommendations

3.10 No equality or social value judgement issues were identified.

The benefits of naldemedine are captured in the cost-effectiveness analysis

3.11 The company considered naldemedine to be innovative because of its permanent binding capacity and higher receptor affinity compared with other

PAMORAs. The committee agreed that these were important benefits of naldemedine. But, it concluded that it had not been presented with evidence of any additional benefits that could not be captured in the QALYs.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has opioid-induced constipation and the doctor responsible for their care thinks that naldemedine is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C. Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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ISBN: 978-1-4731-3861-2

Accreditation

NICE National Institute for Health and Care Excellence

NICE guidance

Fostamatinib for treating refractory chronic immune thrombocytopenia

Technology appraisal guidance
Published: 7 January 2022
www.nice.org.uk/guidance/ta759

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so 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.

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.

Contents

1 Recommendations

1.1 Fostamatinib is not recommended, within its marketing authorisation, for treating refractory chronic immune thrombocytopenia in adults.

1.2 This recommendation is not intended to affect treatment with fostamatinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Rituximab or mycophenolate are treatment options for refractory chronic immune thrombocytopenia after thrombopoietin receptor agonists, or if they are not suitable. Fostamatinib would be used at the same point in the treatment pathway.

Clinical evidence shows that fostamatinib is effective compared with placebo. There is no clinical trial evidence directly comparing fostamatinib with rituximab or mycophenolate. An indirect comparison shows that fostamatinib works better than rituximab at increasing platelet counts.

The cost-effectiveness estimates for fostamatinib compared with rituximab are higher than what NICE normally considers cost effective. So, fostamatinib is not recommended.

2 Information about fostamatinib

Marketing authorisation indication

2.1 Fostamatinib (Tavlesse, Grifols) is indicated 'for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list prices of fostamatinib are:

- £3,090 per 60-tablet pack; each tablet contains 100 mg of fostamatinib (excluding VAT; BNF online, accessed October 2020)
- £4,635 per 60-tablet pack; each tablet contains 150 mg of fostamatinib (excluding VAT; BNF online, accessed October 2020).

The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Grifols, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

People and clinicians would welcome an additional treatment option

3.1 Chronic immune thrombocytopenia (ITP) is an autoimmune condition characterised by platelet destruction, leading to a low number of platelets circulating in the blood. Platelets are a type of cell involved in blood clotting. Thrombocytopenia is usually defined as having fewer than 100,000 platelets per microlitre of blood. Signs and symptoms include bruising easily, the appearance of red spots under the skin (petechiae), fatigue and bleeding. Frequency and severity of bleeding may differ in people with similar platelet counts. Some have no bleeding, some bleed from the skin, nose, or urinary tract and others have more serious intracranial and gastrointestinal bleeding. Because of the risk of bleeding, people may become stressed or depressed. A particular concern is a sudden drop in platelets, which can lead to life-threatening bleeds. Although new treatments called thrombopoietin receptor agonists (TPO-RAs) are available, they do not work for everyone, and some people cannot take them. The patient and clinical experts explained that some of the treatment options suppress the immune system and increase the risk of infection. The committee concluded that people and clinicians would welcome an additional treatment option.

Treatment pathway

The treatment pathway includes thrombopoietin receptor agonists followed mostly by rituximab and mycophenolate

3.2 Initial treatment for ITP involves high-dose oral corticosteroids or intravenous immunoglobulin (IVIg). Later treatments include:

- TPO-RAs (see NICE's technology appraisal guidance on romiplostim and eltrombopag)
- rituximab, which does not have a marketing authorisation for ITP
- surgical removal of the spleen (splenectomy)
- azathioprine, mycophenolate, cyclosporine, dapsone and danazol.

The clinical experts explained that the choice of treatment after corticosteroids or IVIg depends on time to relapse, but clinicians are most likely to offer TPO-RAs. They noted that clinicians avoid offering splenectomy in the first year after diagnosis and are unlikely to offer it as a second line of treatment. After TPO-RAs, rituximab and mycophenolate are the most common treatments, but azathioprine is offered to people who want to conceive. Cyclosporine is rarely used because of adverse effects, and dapsone is used as a last resort. The committee understood that danazol is no longer available in the UK. For people with platelet counts higher than 30,000 per microlitre of blood and at low risk of bleeding, clinicians may adopt a 'watch and rescue' approach. A patient expert explained that once his platelet count had stabilised after treatment with IVIg, he went onto a watch and rescue approach for 15 years. The committee concluded that the treatment pathway after TPO-RAs includes many treatments, most commonly rituximab and mycophenolate.

Treatment decisions are based on more than platelet count

3.3 The clinical experts highlighted that they and people with ITP make treatment decisions based on platelet count and other risk factors for bleeding, such as age and use of anti-platelet treatment. They explained that the objective of treatment is a platelet count higher than 30,000 per microlitre of blood to reduce the risk of bleeding. Platelet counts higher than 50,000 per microlitre may be used as a target for maintenance treatment, to avoid fluctuating platelet levels and minimise the chance of counts dropping below 30,000 per microlitre. The committee appreciated that treatment aims to achieve platelet counts lower than those used to define thrombocytopenia. It concluded that treatment decisions were based on more than platelet count.

The company's positioning of fostamatinib in the treatment pathway is broadly appropriate

3.4 Fostamatinib has a marketing authorisation for treating chronic ITP after previous treatments. The company proposed that fostamatinib is used after

TPO-RAs (romiplostim and eltrombopag) or when TPO-RAs are not suitable. This is narrower than the marketing authorisation. The clinical experts considered the company's proposed positioning to be reasonable. They noted that other treatments such as rituximab and mycophenolate may be used after TPO-RAs at the point when the company proposed using fostamatinib. The clinical experts noted that rituximab is considered more effective for young women and people with other autoimmune conditions. However, some people may be concerned about rituximab's immunosuppressive effects so would prefer an alternative treatment. The clinical experts also highlighted that for people at risk of blood clots, TPO-RAs would not be suitable so fostamatinib would be considered instead. They also noted that other treatments such as rituximab and mycophenolate may be used after TPO-RAs, but before fostamatinib. The committee acknowledged that treatment is individualised. It concluded that the company's positioning of fostamatinib in the treatment pathway was broadly appropriate.

Rituximab and mycophenolate are relevant comparators for fostamatinib

3.5 As relevant comparators, NICE's final scope included the TPO-RAs romiplostim and eltrombopag, rituximab, splenectomy, cytotoxic agents, dapsone, danazol and 'watch and rescue'. However, the company excluded romiplostim and eltrombopag based on its positioning of fostamatinib after TPO-RAs, or when TPO-RAs are unsuitable. The company selected rituximab as the only comparator. For all other comparators, the company argued that there was little evidence to support comparisons with fostamatinib. The clinical experts agreed that many treatments used in practice do not have robust clinical trial data. They also noted that rituximab and mycophenolate are often used in clinical practice at the same point in the treatment pathway as the company proposed for fostamatinib (see section 3.4). The committee concluded that the relevant comparators for fostamatinib are rituximab and mycophenolate.

Clinical effectiveness

Fostamatinib is effective at increasing platelet count compared with placebo, based on the FIT trials

3.6 FIT1 and FIT2 are multinational, double-blind, randomised, phase 3 trials of the

same design comparing fostamatinib with placebo. Both trials included adults with persistent or chronic ITP that had not responded to at least 1 treatment. Their average platelet count was less than 30,000 per microlitre of blood. The primary endpoint in both trials was stable platelet response. This was defined as a platelet count of 50,000 per microlitre or more in at least 4 out of 6 assessments between week 14 and week 24. Secondary outcomes included:

- the percentage of people with a platelet count higher than 50,000 per microlitre at week 12 and week 24
- the percentage of people with a platelet count higher than 30,000 per microlitre and an increase of at least 20,000 per microlitre from baseline at week 12 and week 24, after a platelet count of less than 15,000 per microlitre at baseline
- bleeding frequency and severity, measured by the Immune Thrombocytopenic Purpura Bleeding Scale and World Health Organization bleeding scores.

People randomised to fostamatinib had 100 mg twice a day initially. This could be increased to 150 mg twice a day at week 4 if platelet count remained below 50,000 per microlitre and fostamatinib was well tolerated. Rescue treatments were allowed as needed in both treatment arms. People in FIT1 and FIT2 were invited to take part in FIT3, a 5-year open-label extension study, if they:

- completed the full 24 weeks of treatment or
- stopped the trials after at least 12 weeks of double-blind treatment because of lack of efficacy (including at least 4 weeks at the 150 mg dose of fostamatinib or placebo).

In FIT3, the initial fostamatinib dose was the dose that produced a platelet response in FIT1 and FIT2. If there was no platelet response in FIT1 and FIT2, the initial dose was 100 mg twice a day.

Pooled results from FIT1 and FIT2 showed that rates of stable response were higher in the fostamatinib arm (18%) than in the placebo arm (2%). Fostamatinib led to greater improvements than placebo for all secondary outcomes, but these benefits appeared to decrease over time. For example, the pooled percentage of people with a platelet count higher than 50,000 per microlitre at week 12 in the fostamatinib arm was 23% compared with 16% at week 24. The committee concluded that fostamatinib increased platelet levels, but only about 1 in 5 people had a platelet response, which may decrease over time.

The criteria for non-response and stopping treatment in the FIT trials do not reflect NHS clinical practice

3.7 Starting from week 12, the criteria used to define non-response in FIT1, FIT2 and the FIT3 extension study were:

- a platelet count of less than 50,000 per microlitre of blood or
- an increase of less than 20,000 per microlitre for people with baseline platelet counts of less than 15,000 per microlitre.

People with non-response could withdraw from the study. The clinical experts explained that less stringent definitions of response are typically used in practice. This is because platelet counts can vary as a result of infections or other clinical characteristics and may not affect the overall response to treatment. They noted that generally they would consider platelet counts of more than 30,000 per microlitre and doubling of platelet counts from the treatment starting point as an acceptable response (see section 3.3). They would recommend stopping treatment if:

- response was not acceptable
- adverse effects were intolerable
- platelet counts dropped to baseline levels or below 20,000 to 30,000 per microlitre.

The committee concluded that the criteria for non-response and stopping treatment in the FIT trials did not reflect clinical practice.

The results of the FIT clinical trials are likely to be generalisable to NHS clinical practice

3.8 The average age at baseline in FIT1 and FIT2 was between 53 and 54 years. The ERG was concerned that people enrolled in these trials were about 10 years younger than in clinical practice and had a lower risk of bleeding, which increases with age. The clinical experts highlighted that fostamatinib is likely to work equally well in clinical practice regardless of age. The committee concluded that the results of the FIT clinical trials are likely to be generalisable to NHS practice, but the absolute benefit may differ from the trials.

Network meta-analyses 2 and 3 have limitations but are

considered for decision making

3.9 The committee recalled that there was no evidence directly comparing fostamatinib with rituximab or mycophenolate. The company's base case discussed at the first committee meeting included rituximab as the only relevant comparator. Clinical efficacy data for rituximab was based on clinical expert opinion, rather than published literature. After consultation, the company did a network meta-analysis comparing fostamatinib with rituximab, with an outcome of overall platelet response. The definition of overall platelet response varied across studies included within the meta-analysis, so the company did 3 separate analyses:

- Analysis 1 was based on the primary definition of response in each study and included FIT1, FIT2 and 4 rituximab studies.
- Analysis 2 used alternative definitions for response. Each focused on platelet counts greater than 30,000 per microlitre of blood and at least doubling from baseline, with and without rescue treatments at various time points. It included the same studies as analysis 1.
- Analysis 3 used the definition of response as an increase in platelet count greater than 30,000 per microlitre, at least doubling from baseline and without rescue treatment at 4 weeks. It included only FIT1, FIT2 and the Ghanima et al. (2015) study for rituximab.

The company preferred analysis 2 because the endpoints varied less than in analysis 1. The ERG noted that analysis 2 included both randomised and non-randomised evidence, which the Cochrane Handbook (11.3.4, version 6.2, 2021) does not recommend because of bias. The ERG preferred analysis 3, which included only randomised studies. The analyses showed that fostamatinib was more effective than rituximab, and rituximab was no better than placebo. The committee noted that the size of benefit differed between analyses. Analysis 2 showed a 4-fold increase in the odds of having a response with fostamatinib compared with rituximab, whereas analysis 3 showed a 3-fold increase. Analyses 1 and 2 included 4 different dosages of rituximab:

- 375 mg/m^2 body surface area per week for 4 weeks
- 100 mg fixed dose per week for 4 weeks

- 375 mg/m^2 per week for 2 weeks in people with early response and for 4 weeks in the others and
- 750 mg/m^2 per week for 2 weeks.

Analysis 3 included only the rituximab dosage of 375 mg/m^2 per week for 4 weeks. The ERG clinical adviser noted that 375 mg/m^2 per week for 4 weeks and the 100 mg fixed dose are used in clinical practice and are the most relevant (see section 3.16). The committee noted that the non-randomised study (Zaja et al. 2012) was the only study that included the rituximab 100 mg fixed dose. The ERG explained that when the company used analysis 2 in its model, it did not use the estimates from Zaja et al. (2012) to inform the efficacy of the rituximab 100 mg dose. Instead, the company assumed that the efficacy of rituximab 100 mg was the same as that of rituximab 375 mg/m^2. The ERG advised that this likely favoured rituximab, although it expected the size of bias to be small. When using analysis 3, the company and the ERG also assumed that both doses of rituximab had the same efficacy. The committee noted that analysis 2 also included Arnold et al. (2012), a randomised controlled trial comparing 375 mg/m^2 rituximab with placebo. It noted that the company could have done an additional analysis comparing the FIT trials with only the Ghanima et al. (2015) and Arnold et al. (2012) trials, because both assessed the efficacy of rituximab 375 mg/m^2. The committee agreed that analysis 1 was the least relevant because the endpoint definitions varied most across studies. It concluded that it would consider both analyses 2 and 3 in its decision making, because they both had limitations.

The clinical efficacy of mycophenolate is uncertain

3.10 The company excluded mycophenolate from its network meta-analysis because it did not identify any randomised trials. It noted that mycophenolate does not have a marketing authorisation for ITP. The company presented data from the UK ITP registry and a panel of clinical experts, who indicated that a substantial proportion of people do have mycophenolate after TPO-RAs. (The exact proportion is confidential and cannot be reported here). The committee noted that this further supports its use in NHS clinical practice. The ERG confirmed the lack of evidence for mycophenolate. The committee noted that relevant comparators are selected based on their routine use in NHS clinical practice, regardless of whether they have a marketing authorisation for that indication. It also noted that rituximab does not have a marketing authorisation for ITP, but the company included it as a relevant comparator. The committee maintained that both rituximab and mycophenolate are relevant comparators for

fostamatinib (see section 3.5). But it acknowledged that there is no published evidence showing how well mycophenolate works for people with ITP.

The company's economic model

The company's approach to merging partial and complete response health states has limitations but best reflects clinical practice

3.11 The company used a Markov cohort state transition model to estimate the cost effectiveness of fostamatinib compared with rituximab. The model cohort was split into 2 groups based on whether a person had intracranial bleeding. The company's original model included 3 health states in each group:

- response (a platelet count of more than 50,000 per microlitre of blood)
- partial response (a platelet count of 30,000 to 50,000 per microlitre) and

- non-response (a platelet count of less than 30,000 per microlitre).

The company explained that its thresholds were informed by the latest ITP consensus (2019) and the approach taken in previous NICE submissions for eltrombopag and romiplostim. The company estimated the probability of being in each state on pooled data from FIT1, FIT2 and the FIT3 extension study. The model included a lifetime time horizon. The clinical experts noted that intracranial bleeding is a rare event, but it is associated with substantial disability and morbidity, which may also affect carers' quality of life. The clinical experts explained that health states split into non-response (platelet count less than 30,000 per microlitre) and response (platelet count more than 30,000 per microlitre) would better reflect clinical practice (see section 3.3). After consultation, the company merged partial and complete response into a single response health state. That is, the company's revised model included only 2 health states, non-response (platelet count less than 30,000 per microlitre) and response (platelet count more than 30,000 per microlitre). The company did a scenario analysis using the original health states, noting that it had a small impact on cost effectiveness. The ERG agreed that a model with 2 health states better reflected clinical practice than the 3-health state model. But it had concerns with the company's methodology because the revised model continued to follow a 3-state structure. The company simply set most inputs for partial response to be equal to the full response health state. The ERG noted that the company should have recalculated how likely people are to move between the 2 health states using data from the FIT trials. Instead, the company used the probabilities of moving between 3 health states from its original model. The ERG explained that these probabilities were based on a low number of events in the FIT trials so were uncertain. These uncertainties were further increased when extrapolating the probabilities over the model's lifetime time horizon and by the approach taken to apply the network meta-analysis results. The committee acknowledged the limitations of the company's approach to merging the health states. But it agreed that it preferred the merged 2-health state structure because it better reflected clinical practice than the 3-health state model.

The revised model criteria for non-response and stopping treatment are in line with NHS practice but should be applied at 12 weeks

3.12 The committee recalled that the criteria for non-response and stopping treatment in the FIT trials were not in line with clinical practice (see section 3.7). The company's original model followed the stopping rule from the FIT trials.

However, after consultation, the company changed the stopping rule in its economic model to a platelet count of less than 30,000 per microlitre of blood, in line with clinical practice. The ERG explained that the model applied this stopping rule at 12 weeks, with a half-cycle correction. Applying a half-cycle correction effectively means that treatment would be stopped 2 weeks earlier, at 10 weeks, if a platelet count of 30,000 per microlitre or more was not reached. The company noted this was a conservative assumption because a clinical expert panel advised that treatment could be stopped earlier, by 8 weeks, if platelet response was not reached. The committee noted that fostamatinib's marketing authorisation includes a 12-week stopping rule if platelet count is 'not sufficient'. The ERG explained that removing the half-cycle correction applied to the stopping rule increased the cost-effectiveness estimates. This was because treatment costs for people whose disease does not respond to treatment are incurred for longer. The committee concluded that the revised criteria for non-response and stopping were in line with clinical practice but should be applied at 12 weeks, without a half-cycle correction.

The company's revised approach to modelling subsequent treatments is acceptable

3.13 In the company's original submission, people who had fostamatinib moved to watch and rescue treatment if their platelet count fell below 30,000 per microlitre of blood (non-response). However, people who had rituximab did not move to watch and rescue treatment. Instead, they remained in the less than 30,000 per microlitre health state and could never have a platelet count higher than 30,000 per microlitre after cycle 4 in the model. This led to a worse modelled outcome than was seen with placebo in the fostamatinib clinical trials. The company explained that its clinical experts had advised that in clinical practice, people do not have other treatments at the same time as rituximab. The clinical experts at the committee meeting agreed but noted that rituximab is used only for a short time. After that, treatment is offered to raise platelet counts to a level higher than 30,000 per microlitre. The committee also noted that some people who do not have a response to fostamatinib may get rituximab, rather than watch and rescue treatment. At its first meeting, the committee concluded that subsequent treatments should be modelled consistently between arms and include all relevant sequences. After consultation, the company updated its base case to allow watch and rescue treatment after rituximab, when platelet count is less than 30,000 per

microlitre. The ERG confirmed that the company applied the change correctly. The committee noted that the company's revised approach did not include all relevant treatment sequences. For example, it did not include an option of having rituximab after fostamatinib. The ERG explained that modelling a full treatment sequence across the pathway was difficult because of evidence limitations. This was a key model limitation and contributed to the overall uncertainty. The committee concluded that the company's revised approach to modelling subsequent treatments had limitations but was acceptable for decision making.

It is not appropriate to assume that people can taper or stop treatment without any loss of clinical benefit

3.14 The company explained that its base case did not include tapering dosages or stopping treatment in people with a sustained platelet response. It assumed that those people remain on the full treatment dose until loss of response or death. However, the company stated that tapering was common with other ITP treatments and was likely with fostamatinib. The company did a scenario analysis in which it assumed that 40% of people with a sustained platelet response to fostamatinib (platelet counts above 30,000 per microlitre of blood after 1 year) stop active treatment but maintain the full clinical benefit. This scenario improved fostamatinib's cost-effectiveness estimates, as did an ERG scenario in which only people with a sustained platelet count of more than 50,000 per microlitre taper treatment. But, the company recognised that it did not have data to support tapering or stopping fostamatinib without losing benefit. The committee recognised that maintaining treatment benefit after tapering or stopping treatment was speculative. It also noted that fostamatinib's marketing authorisation does not include treatment tapering or stopping in people with a sustained platelet response. The committee concluded that it is not appropriate to assume that people with sustained platelet response can taper or stop treatment without losing clinical benefit.

Basing the use of rescue treatment on UK ITP registry data is likely to reflect clinical practice

3.15 In its original base case, the company used FIT trials data to inform the frequency and type of rescue treatments. After consultation, it used the UK ITP registry data instead. The use of rescue treatments in the UK ITP registry

depended on platelet count and included IVIg, intravenous methylprednisolone, platelet transfusion, oral prednisolone and oral dexamethasone. The company justified using the UK ITP registry because:

- the FIT trials included locations outside the UK
- in the trials, people had their platelet counts measured more often than expected in clinical practice and
- the trial populations had a relatively lower risk of bleeding.

In its base case, the company applied frequency and type of rescue treatments separately for each health state defined by platelet count. The non-response health state had greater costs, driven by the increased frequency of events needing rescue treatments and increased use of IVIgG compared with oral prednisolone. The ERG accepted that the UK ITP registry data is likely generalisable to NHS clinical practice and used this source in its base case. However, the ERG was concerned that the company did not provide data comparing the populations in the UK ITP registry and FIT trials. The company explained that it could not get demographic information from the UK ITP registry. But it noted that everyone included in the analysis had previously had treatment with TPO-RAs, consistent with the company's positioning of fostamatinib in the treatment pathway (see section 3.4). The ERG was concerned about using different data sources to inform different parts of the model. For example, using the UK ITP registry for frequency and type of rescue treatment, and the company's network meta-analysis for the probability of reaching platelet response with watch and rescue. To address this, the ERG did a scenario analysis using the FIT trial data to inform all inputs for rescue treatments and for prophylaxis before surgery (see section 3.17). The committee acknowledged the limitations of the company's approach. But it concluded that the UK ITP registry was likely to reflect use of rescue treatment in NHS clinical practice.

In clinical practice, 2 doses of rituximab are used, and both should be included in the model

3.16 The committee recalled that the trials included 2 doses of rituximab (see section 3.9). In the 2014 NICE evidence summary for rituximab in ITP, most studies included the higher dose of 375 mg/m^2 per week. Some used a fixed dose of 100 mg per week. International guidelines for ITP recognised that 100 mg per week is an alternative dosing schedule. Statements from several NHS clinical

commissioning groups recommended only the lower dose. One clinical expert explained that she offers a dose of 100 mg per week. She noted that ITP registry data suggested that the effects of this dose are equivalent to the 375 mg/m^2 per week dose. The other clinical expert noted that he uses the higher dose in practice. After consultation, the company analysed the use of rituximab in the UK ITP registry in people who had prior treatment with TPO-RAs. It found that both doses were used (exact usage is confidential and cannot be reported here). The company updated its base case to include a mean dose of rituximab calculated from the UK ITP registry. It also did a scenario analysis using the 100 mg rituximab dose. The ERG was concerned that the company may have underestimated the mean rituximab dose in the UK ITP registry. The ERG corrected this, which led to a small increase in the mean dose. However, it explained that it preferred to use the lower, fixed 100 mg dose which was increasingly recommended for use in NHS clinical practice. The committee considered the clinical advice and UK ITP registry data and agreed that both rituximab doses are used in NHS clinical practice. Therefore, it concluded that both doses are relevant and should be included in the model.

The company's revised approach to modelling prophylaxis before surgery reflects clinical practice

3.17 People who have a platelet count below 30,000 per microlitre of blood may need prophylactic treatment to increase platelet count before surgery. In its original submission, the company assumed that prophylactic treatments were the same as rescue treatments. These include IVIgG, intravenous methylprednisolone and platelet transfusions, but not oral prednisolone. At the first committee meeting, the ERG explained that only 1 course of treatment is used, and this is based on the type of surgery (minor or major). It suggested that IVIgG was used for major surgery, which the ERG's clinical expert estimated accounts for 44% of people having surgery. Oral prednisolone was used for minor surgery in the remaining 56% of people. This affected the cost-effectiveness estimates because prednisolone costs much less than IVIgG. The clinical experts explained that oral prednisolone is used in clinical practice, contrary to the company's assumption. Also, they emphasised that the use of prophylaxis before surgery depends on the timing of the surgery. For example, IVIgG works more quickly than oral prednisolone. After consultation, the company asked a panel of 8 clinical experts about which treatments are used as prophylaxis before surgery in NHS clinical practice. Oral prednisolone was the

most frequently used treatment for both minor (average use 54% [range 0% to 100%]) and major surgery (62% [0% to 100%]). This was followed by IVIgG for both minor (45% [10% to 75%]) and major (49% [10% to 85%]) surgery. The company assumed the same proportions of minor (56%) and major (44%) surgery as the ERG. The ERG agreed with the company's approach to estimating the use of prophylaxis before surgery and noted it was consistent with its expert opinion. The committee was satisfied that the revised company base case was in line with NHS clinical practice.

The company's revised approach to modelling adverse events is acceptable

3.18 The company's base case discussed at the first committee meeting used pooled data from FIT1 and FIT2 for people 65 years and over to estimate the rate of adverse events for fostamatinib. This age group was considered more relevant because it is in line with the starting age in the model. This group had a higher rate of adverse events than the younger people in the trial. The company assumed that the rate of adverse events with rituximab was the same as with fostamatinib. At its first meeting, the committee concluded that adverse events with fostamatinib and rituximab were different and should be modelled separately. After consultation, the company agreed that rituximab was associated with fewer adverse events than fostamatinib and watch and rescue treatments. In its revised base case, adverse events with rituximab were based on a randomised controlled trial comparing 375 mg/m^2 rituximab with placebo (Ghanima et al. 2015). The ERG was satisfied with the company's revised approach but noted some limitations. Rituximab can cause very rare fatal progressive multifocal leukoencephalopathy, which the company excluded from its analysis. The median age in the Ghanima et al. (2015) trial was 46 years, compared with the starting age in the model of 65 years. Adverse events in older people are likely to be more frequent, as seen with fostamatinib in the FIT trials. The committee noted that these assumptions likely favoured rituximab. The ERG explained that the rate of adverse events with the 100 mg weekly dose was likely to be lower than with the higher dose. The committee recalled that at its first meeting, a clinical expert explained that the 100 mg per week dose is well tolerated. The committee noted that assuming equal rates of adverse events with both doses favours fostamatinib. The ERG also explained that the company applied adverse events for rituximab for as long as response was maintained, even though it is only taken for 4 weeks (see section 3.9). However,

the ERG advised that this likely has a small impact on the cost-effectiveness estimates, because cycle-specific costs and disutilities of adverse events with watch and rescue are similar to rituximab. In terms of modelling adverse events with fostamatinib, the company applied the same rate of adverse events for the full duration of treatment when in the response health state. The ERG noted that the company could instead have used the longest available data from the FIT3 extension study to model long-term adverse events with fostamatinib. However, the company explained that this data was not yet available. But it noted that new long-term safety issues were unlikely to emerge because fostamatinib's long-term safety profile in rheumatoid arthritis was consistent with the earlier data in that disease. The committee acknowledged the limitations of the company's approach to modelling adverse events with fostamatinib and rituximab. It noted that overall, it was not clear if this approach favoured rituximab or fostamatinib. However, it concluded that the company's approach was acceptable for decision making.

The company's revised base case overestimates the risk of dying from ITP

3.19 In the company's original base case, it estimated the risk of dying in the non-response health state from the General Practice Research Database (Schoonen et al. 2009). The risk of dying was 1.6 times higher than that of the age- and sex-matched general population, with 13% of deaths from bleeding and 19% from infection. The risk of death was reported for everyone diagnosed with ITP, that is, it was not reported separately by platelet count. The company assumed all excess deaths happened in the lowest platelet count health state (non-response). All other health states had a risk of death that matched the general population. The ERG noted that assuming all deaths in Schoonen et al. (2009) happened in the non-response health state was an important limitation of the company's approach. After consultation, the company identified 2 new studies reporting the risk of dying from ITP and used them in its revised base case. In the 3-health state model, the hazard ratio for mortality was 4.2 in the non-response state (Portielje et al. 2001), 2.5 in the partial response state (Adelborg et al. 2019) and 1.0 in the complete response health state. The 2-health state model used a hazard ratio for mortality of 4.2 in the non-response health state and 1.0 in the merged response health state. The ERG had concerns with the new sources:

- Portielje et al. (2001) reported hazard ratios for mortality specifically in people with platelet counts below 30,000 per microlitre of blood but the study had a small sample size and was not based in the UK.

- Adelborg et al. (2019) was a larger study but reported hazard ratios for everyone with a platelet count less than 50,000 per microlitre.

The clinical experts agreed with the ERG that using Adelborg et al. (2019) for the partial response (platelet count of 30,000 to 50,000 per microlitre) health state was not appropriate. This was because most deaths in people with platelet counts below 50,000 per microlitre could be a result of deaths in people with a platelet count below 30,000 per microlitre. This meant that the model may overestimate mortality in the partial response state. The committee discussed the 3 potential sources of mortality data, noting that all have limitations. It recalled clinical expert advice that many factors influence the risk of dying from ITP, including platelet count, bleeding, age, and treatment. It also recalled advice that treatment had changed over time, and the risk of dying from ITP is now lower than in the past. In the past, deaths related to infection were as high as for bleeding, and likely reflected higher use of splenectomy and heavy immunosuppression. But since the introduction of TPO-RAs, it is rare for people to have chronic platelet counts below 20,000 to 30,000 per microlitre, and rare to have deaths from ITP treatments. The committee agreed that Portielje et al. (2001) may overestimate the current risk of dying from ITP because of the progress in treatment for this disease. It also noted that the risk of dying from intracranial bleeding is already accounted for in the model. So, using hazard ratios for mortality from Portielje et al. (2001) would overestimate mortality in people without intracranial bleeding. Also, the committee discussed that the company did not provide any evidence that fostamatinib reduces the risk of dying from ITP. The model predicts such a reduction, based on less time spent in the non-response health state compared with rituximab. But the committee noted that without any evidence to support this, the effect of fostamatinib on the risk of dying was uncertain. It also noted that mortality assumptions have the biggest effect on the cost-effectiveness estimates. The committee concluded that the company's revised approach overestimates the risk of dying from ITP. It preferred the company's original approach, using estimates from the General Practice Research Database (Schoonen et al. 2009).

The utility values in the model are appropriate, including those for carers

3.20 The company used utility values for the model health states from published

literature because of the low number of responses to the quality-of-life questionnaire used in the FIT clinical trials (SF-36). The committee noted that the company used utility values for the health states of the group without intracranial bleeding from NICE's technology appraisal guidance on romiplostim. The company's original base case applied a lower utility value for people in the partial and no response health states than in the response health state. This was because the romiplostim appraisal used different utility values for people with platelet counts of 50,000 per microlitre of blood or more (response) and those with platelet counts below 50,000 per microlitre (non-response). In its revised base case after consultation, the company applied different utility values to the response (platelet count of 30,000 per microlitre or more) and the non-response health states (platelet count below 30,000 per microlitre). The committee acknowledged that people with platelet counts below 30,000 per microlitre would be unlikely to feel worse than people with platelet counts of 30,000 per microlitre or above. But if a person knows that they are at higher risk of bleeding, this could cause anxiety and affect their daily life if they avoid their usual activities. For the group who had severe intracranial bleeding and for their carers, the company used published utility values. The ERG noted that because intracranial bleeding is rare, including carer quality of life affected the cost-effectiveness estimates minimally. The company also applied a transient disutility for people with other bleeds, adverse events or when needing rescue treatment. The committee concluded that the utility values in the model, including those for carers of people who had severe intracranial bleeding, were appropriate.

The ERG's exploratory analysis for mycophenolate assumes equal efficacy and safety to rituximab, which is uncertain

3.21 The ERG did an analysis for mycophenolate as a comparator, assuming equal efficacy and safety to rituximab. It assumed that mycophenolate is taken twice a day as a 500 mg tablet and stopped at 12 weeks if platelet response is not reached, or later if this response is lost. The analysis predicted that median treatment duration is 12 to 16 weeks, which is longer than the median duration of mycophenolate treatment in the UK ITP registry (exact figures are confidential and cannot be reported here). The model predicted that mycophenolate had higher total treatment costs than 100 mg rituximab at its list price, but lower than 375 mg/m^2 rituximab at its list price. The ERG highlighted that this analysis is exploratory, because assuming equal efficacy of

rituximab and mycophenolate is uncertain. It noted that there were lower complete and partial responses to mycophenolate in Taylor et al. (2015) compared with responses to rituximab in Ghanima et al. (2015). The ERG emphasised that this comparison was highly uncertain because it reflects a naive comparison between 2 different studies, and Taylor et al. (2015) was a small, non-randomised, retrospective study. Clinical experts confirmed that assuming equal efficacy of mycophenolate and rituximab is uncertain. They explained that there are no head-to-head comparisons between these 2 treatments, but they expect their efficacy and safety to differ. The 2 drugs are used for different groups of people. Mycophenolate is generally well tolerated and taken as a tablet, so it does not cause infusion-related reactions. The committee agreed that mycophenolate was unlikely to have the same efficacy and safety as rituximab and this was a limitation of the exploratory analysis. It concluded that it would focus on the comparison of fostamatinib with rituximab in its decision making.

Cost-effectiveness estimates

The most likely cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources

3.22 The committee discussed the company's base case, revised after consultation. It noted how the company attempted to address its preferences from its first meeting, namely:

- using clinical effectiveness estimates for the comparators from a network meta-analysis (see section 3.9)
- modelling subsequent treatments consistently between arms (see section 3.13)
- using prophylactic treatments before surgery in line with clinical practice, that is, including both IVIgG and oral prednisolone (see section 3.17)
- including treatment-specific adverse event rates (see section 3.18)
- considering a scenario analysis in which partial response and response health states are merged (see section 3.11)

- considering a scenario analysis with 100 mg rituximab (see section 3.16).

The ERG had concerns about the company's revised base case. So, the ERG presented its preferred base case, applying the following changes to the company's base case:

- using network meta-analysis 3 rather than analysis 2, to inform clinical effectiveness estimates for the comparators (see section 3.9)
- following the 3-health state model structure, rather than the 2-health state model with merged response health state (see section 3.11)
- using the 100 mg rituximab dose, rather than the average rituximab dose from the UK ITP registry (see section 3.16).

The ERG's analysis also included the confidential NHS Commercial Medicines Unit price for biosimilar rituximab.

The committee did not agree with the updated preferences for the stopping rule (see section 3.12), dosing of rituximab (see section 3.16), and hazard ratios for mortality (see section 3.19) in the company's revised base case. The committee agreed that its preferred analysis included the following assumptions:

- using both network meta-analysis 2 and 3 results (see section 3.9)
- following the 2-health state model structure (see section 3.11)
- stopping fostamatinib at 12 weeks if platelet response had not been reached (see section 3.12)
- using both doses of rituximab used in clinical practice (see section 3.16)
- using lower hazard ratios reflecting the association between the non-response health state and mortality (see section 3.19).

Applying confidential discounts for fostamatinib and rituximab, and considering its preferences, the committee noted that all the cost-effectiveness estimates were higher than what NICE normally considers an acceptable use of NHS resources regardless of which network meta-analysis results or rituximab dose was used. Because of these confidential discounts, the cost-effectiveness results cannot be reported here. Therefore, the committee could not recommend fostamatinib for use in the NHS.

Innovation

Fostamatinib has a novel mechanism of action, but all benefits are captured in the modelling

3.23 The patient and clinical experts value individualised treatment. The committee noted fostamatinib's novel mechanism of action and the lack of immunosuppression associated with it. This is important because the clinical experts highlighted that the rates of death from infection and from bleeding are similar in people with ITP. The committee considered that infections and other benefits are captured in the model (see section 3.18).

4 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

George Braileanu and Summaya Mohammad
Technical leads

Ross Dent and Ewa Rupniewska
Technical advisers

Joanne Ekeledo
Project manager

ISBN: 978-1-4731-4268-8

Accreditation

Death Certification – issuing eMCCD using NIECR*

INDEX

BEFORE

you proceed with completing a Medical Certificate of Cause of Death (MCCD), ask yourself this question,

"Should this Death be reported to the Coroner?"

* = Northern Ireland Electronic Care Record (NIECR)

Do not use the 'Back' button: Use Bookmarks.

Bookmarks

This guidance document has bookmarks available for navigation. If they have not appeared, access depends on which browser you are using:

For Internet Explorer: right click, select 'Show the Navigation Pane', click the icon on the left hand of the screen.

For Chrome: click the icon on the toolbar at the top-left of the screen.

For Microsoft Edge: (which is a new browser included as part of Windows 10), this browser does not currently support the use of bookmarks. Please use Internet Explorer.

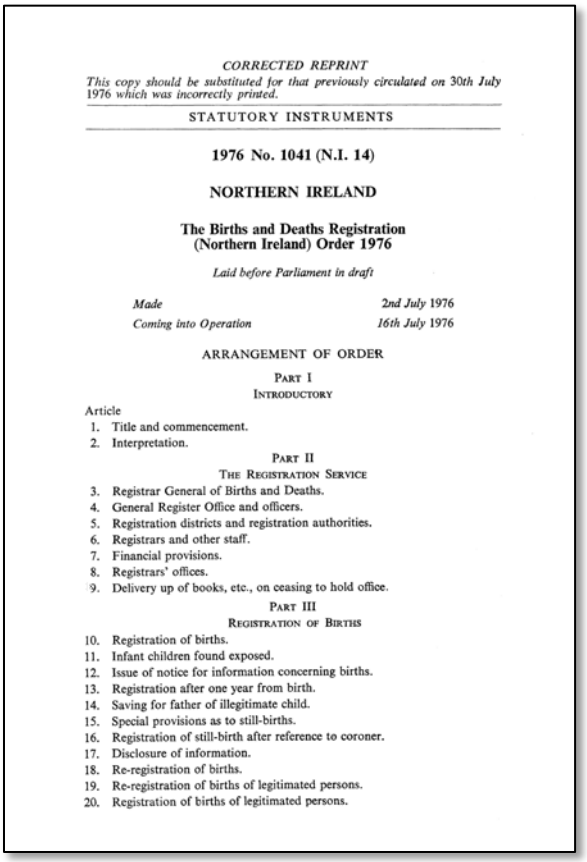
INTRODUCTION

When someone dies, the death must be registered by the General Register Office for Northern Ireland (GRO). Before it can be registered, the Registrar must be provided with notification of the death and either a Medical Certificate of the Cause of Death (MCCD) from a doctor or authorisation from a Coroner. For most deaths, the doctor who attended and provided care within twenty-eight days of death completes the MCCD to the best of their knowledge and belief; a statutory requirement. This is delivered to the local Registrar who issues the formal Death Certificate and an authority for the disposal of the body (Form GRO21).

The purposes of Death Certification

Death Certification serves social, legal and health functions. It,

- allows completion of a permanent legal record of the fact of death in the form of the Death Certificate;
- enables the family to make funeral arrangements; and
- the Registrar can provide copies of the Death Certificate, enabling the family to settle the deceased's estate.



CORRECTED REPRINT

This copy should be substituted for that previously circulated on 30th July 1976 which was incorrectly printed.

STATUTORY INSTRUMENTS

1976 No. 1041 (N.I. 14)

NORTHERN IRELAND

The Births and Deaths Registration (Northern Ireland) Order 1976

Laid before Parliament in draft

Made 2nd July 1976

Coming into Operation 16th July 1976

ARRANGEMENT OF ORDER

PART I
INTRODUCTORY

Article
1. Title and commencement.
2. Interpretation.

PART II
THE REGISTRATION SERVICE

3. Registrar General of Births and Deaths.
4. General Register Office and officers.
5. Registration districts and registration authorities.
6. Registrars and other staff.
7. Financial provisions.
8. Registrars' offices.
9. Delivery up of books, etc., on ceasing to hold office.

PART III
REGISTRATION OF BIRTHS

10. Registration of births.
11. Infant children found exposed.
12. Issue of notice for information concerning births.
13. Registration after one year from birth.
14. Saving for father of illegitimate child.
15. Special provisions as to still-births.
16. Registration of still-birth after reference to coroner.
17. Disclosure of information.
18. Re-registration of births.
19. Re-registration of births of legitimated persons.
20. Registration of births of legitimated persons.

This provides the family with an explanation of how and why their relative died. It also gives them a permanent record of information about their family medical history, which may be important for their own health and that of future generations.

In addition, the MCCD, provides the **underlying cause of death which** influences,

- population health monitoring;
- design and evaluation of public health interventions;
- recognition of priorities for medical research and health services;
- planning of health services; and
- assessment of the effectiveness of services.

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WHO CAN COMPLETE THE MEDICAL CERTIFICATE OF CAUSE OF DEATH?

Doctors certifying deaths do so as a *statutory* duty under the Births and Deaths Registration (Northern Ireland) Order 1976 Section 25(2) which holds that,

> *"Where any person dies as a result of any natural illness for which he has been treated by a registered medical practitioner within twenty-eight days prior to the date of his death, that practitioner shall sign and give forthwith to a qualified informant a certificate in the prescribed form stating to the best of his knowledge and belief the cause of death, together with such other particulars as may be prescribed."*

MCCDs can only be completed by a registered medical practitioner who saw and treated the deceased during their last illness. No other person or practitioner may sign the certificate on his/her behalf. The completion of MCCDs is a statutory duty with doctors being subject to regulation of their conduct by the General Medical Council, rather than a condition of employment in the NHS. They **must** state the cause(s) of death to the best of their knowledge and belief and give the certificate forthwith[1] to the Informant or report to the Coroner if necessary.

The General Medical Council guidance Treatment and care towards the end of life: July 2010, provides a framework for good practice when providing treatment and care for patients who are reaching the end of their lives. Section 85 states, *"You must be professional and compassionate when confirming and pronouncing death and must follow the law, and statutory codes of practice, governing completion of death and cremation certificates. If it is your responsibility to sign a death or cremation certificate, you should do so without unnecessary delay. If there is any information on the death certificate that those close to the patient may not know about, may not understand or may find distressing, you should explain it to them sensitively and answer their questions, taking account of the patient's wishes if they are known."*

In hospital, there may be several doctors in a team caring for the patient who will be able to certify the cause of death. It is ultimately the responsibility of the Consultant in charge of the patient's care to ensure that the death is properly certified. Foundation level doctors should not complete MCCDs unless they have received appropriate training. Discussion of a case with a senior colleague may help clarify issues about completion of an MCCD or referral to a Coroner.

In general practice, more than one GP may have been involved in the patient's care and so be able to certify the cause of death.

A doctor, who had not been directly involved in the patient's care at any time during the illness from which they died, cannot certify the cause of death, but they should provide the Coroner with any information that may help to determine the cause of death.

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[1] Definition of forthwith: In official use, forthwith means immediately; without delay.

GOOD PRACTICE RULES FOR DEATH CERTIFICATION

The MCCD **must** be completed and signed by the doctor who saw and treated the deceased for their cause of death within 28 days of death.

The MCCD should be completed as soon as possible after death occurs and given to the Informant; the legislation indicates that this must be immediately, without delay, remembering that Registration should occur within 5 days of receiving the MCCD and **before** burial or cremation is performed.

Doctors are expected to state the Cause of Death to the best of their knowledge and belief.

It is good practice to keep a paper copy of the printed eMCCD in the patient clinical records.

All registered medical practitioners completing MCCDs should ensure they are competent by updating their knowledge and regularly reflecting on their practice.

- For further guidance and how to obtain an eMCCD using the NIECR, please view How to complete a Medical Certificate of Cause of Death using NIECR - printed.

Abbreviations or symbols

The only abbreviations a Registrar can accept are,

- HIV for Human Immunodeficiency Virus infection;
- AIDS for Acquired Immune Deficiency Syndrome; and
- MRSA for Methicillin Resistant Staphylococcus Aureus.

Do not use other abbreviations on MCCDs. Their meaning may seem obvious to medical staff in the context of their work and their medical history, but it may not be clear to others and therefore may be a source of ambiguity causing potential delay to the registration process. Inappropriate use of abbreviations can result in the cause of death being recorded incorrectly on Death Certificates.

For example, using,

- MI instead of myocardial infarction. Does,
  - a death from “MI” refer to myocardial infarction or mitral incompetence?
- MS instead of multiple sclerosis. Does,
  - MS refer to multiple sclerosis, mitral stenosis or morphine sulphate?
- (L) instead of left;
- medical symbols such as 1° instead of primary; or
- # instead of fracture.

GMC registered name and reference number

There is GMC guidance on what registered doctors must do regarding the use of their registered name and GMC reference number.

http://www.gmc-uk.org/doctors/information_for_doctors/doctors_registration_number.asp

Registered name

This is your **full name**, as it appears in the Medical Register.

GMC reference number

This is the 7-digit number given when you first register with the GMC. Always use your own GMC number when completing a MCCD.

You must,

- Be familiar with your GMC reference number;
- Use your registered name when signing statutory documents; and
- Make your registered name and GMC reference number available to anyone who asks.

Responsibility to the Family and Informant

Please note that once you have signed and dated the eMCCD, best practice indicates that you should give it to a family member or next of kin, if one of them is available.

There is an expectation that you will explain the details contained within the Cause of Death section to family members of the deceased. See Treatment and care towards the end of life: General Medical Council, July 2010, Section 85.

> *"..... If there is any information on the death certificate that those close to the patient may not know about, may not understand or may find distressing, you should explain it to them sensitively and answer their questions, taking account of the patient's wishes if they are known."*
>
> Treatment and care towards the end of life: General Medical Council, July 2010

Signing the eMCCD

Once the printed eMCCD is obtained, the doctor **must** sign and date the certificate. The eMCCD **must** be signed by the doctor who logged into NIECR and completed the Initial Record of Death (IRD); the printed doctor's name and their signature must match.

It is not acceptable for an eMCCD to be signed on behalf of someone else i.e. with the signature preceded by p.p. (per procurationem).

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A STEP-BY-STEP GUIDE TO COMPLETING AN eMCCD

Since November 2016, there have been 2 methods of completing and obtaining a Medical Certificate of Cause of Death (MCCD) in Northern Ireland.

1. Using the Northern Ireland Electronic Care Record (NIECR).
   This is now the standard method of recording a death and producing a MCCD in Health and Social Care (HSC) Trust hospitals. The MCCD is completed electronically on the NIECR producing an eMCCD, which then must be printed and signed – a printed eMCCD.

   This guidance refers to using the NIECR to print the eMCCD.

2. Completion of the handwritten MCCD.
   A handwritten MCCD remains the method of recording a death and producing a MCCD in primary care, community hospitals, nursing homes, hospices, in the home and also as a contingency measure when NIECR is non-functioning.

   If guidance is required regarding handwriting the MCCD, click here.

Using NIECR to produce a printed eMCCD

1. The items of information required before you can go through the steps needed to produce the printed eMCCD are provided here (& printed from here).

2. The steps required to produce the printed eMCCD (& printed from here) are,
   - logon to NIECR using a secure user name and password;
   - if you are a Locum and do not already have a secure NIECR user name and password, you should use the contacts listed here.
   - from the NIECR Home screen, access the correct deceased patient's record;
   - from their Patient Summary screen, enrol the deceased onto Mortality Pathway;
   - complete an Initial Record of Death (IRD);
   - return to their Patient Summary screen;
   - access the Notification & Legal documents section; and
   - print the eMCCD and/or Clinical Summary.

3. Detailed instructions to produce and print the eMCCD can be found here including a diagrammatic flowchart explaining the sequence. To print these instructions click here and for printing the flowchart sequence click here.

Further guidance

Further guidance and how to,

- Edit or Amend an eMCCD, which has not yet been Registered with the GRO;
- Correct an eMCCD entry, which has already been Registered with the GRO;
- Deactivate a eMCCD (Rarely performed - only if eMCCD completed in error)

can be accessed in the Regional M&M Review System guidance (available shortly)
or
viewed in How to complete a Medical Certificate of Cause of Death – eMCCD printed.

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RECORDING THE CAUSE OF DEATH

Recording the Cause of Death

The Cause of Death details (excluding the interval between onset of condition and death), as certified by a medical practitioner, are entered by the Registrar in the GRO's death register and form part of that record. The entry in the death register and the Death Certificate itself are also utilised as material for the mortality statistics published by the Registrar General. These statistics are used in many fields, particularly in the study of preventative medicine, and their value will be materially enhanced if certifying medical practitioners will,

(a) read and adopt, as far as possible, the suggestions as set out below, remembering that the International Classification of Causes of Death is based, not upon terminal clinical states, but upon ***the antecedent and underlying pathological cause(s) of death***, of which the certifier is generally best qualified to form an opinion.

Underlying Cause of Death

Definition

(a) the disease or injury which initiated the train of morbid events leading directly to death; or

(b) the circumstances of the accident or violence which produced the fatal injury.

World Health Organisation

(b) complete the Cause of Death accurately, as absence of information may cause undue delay and anxiety to bereaved families during the registration process. Doctors are expected to state the Cause of Death to the best of their knowledge and belief.

The Cause of Death section of the MCCD is set out in two parts, in accordance with World Health Organisation (WHO) recommendations in the International Statistical Classification of Diseases and Related Health Problems (ICD) as shown below.

		These particulars not to be entered in Death Register
I **Disease or condition directly leading to death***	CAUSE OF DEATH **I** (a) …... IMMEDIATE CAUSE OF DEATH …… due to (or as a consequence of)	Approximate interval between onset and death (years, months, weeks, days, hours) …….
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) …... ANTECEDENT CAUSE(S) …… due to (or as a consequence of) (c) …. UNDERLYING CAUSE(S) OF DEATH ……	…… ……
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** ……OTHER SIGNIFICANT CONDITIONS …… ……	…… ……

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Part I - Sequence leading to death and Underlying Cause

This is used to show the immediate cause of death and any underlying cause(s).

Start with the,

- immediate, direct Cause of Death on line I (a); then
- go back through the sequence of events or conditions that led to death on subsequent lines I (b) and I (c); until
- you reach the one leading ultimately to death = **Underlying Cause of Death**.

This should ALL be in Part I.

If the certificate has been completed properly, the condition on the lowest completed line of Part I will have caused all of the conditions on the lines above it. Remember that the underlying cause may be a longstanding, chronic disease or disorder that predisposed the patient to later fatal complications.

Part II - Contributory causes

You should enter any other significant diseases, injuries, conditions, or events that contributed to the death, but were not part of the direct sequence, in Part II of the certificate.

Part II should not contain the Underlying Cause of Death.

For example, someone with diabetes mellitus who died of cancer might have died sooner than would have been the case if he/she did not have diabetes mellitus. If so, diabetes mellitus should be recorded in Part II as contributing to death.

However, do not enter any diseases, injuries, conditions or events that did not, in your view, contribute to the death. For example, if someone with osteoarthritis died of cancer, it is likely that osteoarthritis would not have significantly contributed to death, so it should not be mentioned in Part II.

Example 1

I	CAUSE OF DEATH	These particulars not to be entered in Death Register
Disease or condition directly leading to death*	**I** (a)...*INTRA-PERITONEAL HAEMORRHAGE*.....	Approximate interval between onset and death (years, months, weeks, days, hours)
	due to (or as a consequence of)	
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)...*RUPTURED METASTATIC DEPOSIT IN LIVER*.....	.....
	due to (or as a consequence of)	
	(c)...*PRIMARY ADENOCARCINOMA OF ASCENDING COLON*.....	.....
II	**II**	
Other significant conditions contributing to the death, but not related to the disease or condition causing it	... *TYPE 2 DIABETES MELLITUS*.....	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Single condition causing death

A single disease, without any antecedents, may be wholly responsible for causing death e.g. subarachnoid haemorrhage or meningococcal meningitis. In this case it is perfectly acceptable to complete only one line. In this case, it should be entered on line (a) and the other lines left blank (Examples 2, 3).

Example 2

	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
I **Disease or condition directly leading to death***	**I** (a)... *MENINGOCOCCAL SEPTICAEMIA* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)..... due to (or as a consequence of) (c).....	....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II**	....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Example 3

	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
I **Disease or condition directly leading to death***	**I** (a)... *LOBAR PNEUMONIA* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)..... due to (or as a consequence of) (c)	....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II**	....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

More than three conditions in the sequence

The MCCD has 3 lines in Part I for the sequence leading directly to death. If you want to include more than 3 steps in the sequence, you can do so by writing more than one condition on a line, indicating clearly that one is due to the next (Example 4).

Example 4

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a)... *POST-TRANSPLANT LYMPHOMA* …… due to (or as a consequence of)	……
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)... *IMMUNOSUPPRESSION FOLLOWING RENAL TRANSPLANT* …… due to (or as a consequence of)	……
	(c)... *GLOMERULONEPHROSIS DUE TO TYPE 2 DIABETES MELLITUS.*	……
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** … *RECURRENT URINARY TRACT INFECTIONS* ……	……
	……	……

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Where two or more causes must be entered it is important, for purposes of correct classification, that the arrangement of causes should accurately represent the certifying practitioner's opinion as to their order of importance and occurrence.

More than one disease led to death

If you know that your patient had more than one disease or condition that was compatible with the way in which he or she died, but you cannot say which was the most likely underlying cause of death, you should include them all on the same line on the MCCD and indicate that you think they contributed equally by writing "joint causes of death" in brackets (Examples 5, 6).

Example 5

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a) ... *CARDIO RESPIRATORY FAILURE* …… due to (or as a consequence of)	……
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	*ISCHAEMIC HEART DISEASE AND CHRONIC OBSTRUCTIVE* (b) ..... *PULMONARY DISEASE (JOINT CAUSES OF DEATH)* ... due to (or as a consequence of)	……
	(c)	……
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** ……	……
	……	……

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Example 6

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a)... *HEPATIC FAILURE*	.....
	due to (or as a consequence of)	
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)... *LIVER CIRRHOSIS* ..... due to (or as a consequence of)	.....
	(c)... *CHRONIC HEPATITIS C INFECTION AND ALCOHOLISM* ..... *(JOINT CAUSES OF DEATH)*	.....
II	**II**	
Other significant conditions contributing to the death, but not related to the disease or condition causing it	.....	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Where more than one condition is given on the lowest used line of part 1, the GRO will use the internationally agreed ICD mortality coding rules to select the underlying cause for routine mortality statistics. This will normally be the first cause that is mentioned on the lowest used line of part I. Therefore, in the example above, “Chronic hepatitis C” infection will be selected as the underlying cause of death for the purpose of producing statistics.

Specific COVID-19 guidance

The World Health Organisation has stated that for the purposes of the International Classification of Diseases (ICD), the official name of the disease is Coronavirus disease (COVID-19). As there are many types of coronavirus, it is recommended not to use “coronavirus” in place of COVID-19. This helps to reduce uncertainty for the classification or coding and to correctly monitor these deaths.

Medical Practitioners complete MCCDs to the best of their knowledge and belief. Where there has been a laboratory confirmed positive COVID-19 test the preferred terminology to be recorded on the MCCD is,

- **COVID-19 (confirmed)**

In the absence of a confirmed COVID-19 diagnosis, the certifying doctor should consider any available evidence and information and apply their clinical judgement as to whether the disease caused, is assumed to have caused, or contributed to the death. If so, it is acceptable to use the following terminology,

- **COVID-19; or**
- **Probable/Suspected COVID-19**

Recording Healthcare Associated Infections (HCAI)

The level of HCAIs remains a matter of concern to clinicians and the public.

The Health Service depends on accurate information gained from MCCDs to record changes in mortality associated with infections. Trends which are identified can highlight new areas of concern or monitor changes in deaths associated with certain infections.

Families may be surprised if an infection the patient was being treated for such as MRSA or clostridium difficile is not mentioned on a MCCD; for some families this can be a very distressing experience (Examples 7, 8, 9).

Example 7

I	CAUSE OF DEATH	These particulars not to be entered in Death Register
		Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I**	
	(a)... *CLOSTRIDIUM DIFFICILE PSEUDO MEMBRANOUS COLITIS* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)... *MULTIPLE ANTIBIOTIC THERAPY* ..... due to (or as a consequence of)	.....
	(c)... *COMMUNITY ACQUIRED PNEUMONIA WITH SEVERE SEPSIS*	.....
II	**II**	
Other significant conditions contributing to the death, but not related to the disease or condition causing it	… *POLYMYALGIA RHEUMATICA*	.....
	… *OSTEOPOROSIS*	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

It is a matter of clinical judgement if a HCAI was,

- the disease directly leading to the death [record at Part I (a)];
- an antecedent cause [record at Part I (b) or I (c)]; or
- a significant condition not directly related to the cause of death [record at Part II].

Where infection does follow treatment, including surgery, radiotherapy, anti-neoplastic, immunosuppressive, and antibiotic or other drug treatment for another disease, remember to specify the treatment and the disease for which it was given.

Example 8

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a)... *BRONCHOPNEUMONIA (HOSPITAL ACQUIRED MRSA)* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)... *MULTIPLE MYELOMA* ..... due to (or as a consequence of)	.....
	(c)	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** … *CHRONIC OBSTRUCTIVE PULMONARY DISEASE*	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Example 9

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a)... *CARCINOMATOSIS AND RENAL FAILURE* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)... *ADENOCARCINOMA OF THE PROSTATE* ..... due to (or as a consequence of)	.....
	(c).....	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** … *CHRONIC OBSTRUCTIVE AIRWAYS DISEASE*	.....
	… *CATHETER ASSOCIATED ESCHERICHIA COLI URINARY TRACT INFECTION*	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Community Acquired and Hospital Acquired Infections

It is important to identify, if possible, the source of a HCAI as either Community Acquired or Hospital Acquired. This will allow Trusts to identify learning to inform and underpin continuous improvement.

Therefore, it is incumbent on clinical staff, when completing a MCCD for patients who require the entry of an infection, for example COVID-19, into either Part I or II, that they qualify the entry with where the infection originated – from the Community, the Hospital environment (probable or definite) or as Indeterminate. (Example 10).

Clinicians should use the following table as the basis for judging whether an infection is Community or Hospital based. Within the crossover period of 2 - 6 days it may be difficult to determine exactly where the infection originated; the term 'indeterminate' may be used. However, where there is clear evidence regarding the origin of the infection e.g. known household contact in the community, clinicians may use their clinical judgement in designating the source of infection.

First positive COVID-19 test after admission to hospital in,		**Defined as**	
0 – 1 days	→	**Community**	
2 – 6 days	→	**Indeterminate Source***	
7 - 13 days	→	**Hospital**	(Probable)
14 or more days	→	**Hospital**	(Definite)

***** if Clinician has clear evidence of the origin of the infection e.g. known household contact in community, they can designate whether Community or Hospital Acquired.

Example 10

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a)... *RESPIRATORY FAILURE*.....	……
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	due to (or as a consequence of) (b)... *confirmed COVID-19 PNEUMONITIS – Hospital Acquired ...* *.....(definite).....* due to (or as a consequence of) (c).....	…… ……
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** … *CHRONIC OBSTRUCTIVE AIRWAYS DISEASE* …….. ……..	…… ……

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

If a patient has died from what is clinically considered to be a COVID-19 infection but there has been no confirmatory testing carried out, the MCCD can be completed as in example 11. The COVID-19 infection should be qualified using the term *probable* or *suspected*.

The clinician may also be able to use their clinical knowledge of the patient to qualify the death as being community or hospital acquired if the length of admission allows that decision to be clearly made.

Example 11

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a)... *RESPIRATORY FAILURE* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)... *Community Acquired, probable COVID-19 PNEUMONITIS* .... due to (or as a consequence of) ..... (c).....	....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** ... *CHRONIC OBSTRUCTIVE AIRWAYS DISEASE* ..... …….....	....

FURTHER GUIDANCE REGARDING CAUSE OF DEATH TERMS

Coroner's cases

Any Cause of Death term on the MCCD which might indicate an industrial disease, trauma, unnatural death or where the wider circumstances may require investigation, might need reporting to the Coroner.

Also, the Extra-statutory list of diagnoses contains terms that may need referred to the Coroner and a Registrar may consider it necessary to refer a case to the Coroner if one of these terms is used.

General principles

1. The statement of the cause of death should be as **specific** as your information allows and to the best of your knowledge and belief.

2. Tentative terms and expressions such as, "likely", "presumably", "probably" or "possibly" are permissible when there is not absolute certainty. They are of better use than no diagnosis at all

3. Pay attention to providing sufficient anatomical detail e.g. aneurysm – indicate whether aortic, other artery, venous, organ affected.

4. Pay attention to providing sufficient pathological detail, for example,
   - indicate underlying disease, if cause of death due to tuberculosis, syphilis or other widely disseminated systemic disease; and
   - try to provide an underlying cause or disease when using certain terms e.g. congestion, embolism, haemoptysis, inflammation, obstruction, oedema, perforation, syncope are used.

5. The use of vague and ill-defined terms is particularly to be avoided. Incorrectly completed forms can cause difficulties for the doctor, Registrar, family, carers and relatives.

6. Do not use abbreviations (except HIV, AIDS and MRSA) or symbols on MCCDs.

7. If a Cause of Death is believed to have had a congenital origin, state this.

8. Do not use the following terms alone and without further additional qualifications or detail,
   - Organ Failure;
   - Cancer;
   - Pneumonia;
   - Infection, sepsis;
   - Malnutrition, Cachexia, Inanition; and
   - Old Age, General Debility of Age, Frailty, Senility and Weakness

Organ failure

Do not certify deaths as due to the failure of any organ or "multi-organ failure", without identifying the organ(s) and specifying the disease or condition that led to the organ failure. Examples which need further information are Liver Failure, Renal Failure and Heart Failure (Example 12).

Example 12

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a)... *RENAL FAILURE* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)... *NECROTISING-PROLIFERATIVE NEPHROPATHY* ..... due to (or as a consequence of)	.....
	(c).... *SYSTEMIC LUPUS ERYTHEMATOSUS*	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** .... *RAYNAUD'S PHENOMENON AND VASCULITIS*	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Cancer

The terms cancer, neoplasm or tumour should be qualified with the detail of the,

a. histological type;
b. whether malignant or benign;
c. whether primary or secondary (any metastatic spread);
    i. anatomical site of primary occurrence, if known;
    ii. anatomical site of secondary occurrence, if known; and
    iii. if secondary, the site of the primary and date of removal if known;

You should make sure that there is no ambiguity about the primary site if both primary and secondary cancer sites are mentioned.

Do not use the terms “metastatic” or “metastases” unless you specify whether you mean metastasis to, or metastasis from, the named site (Example 13).

Example 13

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a) ..... *INTRAPERITONEAL HAEMORRHAGE* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) .... *METASTASES IN LIVER* ..... due to (or as a consequence of)	.....
	(c) .... *from PRIMARY ADENOCARCINOMA OF ASCENDING COLON*	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** *TYPE 2 DIABETES MELLITUS*	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

If there are two sites that are independent primary malignant neoplasms, make that clear (Example 14).

Example 14

		These particulars not to be entered in Death Register
I	CAUSE OF DEATH	Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a) ..... *MASSIVE HAEMOPTYSIS* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) .... *PRIMARY SMALL CELL CARCINOMA OF LEFT MAIN BRONCHUS* due to (or as a consequence of)	.....
	(c)	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II** ..... *PRIMARY ADENOCARCINOMA OF PROSTATE*	....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

If a patient has widespread metastases, but the primary site could not be determined, you should state this clearly (Example 15).

Example 15

		These particulars not to be entered in Death Register
I	CAUSE OF DEATH	Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a) ..... *MULTIPLE ORGAN FAILURE* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) .... *POORLY DIFFERENTIATED METASTASES THROUGHOUT ABDOMINAL CAVITY* due to (or as a consequence of)	.....
	(c) .... *UNKNOWN PRIMARY SITE*	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II**	....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Pneumonia

Bronchopneumonia, chest signs and symptoms are common terminal findings but they do not always point to significant infection being the underlying cause or contributor to death. Bronchopneumonia should not be written as the sole cause of death, if there is another condition which you can also state as the underlying cause of death.

However, if pneumonia is a cause of death, the following details should be provided, if known,

- Type or site of pneumonia (lobar, bronchopneumonia);
- Organism;
- Whether hospital or community acquired; and

- Sequence of conditions leading to pneumonia, including any relationship to aspiration or the use of mechanical ventilation.

Remember to include, in the sequence in Part I, any predisposing conditions, especially those that may have led to paralysis, immobility, difficulty swallowing, depressed immunity or wasting, as well as any chronic respiratory conditions such as chronic bronchitis (Example 16).

Example 16

I	CAUSE OF DEATH	These particulars not to be entered in Death Register
Disease or condition directly leading to death*	**I** (a) ..... *BRONCHOPNEUMONIA* ..... due to (or as a consequence of)	..... Approximate interval between onset and death (years, months, weeks, days, hours)
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) .... *IMMOBILITY AND WASTING* ..... due to (or as a consequence of)	.....
	(c) .... *ALZHEIMER'S DISEASE*	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II**	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Infections, sepsis

Where possible give details about:

- Site (meningitis, peritonitis, wound site, etc);
- Organism;
- Antibiotic resistance;
- Route of infection (needle sharing, food poisoning, etc); and
- Sequence of conditions leading to death.

Malnutrition, Cachexia, Inanition

Because a diagnosis of malnutrition, cachexia, inanition or any term related to starvation may indicate substandard clinical care, as a result of negligence, misconduct or malpractice, it should always be considered for reporting to the Coroner.

However, if it is judged that any of the above conditions is caused by an underlying natural cause, it does not need reporting e.g. end stage dementia, gastro-intestinal pathology. If there is a decision not to refer such a diagnosis to the Coroner, the entry of that term on a MCCD **must** be qualified to indicate an underlying natural cause.

Old Age, General Debility of Age, Frailty, Senility and Weakness

The use of these indefinite terms is not encouraged. It is preferred that they are not used alone in Part I and without further supporting qualifying particulars (Example 17).

Old age should only be given as the sole cause of death when all of the following criteria have been met. The doctor,

- has personally cared for the deceased over a long period (years, or many months);

- has observed a gradual decline in the patient's general health and functioning;
- is confident that the death was expected;
- is unaware of any identifiable disease or injury that contributed to the death;
- is certain that there is no other reason that the death should be reported to the Coroner's Office; and
- the patient is 80 years or older and all the conditions listed above have been met.

It is unlikely that patients would be admitted to an acute hospital if they had no apparent disease or injury. It follows, therefore, that deaths in acute hospitals are unlikely to fulfil the conditions above.

It is possible that families, Registrars and cremation referees may request further explanation of an opinion that 'Old age' was the only cause of death.

Example 17

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a) ..... *HYPOSTATIC PNEUMONIA* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) .... *DEMENTIA* ..... due to (or as a consequence of)	.....
	(c) .... *OLD AGE*	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II**	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Diabetes mellitus

Always specify whether diabetes mellitus was insulin dependent / Type 1, or non-insulin dependent / Type 2. If diabetes is the underlying cause of death, specify the complication or consequence that led to death, such as ketoacidosis (Example 18).

Example 18

I	CAUSE OF DEATH	These particulars not to be entered in Death Register Approximate interval between onset and death (years, months, weeks, days, hours)
Disease or condition directly leading to death*	**I** (a) ..... *END-STAGE RENAL FAILURE* ..... due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) .... *DIABETIC NEPHROPATHY* ..... due to (or as a consequence of)	.....
	(c) .... *TYPE 1 DIABETES MELLITUS*	.....
II **Other significant conditions** contributing to the death, but not related to the disease or condition causing it	**II**	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

Terminal events, modes of dying, clinical signs and other vague terms

Terms that do not identify a disease or pathological process clearly are not acceptable as the only cause of death. This includes terminal events, or modes of dying such as cardiac or respiratory arrest, syncope or shock. Very vague statements such as cardiovascular event or incident, debility or frailty are equally unacceptable.

Natural Causes

There is no ICD code equivalent to “natural causes”, and Registrars will seek clarification from the doctor, or refer the case to the Coroner. If you do not know what disease caused your patient's death, you should discuss the case with the Coroner.

Substance misuse

Deaths from diseases related to chronic alcohol or tobacco use do not need to be referred to the Coroner, provided the disease is clearly stated on the MCCD.

Deaths due to acute or chronic **poisoning**, by **any** substance, and deaths involving drug dependence or misuse of substances other than alcohol and tobacco must be referred to the Coroner.

Pregnancy, Childbirth

Whenever pregnancy, parturition or miscarriage has been in anyway a contributory cause of death, this fact should be mentioned in the MCCD and the nature of the abnormality, if any, should be provided. If, on the other hand, it is not regarded as a contributory cause, it need not be mentioned on the form.

Maternal conditions as causes of death in the newborn

In general, disease conditions recorded on a death certificate will be conditions from which the deceased suffered. However, in certifying the cause of death of a newborn infant, the practitioner may wish to record underlying conditions in the mother of the deceased infant. This may be done, although it is expected that maternal conditions will usually be regarded as a cause of infant death only in the first 28 days of life. Where maternal conditions are recorded, they should be distinguished as "maternal" (Example 19).

Example 19

I	CAUSE OF DEATH	These particulars not to be entered in Death Register
Disease or condition directly leading to death*	**I** (a) ..... *FETAL ANOXIA*	.....
	due to (or as a consequence of)	
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) .... *MATERNAL PRE-ECLAMPSIA*	.....
	due to (or as a consequence of)	
	(c)	.....
II	**II**	
Other significant conditions contributing to the death, but not related to the disease or condition causing it	..... *PREMATURITY*	.....
	.....	.....

* This does not mean the mode of dying e.g. heart failure, asthenia, etc. It means the disease, injury or complication which caused death.

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Information required before completing the Initial Record of Death (IRD) on NIECR.

1	Patient details,	Name Health & Care number DOB
2	Date and Time of Death	
3	Name of who verified death	
4	Place of Death	
5	Initial Reviewing M&M team & Consultant	
6	Clinical Details - SBAR	Admission and clinical course details
		Diagnosis
		Past Medical History
		Medications
		Procedural Details, Surgery
		Investigations
7	Outcome following death	MCCD issued, contact with Coroner details, Death outside NI, etc.
8	Coroner's Reference Number	If you have contacted the Coroner's Office regarding a death, the provided Coroner's Reference Number will need to be entered onto the NIECR.
9	Implant details	Cardiac Device, Pacemaker, Ventricular Assist Device (VAD),
		Implantable Cardio-defibrillator (ICD),
		Implantable drug pumps, Radiopharmaceutical treatment device,
		Radio-active implant,
		Expandable intramedullary device- FIXION™ nail
		Battery Powered or pressurised implant
10	Doctors details	Name
		Work Address
		Work Contact number
		GMC number

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Recording an Initial Record of Death & printing a MCCD on NIECR

Logon to NIECR

- Using your Trust NIECR logon details, logon to NIECR.
- If you do not have NIECR logon credentials, consult DoH "Guidance surrounding Death" website and access 'Details for obtaining NIECR account Requests'.

Access Patient & Enrol on Mortality Pathway

- Ensure you know the deceased patient's name and H&C number.
- From the Home Screen, identify the deceased patient by using the 'Patients' tab.
- If the patient record is locked down, contact NIECR Team to release – Contact details below.
- Once the Patient Summary Screen appears, click on 'Pathways' tab along the top of the screen.
- Click on 'Enroll in Pathway' (located just below 'Pathway Enrollment' heading at top of page).
- From the drop-down list select 'Mortality Pathway' and click on 'Enroll'.
- If you enroll the wrong patient into the pathway, you can "Deactivate" the pathway.

Complete an Initial Record of Death (IRD)

- A form will pop up on the left hand side under 'Mortality Pathway' entitled 'Mortality Initial Record of Death'. Click on this.
- Enter required information on form. Some information will be pre-populated.
- When entering date and time of death, please ensure these are the same as recorded in the handwritten notes as Verification of Life Extinct.
- Answer if the patient died in or out of hospital. Complete the address if they died out of Hospital.
- Place of Death: Select your Trust area, then the appropriate hospital and the ward details.
- Then, the appropriate M&M team and Consultant must be selected to review the death.
- If you do not know the correct Consultant, select the M&M lead for that team. The M&M lead is identified within the team descriptor when you select the M&M team.
- Complete all the required boxes and click '*Complete*' at bottom of form.

Printing MCCD and/or Clinical Summary

- Once you have clicked '*Complete*' on the Initial Record of Death Form there may be output documents for you to print, depending on the outcome you have chosen. These will be an MCCD, a Clinical Summary (for the Coroner), or both.
- To access these, click on the *'Patient Summary'* tab along the top of your screen, followed by 'Notification & Legal Documents' on the left-hand-side. If you would prefer this to appear in a separate window you can select *'Patient Summary Popup'* at the top of the screen.
- After you have clicked on the relevant document there is an option to *Print* at the top of the screen.
- When printing, ensure that 'Fit to Size' is selected within the PRINT dialog box. Otherwise the borders of the MCCD will be cut off.
- Similarly, for printing the Clinical Summary.

Editing a MCCD

- A MCCD can only be edited if it has not yet been provided to the family or left the ward. If it has already been issued and especially if the death has already been registered in the GRO, the MCCD needs corrected during 'Consultant Review' using a MCCD Correction Form.
- To edit the MCCD – enter the patient record, click on the 'Pathways' tab, click 'All' at the top left of the screen under 'Patient Tasks' and click on 'Initial Record of Death' (which will have a ticked green circle beside it). Click '*Re-open Task*' at the top-right of the screen.
- Make the necessary changes to the Cause of Death section & click '*Complete*' at the bottom. The editied MCCD will appear under 'Notification & Legal documents' as before.
- Print the MCCD as before. Ensure the original incorrect MCCD is retained & destroyed.

Contact details

If you are experiencing any issues accessing the NIECR - Mortality Pathway or problems registering a death please contact: NIECR via the Infra portal on the Trust Intranet site (SHSCT, SEHSCT & NHSCT) or supportteam@hscni.net (BHSCT & WHSCT)

August 2018

Steps needed to complete IRD*, install eMCCD into the Notification & Legal document area to allow printing.

	Action	Note
1.	NIECR logon using user name and personal password	Do NOT use anybody else's logon details.
2.	Select correct patient on NIECR, • by direct patient search using H&C number, or • from recently reviewed patients	Ensure the correct patient is identified
3.	Enrol deceased onto Mortality Pathway	
4.	Select Initial Record of Death	To be found within Clinical Document Viewer (CDV) tree
5.	Check correct patient is selected	
6.	Enter date & time of death	Determined by Verification of Life Extinct date & time.
7.	Enter who verified life extinct (VLE)	
8.	Enter Place of Death	
9.	Select M&M reviewing Team	
10.	Select Additional team, if necessary	
11.	Complete Clinical Detail boxes	Brief summary if NOT Coroner's case
12.	Select MCCD Outcome	
13.	If Coroner's Office contacted for advice, enter the Coroner's Reference Number provided.	
14.	Complete Cause of Death boxes	See **RECORDING THE CAUSE OF DEATH**
15.	Complete Implant questions	
16.	Enter Work address and contact numbers	Use Work numbers only
17.	Enter correct GMC number	Only use your own number
18.	Print eMCCD	Select Patient Summary
		Select Notification & Legal Documents
		Select MCCD
		Hover over MCCD pdf
		Select Print icon
		Ensure 'Fit', 'Shrink to Fit' or 'Print to size' button is selected
		Print
19.	Sign and Date eMCCD	
20.	Hand to informant	Explain details of MCCD to family and informant

* = Initial Record of Death

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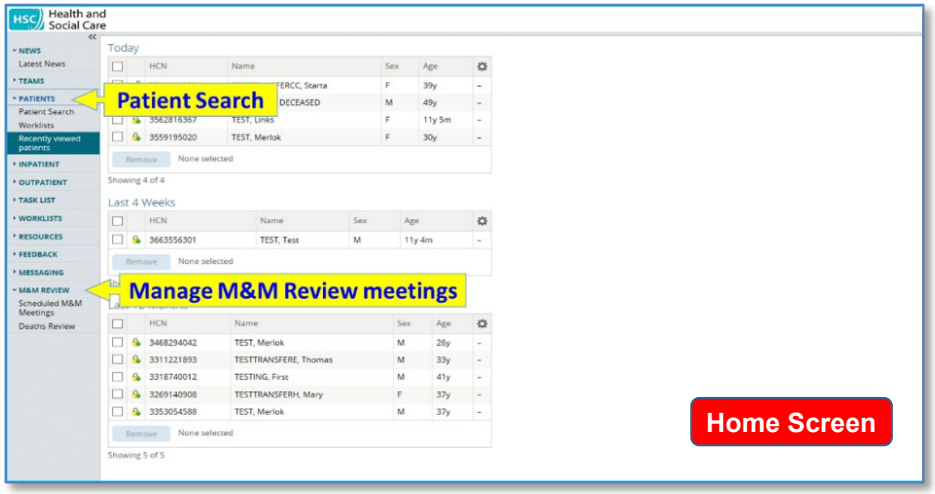
Instructions for printing an eMCCD and/or Clinical Summary from NIECR.

Once logged onto NIECR, there are 3 basic screens that you will need to access during the process of recording a death and printing the eMCCD and/or Clinical Summary.

1. HOME Screen

Following NIECR logon, the first screen entered is the HOME page.



This will allow you to select the correct deceased patient either,

- from their Health & Care number; or
- because they have been a recent encounter on NIECR.

Incidentally, in this screen you can also access “M&M Review” where you can,

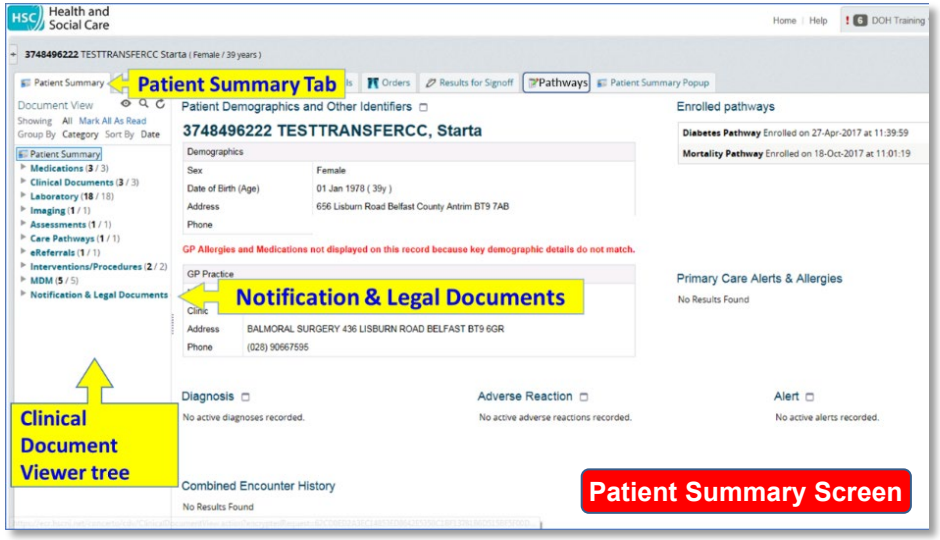
- schedule, access and manage M&M meetings;
- view the Outcome Reports from M&M meetings; and
- access the Death Review List.

Once the correct patient is selected, a second screen, the Patient Summary Screen, will be produced.

2. Patient Summary Screen

The Patient Summary Screen is the main starting point for each patient and includes an area for viewing documents; the Clinical Document Viewer (CDV) tree. In this list, under Notifications & Legal Documents, the following documents are placed which can be accessed and printed from here.

- Medical Certificate of Cause of Death (MCCD);
- Clinical Summary;
- Child Death Notification Form; and
- MCCD Correction Form.



Before doing this, the death must be first be recorded onto the NIECR via the third screen – the Mortality Pathways Screen, which is selected from within the Patient Summary Screen.

3. Mortality Pathway Screen

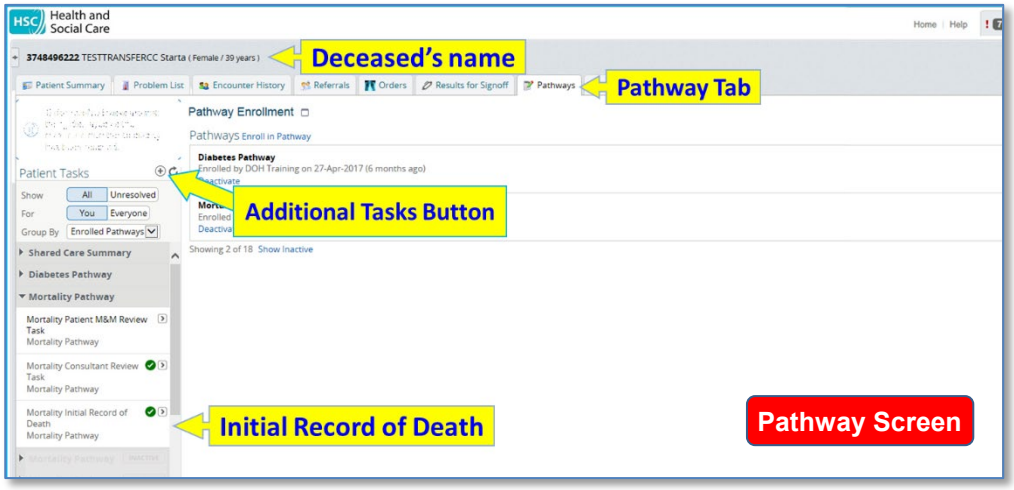
This screen is accessed by selecting the Pathway tab from within the Patient Summary Screen.

The Mortality Pathway Screen allows,

- enrolling the deceased onto a Mortality Pathway which, once completed;
- production of the Initial Record of Death (IRD). This will automatically appear on the left-hand margin.

Completing the IRD requires the following items of information. Once the IRD is completed, printing of the eMCCD and/or Clinical Summary can now be accomplished by returning to the second screen - the Patient Summary Screen, where the Notification and Legal Document area will now contain the eMCCD and/or Clinical Summary.

This whole sequence is summarised in a sequence of screens here



Incidentally, the Mortality Pathways Screen also allows,

- completion of the Consultant Review;
- review of the case at a Patient M&M Review meeting; and finally,
- Patient M&M Signoff.

The Mortality Pathways Screen also contains the "Additional Tasks" button which provides the,

1. ability to 'Add a Document' to the patient NIECR record.
2. opportunity for another patient M&M review, either by the,
    a. Primary Review team; or
    b. an Additional Review Team.

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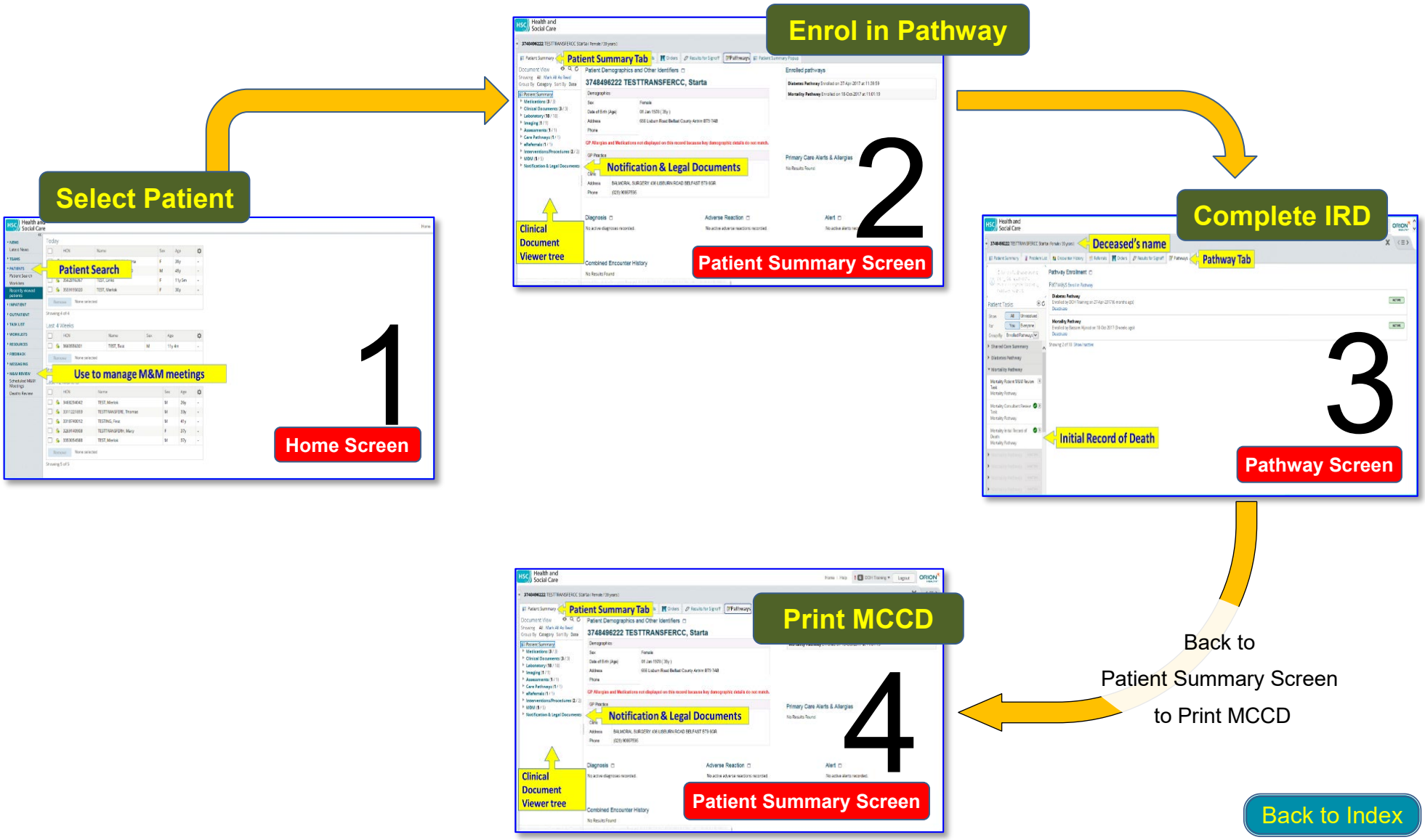
Sequence of Screens required to produce the Medical Certificate of Cause of Death on NIECR



Details for obtaining NIECR Account Requests

Belfast HSCT

The Belfast Trust has a registration site setup at:
http://intranet.belfasttrust.local/directorates/par/it/niecr/Pages/Home.aspx

Personal Information redacted by the USI
Personal Information redacted by the USI

Project Manager
NIECR Project Implementation Manager

Northern HSC Trust

All requests to ECRSupport: Personal Information redacted by the USI

Personal Information redacted by the USI
Personal Information redacted by the USI

NIECR System Manager / Trainer
NIECR Implementation Managers

Southern HSC Trust

Personal Information redacted by the USI
Personal Information redacted by the USI
Personal Information redacted by the USI

IT Service Desk
IT System Support
NIECR Transformational Lead

South Eastern HSC Trust

Personal Information redacted by the USI
Personal Information redacted by the USI

NIECR Implementation Manager
NIECR Project Support Officer

Western HSC Trust

All requests to WHSCT Helpdesk: Personal Information redacted by the USI

or by contacting extn Personal Information redacted by the

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Personal Information redacted by the USI
Personal Information redacted by the USI

NIECR/Encompass Lead
NIECR Project Manager
NIECR Trainer

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Health and Social Care Board

Health & Social Care Board
12-22 Linenhall Street
BELFAST BT2 8BS

Tel: 0300 555 0115
Web: www.hscboard.hscni.net

Our Ref:
NICE/ Technology Appraisals / TA 674

Chief Executives of Trusts - for cascade to:
Medical Directors
Directors of Nursing
Directors of Acute Services
Heads of Pharmacy & Medicines Management
Clinical & Social Governance Leads

Director of Integrated Care, HSCB - for cascade to:
Head of Pharmacy & Medicines Management

1 February 2022

Dear Colleague

NICE Technology Appraisal (TA674) Pembrolizumab for untreated PD-L1-positive, locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (terminated appraisal) (review of TA522)

I am writing to inform you that NICE Technology Appraisal TA674 updates and replaces NICE Technology Appraisal TA522 on pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable. NICE Technology Appraisal TA522 was formally endorsed by the DoH in February 2019.

Thank you for your attention with this matter. If you have any queries please contact Emma McKee Personal Information redacted by the USI in the HSCB Commissioning Directorate in the first instance.

Yours sincerely

Personal information redacted by USI

Paul Cavanagh
Interim Director of Planning & Commissioning

Cc Chief Medical Officer
Chief Executive Patient and Client Council
Chief Executive/Postgraduate Dean, NIMDTA
Chief Executive, NICPLD
Chief Executive, NIPEC
Chief Executive, NIBTS

Chief Executive, RQIA
Chief Executive, PHA
Senior Management Team, HSCB
Assistant Directors of Commissioning, HSCB

From the Chief Medical Officer
Prof Sir Michael McBride

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

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BT4 3SQ

Tel: [redacted]
Email: Personal Information redacted by the USI

HSS(MD) 06/2022

FOR ACTION
Chief Executives, Public Health Agency/Health and Social Care Board/HSC Trusts

PLEASE SEE ATTACHED FULL CIRCULATION LIST

Our Ref: HSS(MD) 06/2022
Date: 1 February 2022

Dear Colleague

ANTIVIRALS OR NEUTRALISING MONOCLONAL ANTIBODIES (nMABs) FOR NON-HOSPITALISED PATIENTS WITH COVID-19 - UPDATE

This letter supersedes and replaces HSS(MD) 81/2021, first issued on 10 December 2021 and the later addenda on 17 December 2021 and 24 December 2021.

The published policy, providing access to monoclonal antibodies or antivirals as treatment options for non-hospitalised patients at highest risk from COVID-19 infection, has been updated to include additional licensed antiviral treatment options; **oral PF-07321332 (may also be known as nirmatrelvir) plus ritonivir (Paxlovid) as a new first-line treatment option, and intravenous remdesivir (Veklury) as a second-line treatment option.** Intravenous sotrovimab (Xevudy) remains in the policy as a first-line treatment option. Oral molnupiravir (Lagevrio) remains a third-line option. Positive PCR tests or formally registered positive lateral flow tests may now be considered to meet the eligibility requirement on confirmed COVID infection.

These changes are for implementation from Thursday 10 February 2022.

This targeted Health Service deployment for patients at highest risk sits alongside the PANORAMIC trial where a different and broader cohort of patients are able to access novel oral antivirals through a clinical study.

Action required

HSC Trusts commissioned to provide Outpatient COVID-19 Treatment Services (OCTs) are asked to:

1. **Consider prescribing and administering an antiviral or monoclonal antibody treatment in line with the published policy** and associated **clinical guide to non-hospitalised patients where:**

- SARS-CoV-2 infection is confirmed by either:
  - Polymerase chain reaction (PCR) testing; OR
  - Lateral flow test (registered via gov.uk or via 119)

AND

- Symptomatic with COVID-19[1] and showing no signs of clinical recovery

AND

- The patient is member of the 'highest' risk group as set out in the policy

  Children aged 12-17 years may only be considered for treatment with sotrovimab or remdesivir. For paediatric/adolescent patients (aged 12-17 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.

2. PF-07321332(nirmatrelvir) plus ritonavir (Paxlovid), and molnupiravir, are **not recommended during pregnancy**. All individuals of childbearing potential who are prescribed molnupiravir should be advised to use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir. The use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping Paxlovid.

3. All healthcare professionals are asked to ensure that any patients who receive a COVID antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909. For more information, go to http://www.uktis.org/.

[1] The following are considered symptoms of COVID-19: feverish, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhoea, headache, red or watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomach ache, rash, sneezing, sputum or phlegm, runny nose

4. Where possible, take samples for relevant serology testing prior to planned treatment with sotrovimab. However, serology results are **not** a requirement for treatment with nMABs under the criteria specified in the policy.

5. **Support additional testing or data requirements where requested under country specific or UK wide surveillance programmes, in line with current guidance.**

6. Ensure clinicians prescribing remdesivir for individuals aged 12-17 years, as an off-label product, follow local governance procedures in relation to the prescribing of off-label medicines.

   Further guidance on the prescribing of off-label medicines can be found below:

- https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities
- https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines
- https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Professional%20standards/Prescribing%20competency%20framework/prescribing-competency-framework.pdf

7. Ensure discharge letters to primary care explicitly record the treatment that has been given, together with the dose and date of administration.

8. Adhere to the guidance which has been developed by the Specialist Pharmacy Service (SPS) to support the administration of antivirals or monoclonal antibodies

9. Training for antimicrobial stewardship teams will be provided via webinar by UKHSA jointly with NHS England and NHS Improvement. HSC Trusts in Northern Ireland should liaise with the Regional Pharmaceutical Procurement Service to register interest.

10. HSC Trusts should liaise with the Regional Pharmaceutical Procurement Service to register interest in COVID-19 specific supply arrangements. Initial allocations for use within the HSC will be determined regionally, informed by nationally determined allocations, with ongoing supplies to each hospital replenished on the basis of relative use/need. Ongoing ordering will be through existing (business as usual) routes, supported by volume-based caps (reflecting estimated eligible patient volumes) if required.

11. Organisations should note that initial supply of COVID-19 medicines may be available within 'emergency supply' packaging, which differs from the planned Great Britain (GB) packaging/labelling aligned to the product's GB licence (or the equivalent product packaging/labelling aligned to a Regulation 174 authorisation or European Medicines Agency marketing authorisation as

applicable in Northern Ireland). **To preserve available supply, providers must ensure that packs with shorter use by dates are used first**.

12. Regular stock updates should be provided to HSC Trust Heads of Pharmacy and Medicines Management, HSC Trust pharmacy procurement leads, and the Regional Pharmaceutical Procurement Service. Trusts should enter the products onto stock control and prescribing systems as described below:

- PF-07321332(nirmatrelvir) (150mg tablets) plus Ritonavir (100mg tablets), 30 tablet pack
- Remdesivir 100mg powder for concentrate for solution for infusion
- Sotrovimab 500mg/8ml solution for infusion vials
- Molnupiravir 200mg capsules, 40 capsules

The Health and Social Care Board is asked to:

13. Work with HSC Trusts and the Regional Pharmaceutical Procurement Service to develop proportionate interim arrangements to monitor uptake of treatment, pending consideration for routine commissioning in line with extant Managed Entry arrangements.

Summary

Antiviral treatments inhibit the development and replication of viruses such as SARS-CoV-2. Neutralising monoclonal antibodies (nMABs) bind to specific sites on the spike protein of the SARS-CoV-2 virus particle, blocking its entry into cells and therefore inhibiting its replication.

Recent evidence suggests that antivirals and neutralising monoclonal antibodies (nMABs) significantly improve clinical outcomes in non-hospitalised patients with COVID-19 who are at high risk of progression to severe disease and/or death.

The updated UK-wide clinical commissioning policy **(for implementation from 10 February 2022)** applies to non-hospitalised patients with COVID-19 who are symptomatic and showing no evidence of clinical recovery. It provides the following treatment options:

- First-line**:** PF-07321332(Nirmatrelvir) plus Ritonavir (antiviral) OR Sotrovimab (nMAB), as clinically indicated
- Second-line: Remdesivir (antiviral)
- Third-line: Molnupiravir (antiviral)

Either PCR tests or formally registered positive lateral flow tests[2] (registered via gov.uk or via 119) may now be considered to meet the eligibility requirement on confirmed COVID infection.

[2] Individuals who are symptomatic, and those with a positive lateral flow test result are strongly encouraged to continue to take a confirmatory PCR test

Further information on selecting the most appropriate treatment can be found in the clinical guide associated with this policy.

Please also refer to the published (revised) policy for a summary of the supporting evidence, further details on eligibility (and exclusion criteria) and for additional guidance.

Co-Administration

For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

COVID treatments should not be infused concomitantly in the same IV line with other medications.

Monitoring, tracking and follow-up

Monitoring of longer-term progress is strongly recommended via recruitment of patients receiving COVID therapies to the ISARIC-CCP study.

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) should explicitly record the treatment that has been given together with the dose and date of administration.

Healthcare professionals are asked to report any suspected adverse reactions (including congenital malformations and or neurodevelopmental delays following treatment during pregnancy) via the United Kingdom Yellow Card Scheme www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Further enquiries should in the first instance be directed to your hospital pharmacy team.

Yours sincerely

Personal Information redacted by USI

PROF SIR MICHAEL McBRIDE
Chief Medical Officer

Personal information redacted by USI

MRS CATHY HARRISON
Chief Pharmaceutical Officer

Circulation List

Executive Medical Director/Director of Public Health, Public Health Agency (for onward distribution to all relevant staff)
Director of Nursing, Public Health Agency
Directors of Pharmacy HSC Trusts
Director of Social Care and Children, HSCB

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Nursing Directors, HSC Trusts (for onward distribution to all relevant staff)
RQIA (for onward transmission to independent hospitals)
Regional Medicines Information Service, Belfast HSC Trust
Regional Pharmaceutical Procurement Service, Northern HSC Trust
Dr Margaret O'Brien, Head of General Medical Services, Health and Social Care Board
Joe Brogan, Head of Pharmacy and Medicines Management, Health and Social Care Board

This letter is available on the Department of Health website at https://www.health-ni.gov.uk/topics/professional-medical-and-environmental-health-advice/hssmd-letters-and-urgent-communications

From the Chief Medical Officer
Prof Sir Michael McBride

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

HSS(MD) 04/2022

FOR ACTION
Chief Executives, Public Health Agency/Health and Social Care Board/HSC Trusts/NIAS
GP Medical Advisers, Health and Social Care Board
All General Practitioners and GP Locums (for onward distribution to practice staff)
OOHs Medical Managers (for onward distribution to staff)

PLEASE SEE ATTACHED FULL CIRCULATION LIST

Castle Buildings
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BELFAST
BT4 3SQ

Tel: [redacted]
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Our Ref: HSS(MD) 04/2022
Date: 31 January 2022

Dear Colleague

COVID-19 THERAPEUTIC ALERT: ANTIVIRALS AND NEUTRALISING MONOCLONAL ANTIBODIES IN THE TREATMENT OF COVID-19 IN HOSPITALISED PATIENTS - EFFECTIVE FROM 10 FEBRUARY 2022

This letter supersedes and replaces HSS(MD) 90/2021.

Actions required

HSC Trusts are asked to take the following steps to support the treatment of patients in hospital with COVID-19 infection:

1. **Organisations are recommended to consider prescribing an antiviral or monoclonal antibody treatment to adults, and children aged 12 and over and weighing at least 40kg, in line with the published policy.**
   In the absence of a confirmed virological diagnosis, the treatment should only be used when a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis.

2. PF-07321332(nirmatrelvir) plus ritonavir (Paxlovid), and molnupiravir, are **not recommended during pregnancy.** All individuals of childbearing potential who are prescribed molnupiravir should be advised to use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir. The use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping Paxlovid.

3. All healthcare professionals are asked to ensure that any patients who receive a COVID antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909. For more information, go to http://www.uktis.org/

4. Clinicians are encouraged to proactively support recruitment into trials developing further evidence in the treatment of COVID-19. Patients admitted to hospital due to COVID who are ineligible for the casirivimab and imdevimab combination monoclonal antibody due to confirmed infection with the Omicron variant may be considered for entry into the RECOVERY trial, which is studying sotrovimab versus standard of care.

5. **Organisations are encouraged to undertake anti-s spike antibody testing[1] for all patients hospitalised due to COVID at, or as soon as possible after, the point of admission**. **Patients with hospital-onset COVID should also be antibody tested, with appropriate consent, to support further treatment evaluation and surveillance *(antibody status does not affect treatment eligibility in this, second, cohort)*.** If there are concerns or questions around laboratory sensitivity or thresholds these should be discussed in the first instance with local laboratory leads who will have access to comparative and performance data from external quality assessment (EQA) scheme participation. Supporting laboratory networks should ensure that the maximum turnaround time for anti-s antibody tests is no greater than 24 hours from the sample being taken to the result being returned. Positive and negative antibody tests should be reported via the Second Generation Surveillance System (SGSS), or equivalent systems in Northern Ireland, to support surveillance and enable reimbursement of associated assay costs.

6. **Genotyping is a key element of the management of inpatients admitted due to COVID-19 infection. Where critical to a treatment decision, genotyping requests should be marked 'urgent – treatment is variant dependent' to assist laboratories in their prioritisation.** Genotyping results should be reported via the Second Generation Surveillance System (SGSS), or equivalent systems in Northern Ireland, to support surveillance and enable reimbursement of associated assay costs.

7. **Noting the critical role of surveillance, treating clinicians are strongly encouraged to actively support additional testing or data requirements as requested under country specific or UK wide surveillance programmes, in line with further guidance to be issued.**

8. Discharge letters to primary care should explicitly record the treatment that has been given, together with the dose and date of administration.

[1] Patients may be tested for anti-S1 or anti-S2 antibodies using any validated quantitative or qualitative anti-S assay that measures either IgG or total antibody levels. Serostatus should be established in line with the pre-determined thresholds relevant to the assay being used by the testing laboratory. Quantitative assays with pre-specified thresholds for seropositivity should return clear binary (i.e. either 'negative' or 'positive') results based on these thresholds. For quantitative assays without a formal threshold for serostatus, clinical decision-making should guide treatment decisions.

9. Any organisation treating patients admitted due to COVID-19 under this policy with the off-label 2.4g dose casirivimab and imdevimab antibody combination, or prescribing remdesivir to children aged 12-17 years and not on supplementary oxygen, as off-label products, will be required to assure itself that the necessary internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the HSC Trust's drugs and therapeutics committee, or equivalent.

10. Adhere to the guidance which has been developed by the Specialist Pharmacy Service (SPS) to support the administration of antivirals and monoclonal antibodies.

11. HSC Trusts in Northern Ireland should liaise with the Regional Pharmaceutical Procurement Service to register interest in COVID-19 specific supply arrangements. Allocations for use within the HSC will be determined regionally, informed by nationally determined allocations, with ongoing supplies to each hospital replenished on the basis of relative use / need. Ongoing ordering will be through existing (business as usual) routes, supported by volume-based caps (reflecting estimated eligible admissions) where required.

12. Organisations should note that initial supply of COVID-19 medicines may be available within 'emergency supply' packaging, which differs from the planned Great Britain (GB) packaging / labelling aligned to the product's GB licence (or the equivalent product packaging / labelling aligned to a Regulation 174 authorisation or European Medicines Agency marketing authorisation as applicable in Northern Ireland). **To preserve available supply, providers must ensure that packs with shorter use by dates are used first**.

13. Provide regular updates on the stock position to HSC Trust Heads of Pharmacy and Medicines Management, pharmacy procurement leads and the Regional Pharmaceutical Procurement Service. Hospitals should enter the product onto stock control and prescribing systems as described below:

- Casirivimab 300 mg per 2.5 mL (120 mg/mL) with Imdevimab 300 mg per 2.5 mL (120 mg/mL) with the dose description as: 2 vial pack
- Casirivimab 1332 mg per 11.1 mL (120 mg/mL) with Imdevimab 1,332 mg per 11.1 mL (120 mg/mL) with the dose description as: 2 vial pack
- PF-07321332(nirmatrelvir) (150mg tablets) and ritonavir (100mg tablets), 30 tablet pack
- Remdesivir 100mg powder for concentrate for solution for infusion
- Sotrovimab 500mg/8ml solution for infusion vials

The Health and Social Care Board is asked to:

14. Continue to work with HSC Trusts and the Regional Pharmaceutical Procurement Service to monitor uptake of treatment, pending consideration for routine commissioning in line with extant Managed Entry arrangements.

The Public Health Agency is asked to:

15. Continue to work with HSC Trusts and the Business Services Organisation to report positive and negative tests to enable retrospective reimbursement of associated assay costs.

The previously published UK-wide interim clinical commissioning policy providing access to neutralising monoclonal antibodies (nMABs) and intravenous antivirals for hospitalised patients with COVID-19 infection has been further updated **(effective from 10 February 2022)** to add an additional antiviral treatment option – PF-07321332 (may also be known as nirmatrelvir) plus ritonavir (Paxlovid) as a first-line treatment option for patients with hospital onset COVID infection. The intravenous antiviral remdesivir (Veklury) and the monoclonal antibody sotrovimab (Xevudy) remain available as alternative treatment options in this cohort.

Patients admitted due to COVID-19 continue to have a range of treatment options under published UK policies, but will only be able to routinely access a monoclonal antibody treatment, casirivimab and imdevimab (Ronapreve), if genotyping confirms infection with a non-Omicron variant. Patients ineligible for the casirivimab and imdevimab combination may be considered for entry into the RECOVERY trial, which is studying sotrovimab versus standard of care. Genotyping of all inpatients continues to be recommended to assist in treatment decisions and / or to support wider surveillance.

Summary

Neutralising monoclonal antibodies (nMABs) bind to specific sites on the spike protein of the SARS-CoV-2 virus particle, blocking its entry into cells and therefore inhibiting its replication. Antiviral treatments inhibit the development and replication of viruses such as SARS-CoV-2.

Recent evidence suggests that antivirals and nMABs significantly improve clinical outcomes in patients with COVID-19 who are at high risk of progression to severe disease and/or death.

Group 1 Patients - There are no material changes in the policy for patients who have been admitted to hospital DUE to COVID-19. Patients hospitalised due to acute COVID-19 illness who are PCR positive with a non-Omicron variant and who are antibody seronegative may be treated at the off-label total dose of 2.4g of casirivimab and imdevimab.

Clinicians are encouraged to consider entering all other patients admitted to hospital due to COVID-19 infection (including those infected with the Omicron variant, regardless of antibody status) into the RECOVERY trial, which is studying sotrovimab versus standard of care. Please also refer to other published UK clinical access policies for treatment options for patients admitted due to COVID-19 infection.

Group 2 Patients – Options for patients admitted to hospital for a non-COVID-19 related reason but who nonetheless test positive during their hospital stay with and meeting additional eligibility criteria have been revised to provide access to an additional first-line treatment option - PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid). Remdesivir (Veklury) is now a licensed second-line treatment option. Sotrovimab (Xevudy) remains available as a third-line treatment option in this cohort. Further information to support clinical decision making for patients with hospital-onset COVID-19 can be found in the supporting clinical guide.

Further details on supporting evidence and eligibility, together with further guidance, can be found in the published policy

Product Details

Ronapreve is supplied to the UK by Roche. It is a combination neutralising monoclonal antibody (casirivimab plus imdevimab) used to inhibit viral replication in individuals who have not yet mounted an adequate antibody response to the SARS-COV-2 virus following either exposure or vaccination. The casirivimab plus imdevimab combination for intravenous and subcutaneous use is authorised for use in the treatment and prophylaxis of COVID-19 positive adults, and children aged 12 and above and weighing at least 40kg. Supply of the casirivimab and imdevimab combination is subject to the same requirements in both Great Britain and Northern Ireland, and the product information in the Summary of Product Characteristics should be considered applicable across the UK.

PF-07321332(nirmatrelvir) plus ritonavir (Paxlovid) is a combination oral antiviral supplied by Pfizer that works by inhibiting a protease required for viral replication. It is supplied as a pack providing a five-day treatment course containing both PF-07321332(nirmatrelvir) (150mg tablets) and ritonavir (100mg tablets). PF-07321332(nirmatrelvir) plus ritonavir has a conditional market authorisation in Great Britain (under the Medicines and Healthcare products Regulatory Authority (MHRA)), and a Regulation 174 approval covers use in Northern Ireland, for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

Remdesivir (Veklury) is supplied by Gilead. Delivered intravenously, it has a conditional market authorisation for use as a treatment for COVID-19 in both Great Britain (under the Medicines and Healthcare products Regulatory Authority (MHRA)) and in Northern Ireland (under the European Medicines Agency (EMA)) for 1) adults, and adolescents aged 12 and over weighing at least 40kg, with pneumonia requiring supplemental oxygen and 2) for adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Sotrovimab (Xevudy) is supplied by GlaxoSmithKline and Vir Biotechnology. Delivered intravenously, sotrovimab has a conditional marketing authorisation in Great Britain (England, Scotland and Wales) and in Europe (under the European Medicines Agency, covering Northern Ireland) for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection.

Prescribing

The casirivimab plus imdevimab combination product (Ronapreve) is now authorised as a treatment for COVID-19 by the European Medicines Agency but the published policy includes an off-label use at a dose of 2.4g. The use of remdesivir for COVID-19 in adolescents aged 12-17 years not yet requiring supplemental oxygen is also off-label. As such, clinicians prescribing either treatment should follow HSC Trust governance procedures in relation to the prescribing of off-label medicines.

Further guidance on the prescribing of off-label medicines can be found below:

- https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities
- https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines
- https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Professional%20standards/Prescribing%20competency%20framework/prescribing-competency-framework.pdf

Co-Administration

There is no interaction expected of the monoclonal antibodies or antiviral treatments covered under the policy with other treatments available for COVID under published UK clinical access policies - dexamethasone or hydrocortisone, remdesivir, or tocilizumab or sarilumab.

For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Monoclonal antibodies and / or antivirals should not be infused concomitantly in the same IV line with other medications.

Monitoring, tracking and follow-up

Monitoring of longer-term progress is strongly recommended via recruitment of patients receiving COVID therapies to the ISARIC-CCP study.

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) should explicitly record that a monoclonal antibody has been given together with the dose and date of administration.

Healthcare professionals are asked to report any suspected adverse reactions via the United Kingdom Yellow Card Scheme www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Further enquiries should in the first instance be directed to your hospital pharmacy team.

Yours sincerely

Personal information redacted by USI

PROF SIR MICHAEL McBRIDE
Chief Medical Officer

MRS CATHY HARRISON
Chief Pharmaceutical Officer

Circulation List

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Dr Margaret O'Brien, Head of General Medical Services, Health and Social Care Board
Joe Brogan, Head of Pharmacy and Medicines Management, Health and Social Care Board

This letter is available on the Department of Health website at https://www.health-ni.gov.uk/topics/professional-medical-and-environmental-health-advice/hssmd-letters-and-urgent-communications

Testing and HCAIs Update

No outbreak

Patients

Patient has point of care test (Lumira/LIAT) in ED and repeated every 24 hours if still in ED

Patient has PCR on arrival in the ward.

Patient tested every 5 days

Healthcare Workers

Regular testing twice a week of asymptomatic workers using LFTs or LAMP

HCAI Outbreak

Assumes outbreak control team (OCT) convened

The need for enhanced testing is a standing agenda item and outcome of discussion regarding testing to be carried out is formally recorded*.

Outbreak confirmed :

All staff** and patients who are close contacts in ward are PCR tested and then proceed to

Daily testing of close contacts using LFTs or daily PCRs. Daily PCRs instead of LFDs **may only be considered following discussion with local testing laboratory and is dependent on laboratory capacity**.

Daily testing of staff using LAMP (Mon to Friday if available with LFTs at weekend) or LFTs.

IH POCTSF-POL-001
NI Regional POCT Pol

*In choosing which form testing should take, OCT need to consider and discuss with local laboratory local PCR testing capacity, turnaround time for results and ensure LFT results are incorporated into patients notes in line with regional Point of Care (POC) testing protocol developed by Pathnet.

**Staff should be able to be PCR tested in their workplace.

UPDATE: 9th February 2022

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Our Ref:
NICE/ Technology Appraisals / TA724

Chief Executives of Trusts - for cascade to:
Medical Directors
Directors of Nursing
Directors of Acute Services
Heads of Pharmacy & Medicines Management
Clinical & Social Governance Leads

Director of Integrated Care, HSCB - for cascade to:
Head of Pharmacy & Medicines Management

21 January 2022

Dear Colleague

NICE Guidance TA724 - NOT RECOMMENDED - Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer.

I refer to the above NICE guidance and the required arrangements to ensure compliance with the NICE decision **not to recommend** this regime for the treatment of this condition.

Background

NICE TA724 **does not recommend** the use of nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer. This position has been endorsed by the DOH and represents the Department's formal policy position on this NICE guidance.

Action required

Trusts should take immediate action to ensure compliance with NICE TA724. Trusts should ensure that within one month:

- targeted dissemination takes place;
- a clinical / management leader is in place to ensure the discharging of the Trust's responsibilities; and,
- no no patients requiring treatment for untreated metastatic non-small-cell lung cancer commence treatment with nivolumab with ipilimumab and chemotherapy.