

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Therapeutics for people with COVID-19

This draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19. During the consultation phase, and up until the final guidance is published and implemented, NHS treatment choices should continue to be guided by published UK-wide [interim clinical commissioning policies](#).

In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as:

- the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or
- local or national circumstances of high rates of hospitalisation for COVID-19.

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using baricitinib, casirivimab plus imdevimab, molnupiravir, nirmatrelvir plus ritonavir, remdesivir, sotrovimab, tixagevimab plus cilgavimab and tocilizumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the [committee papers](#)).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using baricitinib, casirivimab and imdevimab, molnupiravir, nirmatrelvir and ritonavir, remdesivir, sotrovimab, tixagevimab and cilgavimab, and tocilizumab for routine use in the NHS in England.
- The Scottish Medicines Consortium (SMC) will use the final recommendations to produce separate advice for the NHS health boards in Scotland

For further details, see [NICE's manual on health technology evaluation](#).

The key dates for this evaluation are:

- Closing date for comments: 07 December 2022
- Second evaluation committee meeting: 24 January 2023
- Details of membership of the evaluation committee are given in section 5

1 Recommendations

- 1.1 Nirmatrelvir plus ritonavir is recommended as an option for treating COVID-19 in adults, only if they:
- do not need supplemental oxygen for COVID-19 and
 - have an increased risk for progression to severe COVID-19, as defined in the [independent advisory group report commissioned by the Department of Health and Social Care](#).
- 1.2 Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who:
- are having systemic corticosteroids and
 - need supplemental oxygen or mechanical ventilation.
- Tocilizumab is only recommended if the company provides it according to the commercial arrangement (see section 2).
- 1.3 Baricitinib is recommended as an option for treating COVID-19 in adults, subject to it receiving a marketing authorisation in Great Britain for this indication.
- 1.4 Casirivimab plus imdevimab is not recommended, within its marketing authorisation, for treating acute COVID-19 in adults.
- 1.5 Molnupiravir is not recommended, within its marketing authorisation, for treating mild to moderate confirmed COVID-19 in adults who have at least 1 risk factor for developing severe COVID-19.
- 1.6 Remdesivir is not recommended, within its marketing authorisation, for treating COVID-19 in:
- people aged at least 4 weeks and weighing at least 3 kg with pneumonia who need supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation) at start of treatment

- young people weighing at least 40 kg and adults who do not need supplemental oxygen and have an increased risk for progression to severe COVID-19.

1.7 Sotrovimab is not recommended, within its marketing authorisation, for treating symptomatic acute COVID-19 in people aged 12 years and over and weighing at least 40 kg who:

- do not need oxygen supplementation and
- have an increased risk for progression to severe COVID-19.

1.8 Tixagevimab plus cilgavimab is not recommended, within its marketing authorisation for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

1.9 People may be offered treatment from supplies already purchased by the Department of Health and Social Care before this guidance was published under the [interim clinical commissioning policies](#), if clinicians consider it an appropriate option for people with COVID-19.

Why the committee made these recommendations

People with COVID-19 who have a high risk for progression to severe COVID-19 are offered treatments to stop their symptoms worsening. Usually, people would be offered nirmatrelvir plus ritonavir, sotrovimab, remdesivir or molnupiravir. These treatments are recommended through the [NHS interim clinical commissioning policy on antivirals or neutralising monoclonal antibodies for people with COVID-19 who are not in hospital](#). An [independent advisory group report commissioned by the Department of Health and Social Care](#) defines who has an increased risk.

People in hospital with severe COVID-19 are offered different treatments based on their oxygen needs. For people who need supplemental oxygen, [NICE's rapid guideline on managing COVID-19](#) recommends corticosteroids. For people who are having corticosteroids and who need supplemental oxygen, the [NHS secondary care interim clinical commissioning policy](#) and NICE's managing COVID-19 guideline

recommend, in certain circumstances, tocilizumab, off-label (outside of marketing authorisation in Great Britain) use of baricitinib, or remdesivir. They also recommend nirmatrelvir plus ritonavir, sotrovimab or remdesivir for people who have no, or low, oxygen needs and a high risk for progression to severe disease.

This evaluation reviews the clinical and cost effectiveness of baricitinib, casirivimab plus imdevimab, molnupiravir, nirmatrelvir plus ritonavir, remdesivir, sotrovimab, tixagevimab plus cilgavimab and tocilizumab as treatment options for COVID-19.

Most of the clinical evidence is from studies done before the Omicron variant of SARS-CoV-2 (the virus that causes COVID-19). So there are significant uncertainties in the clinical evidence. There is some clinical evidence suggesting that baricitinib, molnupiravir, nirmatrelvir plus ritonavir, remdesivir and tocilizumab are effective at treating COVID-19. But, it is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (all neutralising monoclonal antibodies) are effective against the Omicron variant.

The cost-effectiveness estimates are highly dependent on hospitalisation and mortality rates. These rates are lower with the Omicron wave than earlier variants in the pandemic. Lower rates increase the cost-effectiveness estimates.

Nirmatrelvir plus ritonavir and tocilizumab are recommended because the likely cost-effectiveness estimates are within what NICE usually considers an acceptable use of NHS resources. Baricitinib is recommended subject to it receiving a marketing authorisation in Great Britain for this indication.

Casirivimab plus imdevimab, molnupiravir, remdesivir, sotrovimab and tixagevimab plus cilgavimab are not recommended because the likely cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources.

2 Information about the treatments

Marketing authorisation indications and anticipated marketing authorisation indications

- 2.1 Casirivimab plus imdevimab (Ronapreve, Roche Products) is 'indicated for the prophylaxis and treatment of acute Covid-19 infection'.
- 2.2 Molnupiravir (Lagevrio, Merck Sharp & Dohme) is 'indicated for treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness'.
- 2.3 Nirmatrelvir plus ritonavir (Paxlovid, Pfizer) is 'indicated 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'.
- 2.4 Remdesivir (Veklury, Gilead Sciences) is 'indicated for the treatment of coronavirus disease 2019 (COVID-19) in:
- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)'.
 - adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19'.
- 2.5 Sotrovimab (Xevudy, GlaxoSmithKline) is indicated '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 infection'.
- 2.6 Tocilizumab (RoActemra) is indicated 'for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic

corticosteroids and require supplemental oxygen or mechanical ventilation’.

- 2.7 Tixagevimab and cilgavimab (Evusheld, AstraZeneca) is indicated ‘for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19’.
- 2.8 Baricitinib (Olumiant, Eli Lilly and Company) does not have a marketing authorisation in Great Britain yet for treating COVID-19.

Dosage in the marketing authorisation

- 2.9 The dosage schedule for casirivimab and imdevimab is available in the [summary of product characteristics for casirivimab plus imdevimab](#).
- 2.10 The dosage schedule for molnupiravir is available in the [summary of product characteristics for molnupiravir](#).
- 2.11 The dosage schedule for nirmatrelvir and ritonavir is available in the [summary of product characteristics for nirmatrelvir plus ritonavir](#).
- 2.12 The dosage schedule for remdesivir is available in the [summary of product characteristics for remdesivir](#).
- 2.13 The dosage schedule for sotrovimab is available in the [summary of product characteristics for sotrovimab](#).
- 2.14 The dosage schedule for tocilizumab is available in the [summary of product characteristics for tocilizumab](#).
- 2.15 The dosage schedule for tixagevimab plus cilgavimab is available in the [summary of product characteristics for tixagevimab plus cilgavimab](#).
- 2.16 The dosage schedule for baricitinib will be available in the summary of product characteristics for baricitinib.

Price

- 2.17 The list price for casirivimab plus imdevimab is currently confidential.

- 2.18 The list price for molnupiravir is currently confidential.
- 2.19 The list price for nirmatrelvir plus ritonavir is £829 for a 20-pack of 150-mg nirmatrelvir tablets and a 10-pack of 100-mg ritonavir tablets (excluding VAT; MIMS online, accessed October 2022). Costs may vary in different settings because of negotiated procurement discounts.
- 2.20 The list price for remdesivir is £340 per 100 mg vial (excluding VAT; BNF online, accessed October 2022). Costs may vary in different settings because of negotiated procurement discounts.
- 2.21 The list price for sotrovimab is £2,209 for 500 mg/8 ml concentrate for solution for infusion vial (excluding VAT; BNF online, accessed October 2022). Costs may vary in different settings because of negotiated procurement discounts.
- 2.22 The list price for tixagevimab and cilgavimab is currently confidential.
- 2.23 The list price for tocilizumab is £256 per 200 mg/10 ml and £512 per 400 mg/20 ml concentrate for solution for infusion vial (excluding VAT; BNF online, accessed October 2022). The company has a commercial arrangement (simple discount patient access scheme). This makes tocilizumab 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.
- 2.24 The list price for baricitinib is £805.56 for a 28-pack of 4 mg tablets (excluding VAT; BNF online, accessed October 2022). The company has a commercial arrangement (simple discount patient access scheme). This makes baricitinib 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 [evaluation committee](#) considered evidence from several sources. See the [committee papers](#) for full details of the evidence.

Background

Impact of COVID-19

3.1 COVID-19 is the acute respiratory illness caused by the SARS-CoV-2 virus. It can range from mild to severe infections. In severe infections, excessive immune response to the virus may cause severe complications associated with hospitalisation and death. The need for organ system support, particularly respiratory support, is also a key feature of severe disease and can lead to substantial longer-term morbidity. COVID-19 may cause long-term symptoms that continue or develop after acute infection called 'long COVID'. These are health problems that can last several months which severely impact a person's physical or mental health, or both, and potentially affect their ability to work or do their usual activities. Many people are at increased risk of hospitalisation or death from COVID-19, including people who are immunosuppressed (who have, for example, inflammatory diseases, primary immunodeficiency, chemotherapy, or a transplant) or who have comorbidities (such as heart disease, respiratory disease, diabetes, neurological conditions). Some immunocompromised people are at risk of persistent viral infection if no immunological control is established. Patient experts explained that the increased risk of hospitalisation and death has led to changes in treatment, lifestyle and behaviour during the COVID-19 pandemic because of the need to shield. Patient organisations emphasised the need for treatments to prevent progression to severe COVID-19. They considered that routine availability of these treatments would support a return to normality for many people who already have disease burden from other comorbidities. The committee agreed that the risk of hospitalisation and death, and other longer-term impacts of COVID-19, can result in severe physical and mental burden.

The rapidly evolving SARS-CoV-2 virus

3.2 The global COVID-19 pandemic has caused unprecedented challenges to the healthcare system and this is reflected in the evidence collected on COVID-19 and treatments for it. The SARS-CoV-2 virus has evolved throughout the pandemic, as has the healthcare system's ability to respond to the virus. New variants of the virus and subvariants, referred to as variants of concern, have emerged throughout the pandemic. Each variant can have different properties, such as levels of transmissibility and disease severity. The clinical experts explained that understanding of the disease has changed throughout the pandemic, with increasingly effective supportive care, vaccination and greater natural immunity. At the time of first evaluation committee meeting, the dominant variant of concern in the UK was the Omicron variant, which also has multiple subvariants based on mutations in specific spike proteins. The clinical experts explained that changes in the epidemiology and context of COVID-19 have led to different characteristics of people with COVID-19 than seen earlier in the pandemic. Overall, hospitalisation and mortality from COVID-19 has reduced, and the incidence of COVID-19 pneumonitis in hospital has lowered, as has the need for supplemental oxygen or mechanical ventilation. People may stay longer in hospital, but this is to avoid potential onwards transmission to people with underlying conditions rather than because of complications. The committee noted the changing nature of SARS-CoV-2 and context of the pandemic would impact the generalisability of the evidence for the treatments being evaluated. It agreed that the most appropriate approach would be considering how relevant the clinical data are to the most current context of the disease, but noted that the context and relevant variants are still changing at a fast pace.

Defining high risk

Key definitions

3.3 The committee noted that the marketing authorisations for casirivimab plus imdevimab, molnupiravir, nirmatrelvir plus ritonavir, sotrovimab and remdesivir which aim to lower risk of progressing to severe COVID-19 were based on evidence from populations with slightly different definitions of high risk. For example, some trials included people with at least 1 risk factor for severe COVID-19 whereas some had specific age requirements. Understanding of the prognostic effects of risk factors has developed throughout the pandemic, and therefore the available evidence may represent a heterogeneous population. The committee acknowledged the potential limitations of the available evidence but considered it important to clearly define treatment eligibility. The PANORAMIC trial was a large UK platform trial that included people with many different potential risk factors, including chronic conditions and immunosuppression, and allowed enrolment of people over 50. It also allowed for clinical judgement of clinical vulnerability. The [independent advisory group report commissioned by the Department of Health and Social Care](#) defined groups of people at highest risk for adverse COVID-19 outcomes, including hospitalisation and death (the McInnes report from here on). The McInnes report was used by the [NHS interim commissioning policy on antivirals or neutralising monoclonal antibodies for people with COVID-19 who are not in hospital](#) to define high risk and is a narrower definition than that in PANORAMIC. The clinical experts noted that access to some drugs was available through the commissioning policy at the time of PANORAMIC enrolment. These interim policies and McInnes report's high-risk definition would have influenced the risk level of people who enrolled in PANORAMIC. The committee considered this in its evaluation of the clinical evidence. The patient experts considered that the broadest definition of high risk should be used to maximise the number of people who could benefit from treatment. But 1 patient expert thought that subgroups should be considered separately because considering a mixed group of risk definitions disadvantages the highest risk groups. The committee considered the different definitions of risk and noted that the

definition of high risk in the McInnes report is more restrictive than in PANORAMIC.

Other key risk groups

3.4 The clinical experts gave examples of additional considerations around how high-risk groups are affected differently:

- They highlighted different observed responses to vaccination. The OCTAVE study assessed vaccine response in immunocompromised people, including people with inflammatory arthritis, liver disease and kidney disease. OCTAVE showed differential antibody reactivity depending on disease group. The committee considered how this may affect who is at high risk. This is because people with a lower vaccine response have increased risk compared with the general population, particularly if they are having rituximab.
- They cited the OPENSAFELY cohort analysis study that assessed the risk of severe COVID-19 in people with immune-mediated inflammatory diseases. This showed that people with inflammatory diseases who are having systemic therapies had similar rates of hospitalisation and death as people having targeted therapies, except for rituximab. The committee considered the different risk of progressing to severe COVID-19 may be related to which immunosuppressant drugs are taken, but the relationship may be complex and differ in other disease areas.

Age as an independent risk factor

3.5 PANORAMIC allowed enrolment of people over 50 years who did not have any comorbidities. The committee questioned the inclusion of age over 50 years as an independent risk factor for progression to severe COVID-19. The clinical experts considered that age was an important risk factor, citing the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) study of mortality in the earlier stages of the pandemic that defined age over 50 as a risk factor (Knight et al. 2020). They noted that age over 70 years may be an important determinant of

mortality but also considered that the relationship between age and comorbidities is complex, particularly for immunocompromised people. One of the companies considered that age was an important risk factor but noted ongoing debate about what age is appropriate for inclusion in the high-risk group. The clinical experts agreed it was challenging to define an exact age that defines high risk. The committee was concerned that making a recommendation based on age might cause inequality, given that age is a protected characteristic. For this reason, NICE technology appraisal guidance on medicines for cardiovascular disease do not include criteria based on age, despite it being a well-recognised risk factor. The committee noted that age is a protected characteristic and any recommendation including age would need to be assessed for impact on equity of treatment. The committee concluded that more evidence is needed on the impact of age to justify including it as an independent factor that increases risk at similar levels to other comorbidities defined in the McInnes report. This should include evidence, adjusted for comorbidities, from a vaccinated population with the Omicron variant.

High-risk definition conclusion

3.6 The assessment group (AG) explained the approach used to model high-risk groups in its economic model (see [section 3.13](#)). It assumes that people have general population survival, have a starting age of 56.6 years and the same hospitalisation rate as PANORAMIC. Therefore, no individual high-risk group is modelled through any other baseline characteristic, and these variables are explored in sensitivity analyses to represent the entire group that would be eligible for treatment. The experts acknowledged the difficulties of defining high risk by various subgroups. The committee recognised that the decision problem required a definition of who has a high risk for progressing to severe COVID-19. It recognised the limitations of the model in characterising a group at high risk but considered the hospitalisation rate to be the most important variable for sensitivity to the clinical inputs (see [section 3.13 - 3.14](#)). The committee considered that a single definition of high risk should be used

because of the model limitations. Additional functionality would be required to make differential subgroup recommendations and this would not be practical or proportionate to the decision problem. This increased uncertainty of individual subgroup definitions and the need to include the most appropriate risk groups. It considered that the McInnes report's definition of high risk included the most robust evidence of people who have a high risk for progressing to severe COVID-19, and this did not include age as an independent risk factor. The committee considered the use of the Q-COVID risk calculator in clinical practice but concluded it had limited applicability because of the limitations of the model. The committee noted a wider definition of risk in PANORAMIC was included in the marketing authorisations for each of the treatments. But, it concluded that the definition of risk in the McInnes report is the most robust definition..

Current clinical management of COVID-19

Treatments for mild COVID-19

3.7 Current clinical management of COVID-19 in people who have a high risk for progressing to severe COVID-19 includes treatments available through an NHS interim commissioning policy (see [section 3.3](#)). As of June 2022, the policy recommendations are as follows:

- first-line treatment: nirmatrelvir plus ritonavir (antiviral) or sotrovimab (a neutralising monoclonal antibody)
- second-line treatment: remdesivir (antiviral)
- third-line treatment: molnupiravir (antiviral)
- combination treatment with a neutralising monoclonal antibody and an antiviral is not routinely recommended.

People who have symptoms and are not showing signs of a clinical recovery must start treatment shortly after testing positive for COVID-19. The professional organisations explained there are different aims of treatments at this stage of COVID-19. Antivirals aim to reduce viral load and viral replication which may reduce risk of severe disease.

They are administered orally. Neutralising monoclonal antibodies also aim to do this by binding to specific viral proteins to block viral infection. They are administered as injections (intravenously, intramuscularly or subcutaneously, depending on the treatment).

Treatments for severe COVID-19 in hospital

3.8 In hospital, anti-inflammatories are used along with antivirals and neutralising monoclonal antibodies in people with severe disease. Anti-inflammatories treat the multisystem inflammation which develops later in the COVID-19 disease pathway. The clinical experts said a hierarchical flow of treatments is followed in the hospital and recommending one treatment over another is challenging. The suitability of certain interventions can vary based on respiratory support requirements, minimum COVID-19 symptom duration or renal impairment status. Dexamethasone is standard of care for people who need supplemental oxygen because of COVID-19 progression. Both tocilizumab and baricitinib are available through NHS commissioning policies. Sarilumab is also an option, but only if tocilizumab is not available. Remdesivir is offered to people who need low-flow oxygen. The clinical experts considered that antivirals may have a limited role for people in hospital with COVID-19 because their mechanism of action focuses on blocking viral replication rather than controlling inflammation.

Clinical effectiveness

AG's indirect comparison approach

3.9 In line with best practice guidance for assessing COVID-19 treatments (Elvidge et al. 2021), the AG used systematic reviews and network meta-analyses from publicly available sources. These reviews (COVID-NMA and metaEvidence) are updated regularly as 'living' systematic reviews.

The non-hospital setting included these clinical endpoints:

- relative risk of hospitalisation or death
- relative risk of all-cause mortality at 28 days.

The hospital setting included these clinical endpoints:

- hazard ratio of time to death
- hazard ratio of time to discharge
- relative risk of clinical improvement at 28 days.

The AG highlighted some significant limitations of the approach, because of the changing nature of COVID-19 (see [section 3.2](#)). Each trial included in the analysis was done at a different time in the pandemic. Most trials compared an individual treatment against the standard care at the time. This care has evolved in response to better understanding of the disease course, changes to respiratory support and use of dexamethasone. The context of the disease also changed with different circulating variants of concern, and changes in protection through vaccinations and natural immunity over time. Each of these limitations were compounded by significant differences in trial design, baseline characteristics and geographical locations. The AG explained that the analysis assumed any relative effect of treatment is transferable to current clinical management. The clinical experts commented that meta-analysing the trial results may not be appropriate. This is because the weighting of each trial in a meta-analysis may not consider the relevance of the context of each trial within the analysis, for example, with different variants. The committee recognised the high levels of uncertainty with each treatment effect and the context-specific nature of the evidence. To characterise the uncertainty, rather than use probabilistic sensitivity analysis, the AG ran scenarios using the upper and lower confidence limits of each efficacy estimate. This provided scenarios showing 'lower efficacy' and 'higher efficacy' estimates. The AG cautioned the committee that these efficacy scenarios also had limitations because they represented a different uncertainty to that in the evidence base; they represented uncertainty on the estimates in the trial and were therefore sensitive to the number of events in each trial, rather than the context in which the trial happened. Therefore, they would not be sensitive to changes in efficacy against new circulating variants of concern. The committee understood the limitations

of the scenario analysis. The committee considered it represented an attempt to address some aspects of uncertainty in the absence of alternative methods to model the uncertainty.

Generalisability to the Omicron variant

3.10 The committee acknowledged that most trials informing the clinical efficacy data pre-dated the Omicron wave, which was the dominant circulating variant of concern at the time of this evaluation. Clinical experts said extrapolating data from past trials was misleading because epidemiology and virus characteristics have changed (see [section 3.2](#)). All experts and the committee considered it appropriate to consider how the clinical evidence would generalise to the Omicron variant and its subvariants. The committee recognised that the different treatment mechanisms need to be considered separately as follows:

- Anti-inflammatories (baricitinib, tocilizumab): Most evidence on these was generated during the earliest waves of the pandemic. Although later circulating variants have substantially lower mortality than earlier variants, the committee considered the relative benefit of treatments largely generalisable to later waves. This is because the mechanism of action regulates hyperinflammation, which it did not consider specific to a particular variant.
- Antivirals (molnupiravir, nirmatrelvir plus ritonavir, remdesivir): Most evidence on these was generated before later circulating variants. This is except for evidence on molnupiravir from PANORAMIC that recruited participants while the Omicron variant was circulating. The committee noted that some observational data supported efficacy of antivirals against later variants, but noted that these were not considered in a systematic approach. It also noted some concerns that resistance to antiviral treatments could plausibly occur as new variants emerge, but no evidence was available on this. The committee concluded that the evidence on antivirals is uncertain for newer variants. It therefore

considered a broader range of efficacy estimates to account for the uncertainty, prioritising efficacy evidence against current variants.

- Neutralising monoclonal antibodies (casirivimab plus imdevimab, sotrovimab, tixagevimab plus cilgavimab): The committee recognised that these treatments bind to spike proteins that may change with each new variant. Therefore, neutralising monoclonal antibodies may lose the ability to neutralise the virus over time. This could create uncertainty in any assessment of generalisability of response from previous clinical trials and clinical efficacy estimates. The committee noted the WHO's and FDA's strong recommendations against using casirivimab plus imdevimab and sotrovimab for the Omicron variant. It also noted in vitro evidence suggesting that tixagevimab plus cilgavimab lacks clinical effectiveness against the dominant circulating Omicron BA.5 subvariant (Focosi et al. 2022). The companies and patient experts noted that this evidence is currently being challenged in the academic literature because:
 - observational evidence (OPENSAFELY) suggests continued efficacy of sotrovimab against the Omicron BA.2 subvariant
 - The Francis Crick Institute's COVID surveillance unit suggest that neutralising monoclonal antibodies have only a reduced effect that may be mitigated by an increased dose.

The committee recognised that the neutralising monoclonal antibodies had shown effectiveness against previous variants. However, it considered that the generalisability concerns in relation to Omicron were too substantial to ignore. It could not comment on the validity of the in vitro data and welcomes comments in response to consultation on this. The committee also could not comment on altering dosages outside of marketing authorisations because the risk–benefit profiles of increased doses have not been assessed by the Medicines and Healthcare Regulatory products Agency (MHRA). The committee considered it unclear how much reduced neutralising effect impacted clinical efficacy and therefore how that uncertainty could be characterised in the different

clinical efficacy scenario analyses. It concluded that the WHO's recommendations against the use of casirivimab plus imdevimab and sotrovimab were reasonable. Based on similar evidence suggesting reduced neutralisation effect against new variants, the committee considered it reasonable to extend the likelihood of reduced efficacy to tixagevimab plus cilgavimab. The committee noted that the effectiveness of neutralising monoclonal antibodies will need continuous monitoring for each variant. It considered that antivirals and anti-inflammatories are more likely to maintain effectiveness against new variants but there are still substantial generalisability concerns with the clinical efficacy evidence.

Relative treatment effects for the non-hospital setting

3.11 For the non-hospital setting, the clinical experts considered the relative treatment effects of each treatment to be uncertain without considering the wider context of the trials (see [section 3.2](#)). They also noted that multiple interventions could be required and cautioned against the side-by-side comparison of treatment effects (as a fully incremental analysis).

- **Nirmatrelvir plus ritonavir:** The clinical experts considered that in clinical practice nirmatrelvir plus ritonavir appears to be the most effective at reducing progression to severe disease. But, they noted that there are many contraindications for nirmatrelvir plus ritonavir, including severe renal and hepatic impairment, and interactions with many common treatments. The committee noted that evidence on nirmatrelvir plus ritonavir was from 1 large study done in an unvaccinated population in an earlier wave of the pandemic. It considered there to be substantial uncertainty with the mean efficacy estimate. This was because there were few deaths despite the size of the study and the relative risk of death could change in the current context of COVID-19. Therefore, the committee considered it appropriate to also consider lower efficacy estimates, despite the limitations with this approach (see [section 3.9](#)). It noted

that PANORAMIC was also recruiting a nirmatrelvir plus ritonavir treatment arm.

- **Molnupiravir:** The committee noted that published PANORAMIC results (Butler et al. 2022) showed no significant difference between molnupiravir and standard care on hospitalisation or death in a high-risk population. However, there was a significant difference in the secondary endpoint of time to self-reported recovery. The committee noted that PANORAMIC may have excluded some of the highest risk groups that could have powered the study to see benefits in hospitalisation or mortality. However, the mean efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were likely to overestimate the benefits of molnupiravir. The committee would have preferred to see the results from PANORAMIC alone rather than pooled with results from trials less generalisable to current conditions. But it considered the mean efficacy and lower efficacy scenarios in its assessment of clinical effectiveness.
- **Remdesivir:** The committee noted the lack of evidence of any survival benefit for remdesivir in the non-hospital setting from the evidence synthesis based on the PINETREE trial (a double-blind, randomised controlled trial of remdesivir in the non-hospital setting, Gottlieb et al. 2022) with no events in either arm. It considered all efficacy estimates for the efficacy of remdesivir in the non-hospital setting because of the uncertainty.

The committee noted the potential for bias in all the comparisons because the indirect comparison used pairwise analysis rather than a network to produce its comparisons. However, the committee considered the heterogeneity of trial outputs and generalisability contributed greater uncertainty to the decision problem.

Relative treatment effects for the hospital setting

3.12 For the hospital setting, the clinical experts noted that standard care had significantly changed over time (see [section 3.2](#)). They also cautioned against directly comparing treatments because there is a distinct pathway of care in the hospital setting. This includes when to use respiratory support, anticoagulation treatments and corticosteroids.

- **Remdesivir:** The clinical experts considered that remdesivir is currently used in some people with lower oxygen needs but its use is not as clearly defined. The committee noted that remdesivir, a broad-spectrum antiviral, was one of the first available treatments and has historic use as a standard care early on in the pandemic. The company considered that the evidence synthesis did not include all the relevant information from the SOLIDARITY trial because of the format in which the results were presented (SOLIDARITY was an international randomised trial of additional treatments for COVID-19 in people who were in hospital and having the local standard care). The company noted that the mortality risk ratio in the non-ventilated cohort of SOLIDARITY for remdesivir compared with the control arm was significant. The mortality rate ratio was 0.91 (95% CI 0.82 to 1.02) in the overall group, 1.13 (95% CI 0.89 to 1.42) in people having ventilation and 0.87 (95% CI 0.76 to 0.99) in people not having ventilation and on oxygen. Inclusion of these results in the AG's evidence synthesis would have likely impacted the final conclusions for remdesivir. The committee considered that all available evidence should be included if possible. But, it also noted that SOLIDARITY was an early study in the pandemic and there was no clinical evidence available for remdesivir in the context of a vaccinated population and the Omicron variant. Therefore, the value of including this information would be uncertain. The committee considered that remdesivir's mechanism of action may not fit the stated treatment aims. This is because antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the

disease that is associated with hospitalisation. This could reduce the relative effect of treatment with respect to a disease with lower mortality. The committee therefore interpreted the available evidence with caution and considered both mean- and low-efficacy scenarios for the clinical effectiveness of remdesivir.

- **Baricitinib and tocilizumab:** For both the anti-inflammatory immunomodulator treatments, baricitinib and tocilizumab, the committee noted statistically significant results. The clinical expert considered that these immunomodulator treatments should be used with caution in clinical practice and noted uncertainty with relative effect in the changing context of COVID-19. The committee was more confident in the mean efficacy results of the immunomodulator treatments, but still considered the uncertainty in the likely clinical effect of these treatments.

Economic model

Model structure and key drivers of cost-effectiveness

3.13 The economic model for this appraisal was developed by the AG and informed by a previous publication (Rafia et al. 2021) that evaluated COVID-19 treatment in a pre-hospital setting. The AG used a decision tree model structure for treatments in the non-hospital setting that joined with a partitioned survival model in the hospital setting. The decision tree had either an active treatment or standard care arm offered to people with COVID-19. People were hospitalised at a baseline standard care rate, or not hospitalised. Those that were hospitalised entered the partitioned survival model. This section of the model had 3 mutually exclusive health states: discharged from hospital and alive, hospitalised with or without COVID-19, and death (from COVID-19 or any other cause). For people in hospital, level of respiratory support was assumed based on COVID-19 severity, with associated costs and disutilities by health state. The clinical inputs for each of the clinical efficacy scenarios were from the indirect treatment comparison (see [section 3.9](#)). The AG fitted parametric

distributions to long COVID data from the Office of National Statistics (ONS) and estimated the mean duration of long COVID to be 108.6 weeks. The AG assumed that 100% of people in the hospital setting and 10% in the non-hospital setting would have long COVID. The committee noted that the treatment efficacy was highly uncertain and the most important driver of cost effectiveness, but also noted the following other key drivers of model outputs:

- The key driver of the outputs in the non-hospital setting was the baseline rate of hospitalisation. This is because it determined how many people were put into the high-cost and low-utility hospital setting.
- The key drivers of the outputs in the hospital setting were the baseline standard care assumptions for overall survival and time to discharge. The model was adjusted so the baseline standard care assumptions were reflective of current UK clinical practice. NICE's rapid guidelines on COVID-19 were used to make this adjustment.

The clinical experts commented that, because of changes to the disease, the outcomes for these treatments are now more nuanced than hospitalisation and mortality. The committee considered that reduced hospitalisation and mortality rates are key drivers of benefit, but acknowledged that the model was not sensitive to other benefits of treatment like faster resolution of symptoms. The committee considered the model broadly appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19.

Hospitalisation rates

3.14 The rate of hospitalisation is a key driver of model outputs (see [section 3.13](#)) with multiple potential evidence sources. Hospitalisation rate is one the key model input variables that define the group at high risk. To closely align with the marketing authorisations, the AG used a hospitalisation rate of 0.77% from PANORAMIC in its base case to

generate the decision-making incremental cost-effectiveness ratios (ICERs) presented in the confidential appendix. PANORAMIC was reflective of the current COVID-19 landscape, including the Omicron variant, but may have excluded some people at higher risk who were eligible for treatment through interim NHS clinical commissioning policies (see [section 3.3](#)). Hospitalisation rates varied in other sources of data, including: 1.45% (OPENSAFELY study, people having sotrovimab and molnupiravir); 2.79% (DISCOVER-NOW database interim analysis, UK observational study of people covered in the McInnes report); and 18.4% (study of people with primary and secondary immunodeficiency [Shields et al. 2022]). The clinical experts agreed given the committee's preferred definition of high risk (see section 3.6) that 0.77% could be an underestimation because the highest risk group may have been underrepresented in PANORAMIC (see [section 3.3](#)). They acknowledged the difficulty of determining hospitalisation rate without analysing the baseline population and all appropriate groups at risk. The rate is likely to vary substantially based on types of underlying conditions in the high-risk group, with potentially higher rates for severely immunocompromised people, such as transplant recipients and people having chemotherapy. The committee acknowledged significant uncertainty in estimating the hospitalisation rate for the population who have high risk of progressing to severe COVID-19. Based on the strength of the evidence it concluded that it was likely to fall between the underestimate of PANORAMIC at 0.77% and the estimate of 2.79% from the interim database analysis.

Time to discharge

- 3.15 The amount of time spent in hospital is a key driver of cost effectiveness because of the costs of hospitalisation. Evidence on each treatment showed a relative reduction in time spent in hospital. But the AG noted that this evidence was collected during the pandemic, which could lead to substantial generalisability concerns because the context of care has changed. The committee noted that in clinical practice, time to discharge can sometimes overestimate time in high-cost health states because it

can depend on multiple factors (for example, waiting for a negative COVID-19 test). Time to discharge was also considered more important for people who are being discharged to a care home. The AG included scenarios that removed treatment effects on time to discharge and clinical improvement at 28 days to try and account for these potential uncertainties. It noted that the model was not sensitive to these parameters and they had minimal impact on the cost-effectiveness estimates. The committee considered these scenarios to be plausible but potentially conservative if treatments had effects outside of hospitalisation and mortality. However, it considered these were difficult to disentangle from the evidence available.

Utility values

Utility value assumptions

3.16 The AG used UK age- and sex-adjusted utility values (EQ-5D-3L) for the baseline utility estimates in the model. The AG did not apply additional utility decrements in the non-hospital setting for people who did not have long COVID. The age- and sex-adjusted UK general population utility estimates were used for this population instead. During consultation on the AG's draft report, stakeholders critiqued this assumption. They said this may not capture the full benefit of the treatments versus standard care and disadvantage community-based treatments. The AG agreed this was a simplified assumption, but scenario analysis showed it had limited impact on the final ICERs. The committee agreed with the AG's assumption and acknowledged the minor impact on the ICERs. For the hospital setting, the AG used utility decrements from a recent publication of a cost-effectiveness analysis of remdesivir. The utility decrements were originally from a population with recurrent *Clostridium difficile* infection and influenza. The same in-hospital utility decrements were also applied across ordinal scales 3 to 5. The ordinal scale was an 8-point scale (1 to 8) used to define progression of COVID-19 severity in the model. During consultation, stakeholders critiqued the use of utility decrements from a non-COVID-19 population. An alternative approach for a utility study was

proposed. The approach was to use COVID-19 severity-specific vignettes with EQ-5D-3L questionnaires completed by the UK general population. Some stakeholders also highlighted recent COVID-19 utility-specific systematic reviews that could be used. The AG said a vignette study would not be possible because of the restricted timelines. Across both settings, the AG did not find alternative COVID-19 utility decrements from the stakeholder-suggested systematic reviews. The AG used post-discharge long COVID utility decrements from Evans et al. 2022. The same utility decrement was assumed regardless of ordinal scale status at hospital admission. At AG report consultation, stakeholders suggested an alternative source of post-discharge utility decrements split by history of ordinal scale status. The AG explained that the model structure was unable to allocate post-discharge utility based on historical ordinal scale admission status. It also said that these utility decrements are only applied for the duration of long COVID and are not a key driver of ICERs. The committee agreed with the AG's rationale and the long COVID utility decrement assumptions.

Costs

Long COVID costs

3.17 The AG assumed the annual per person management costs of long COVID to be comparable with chronic fatigue syndrome (£1,013). The clinical experts explained there were differences between people with long COVID who were in hospital versus not in hospital. People in hospital would be more likely to have severe complications that incur greater costs from multisystem complications. The AG considered the costs had minimal impact on the cost-effectiveness estimates because they were only applied for the duration of long COVID. But, it also provided scenario analyses with increased average yearly costs (£2,500). The committee agreed these scenarios had minimal effect on the cost-effectiveness estimates but considered that any new UK-specific evidence on long COVID costs should be included if available.

Administration costs

3.18 The AG did not originally include administration costs for oral or subcutaneous treatments. For intravenous treatments a cost of £221 was assumed based on NHS reference code SB12Z. After consultation, the AG updated the assumptions in the model with costs provided by NHS England. NHS England provided Covid Medicines Delivery Unit (CMDU) deployment costs for the administration of oral antivirals (£410) and neutralising monoclonal antibodies (£820). Some companies disagreed with using CMDU deployment costs because these include costs based in secondary care. However, future delivery may be in primary care, which would likely reduce these costs. The NHS England representative explained that the delivery of service is subject to change. In future, integrated care boards will be responsible for treatment delivery currently done by the CMDUs. They also noted that these costs were calculated before implementation of nirmatrelvir plus ritonavir which may increase resource use because of expected requirements to assess contraindications. The committee considered that CMDU deployment costs would likely be similar in the future. This is because the resource required to deliver the treatments would be proportionately similar although in the format of a permanent staffing structure.

Hospitalisation costs

3.19 The AG used unit costs per hospital bed-day from the NHS National Schedule of NHS costs. Before AG draft report consultation, the AG used the following codes for the respective ordinal scales:

- ordinal scale 3: cost for non-elective excess bed days
- ordinal scale 4: weighted average cost for rehabilitation for respiratory disorders (VC40Z)
- ordinal scale 5: cost of regular day or night admission; other respiratory disorders, single intervention, complications and comorbidities (CC) score 0 to 4 (DZ19K)
- ordinal scale 6: cost for adult critical care, 0 organs supported (XC07Z)

- ordinal scale: weighted average cost for adult critical care, 1 or more organs supported (XC01Z to XC06Z).

During AG report consultation, 1 stakeholder had suggested using alternative codes for ordinal scales 3, 4 and 5 which were as follows: for ordinal scale 3, a weighted average of currency codes DZ11R to DZ11V (lobar, atypical or viral pneumonia, without interventions); for ordinal scale 4, a weighted average of currency codes DZ11N to DZ11Q (lobar, atypical or viral pneumonia, with single interventions); and for ordinal scale 5 a weighted average of DZ11K to DZ11M (lobar, atypical or viral pneumonia, with multiple interventions).

The AG explained these codes were plausible but when it calculated the cost per bed-day, the results lacked face validity. The cost for the more severe ordinal scale 5 was cheaper than ordinal scales 3 and 4. The AG used the stakeholder-suggested approach for ordinal scale 3. An alternative approach was taken for ordinal scales 4 and 5 with more plausible results. The committee acknowledged the changes implemented by the AG and agreed with the AG's final approach.

Cost-effectiveness estimates

Incremental cost effectiveness

Non-hospital setting

3.20 For the non-hospital setting, ICERs were calculated for casirivimab plus imdevimab, molnupiravir, nirmatrelvir plus ritonavir, tixagevimab plus cilgavimab, sotrovimab and remdesivir. The committee looked at the following outcomes presented by the AG:

- a fully incremental analysis
- pairwise ICERs compared with standard care.

The fully incremental ICERs and ICERs for casirivimab plus imdevimab, molnupiravir and tixagevimab plus cilgavimab compared with standard care cannot be reported here because of confidential prices. The

committee reviewed results for the low-, mean- and high-efficacy scenarios (see [section 3.9](#)). The committee noted its preferred assumptions to include combinations of the following:

- hospitalisation rates between 0.77% and 2.79%
- mean and low efficacy relative treatment effects (noting the limitations of the scenarios in section 3.9).

The committee noted substantial uncertainty with the relative treatment effects of casirivimab plus imdevimab and sotrovimab (see [sections 3.10 to 3.11](#)).

The ICERs for the treatments compared with standard care using (a) mean efficacy and 2.79% hospitalisation rate (most favourable) and (b) low efficacy and 0.77% hospitalisation (least favourable) were as follows:

- sotrovimab (a) £37,143 per quality-adjusted life year (QALY) gained (b) dominated (more expensive and less effective than standard care)
- remdesivir (a) £96,485 per QALY gained (b) dominated (more expensive and less effective than standard care)
- nirmatrelvir plus ritonavir (a) £7,053 per QALY gained (b) £60,415 per QALY gained.

Based on the committee's preferred assumptions, it considered that nirmatrelvir plus ritonavir was likely a cost-effective use of NHS resources compared with standard care. This is particularly because the ICERs for both the mean- and low-efficacy scenarios with hospitalisation rates in the middle of the range were under £30,000 per QALY gained. The equivalent ICERs for casirivimab and imdevimab and tixagevimab plus cilgavimab were either above £30,000 per QALY gained or dominated (more expensive and less effective than standard care). The equivalent ICERs for molnupiravir were most sensitive to changing the efficacy scenarios (from mean to low), but the range of ICERs was likely to be substantially above £30,000 per QALY gained. The committee concluded that casirivimab plus imdevimab, molnupiravir, sotrovimab, remdesivir and

tixagevimab plus cilgavimab were not a cost-effective use of NHS resources.

Hospital setting without supplemental oxygen

3.21 For the hospital setting without supplemental oxygen, ICERs were calculated for casirivimab plus imdevimab and remdesivir. Similar to the non-hospital setting, fully incremental results and the pair-wise ICERs versus standard care were presented. The committee reviewed results for the low- and mean-efficacy scenarios (see [section 3.9](#)). The committee noted its preferred assumptions to include:

- hazard ratios of time to discharge and clinical improvement at 28 days of 1
- mean and low efficacy relative treatment effects (see section 3.9 for limitations).

The ICERs for casirivimab plus imdevimab cannot be reported here because of confidential prices. The ICERs for remdesivir compared with standard care were £10,114 and dominated (more expensive and less effective than standard care) for the mean- and low-efficacy scenarios, respectively. The committee considered that because of uncertainty about the clinical effectiveness of remdesivir in this setting, it preferred the low-efficacy scenario. The committee did not consider any interventions were likely to be a cost-effective use of NHS resources compared with standard care.

Hospital setting with supplemental oxygen

3.22 For the hospital setting with supplemental oxygen, ICERs were calculated for baricitinib, casirivimab plus imdevimab, remdesivir and tocilizumab. Fully incremental results and pair-wise ICERs compared with standard care were presented. The committee reviewed results for the low- and mean-efficacy scenarios (see [section 3.9](#)). The committee noted its preferred assumptions to be the same as for the hospital setting without supplemental oxygen (see [section 3.21](#)).

The ICERs for casirivimab and imdevimab, tocilizumab and baricitinib cannot be reported here because of confidential prices. For the low-efficacy scenario, casirivimab plus imdevimab was cheaper and less effective than standard care. In the mean-efficacy scenario, the ICER for casirivimab plus imdevimab compared with standard care was below £20,000 per QALY gained. The ICERs for tocilizumab and baricitinib compared with standard care were below £20,000 per QALY gained for both the mean- and low-efficacy scenarios.

The ICERs for remdesivir compared with standard care were £10,936 and dominated (more expensive and less effective than standard care) for the mean and low efficacy scenarios, respectively. The committee noted that in the fully incremental analysis for the mean-efficacy scenario, remdesivir was also dominated by cheaper and more clinically effective treatments. The committee considered that because of uncertainty about the clinical effectiveness of remdesivir in this setting, it preferred the low-efficacy scenario. Based on its preferred assumptions, the committee considered tocilizumab and baricitinib likely to be a cost-effective use of NHS resources compared with standard care.

Other factors

Uncaptured benefits

3.23 Clinical experts said hospitalisation and mortality rates are becoming less relevant clinical efficacy measures for COVID-19 treatments. They explained this was because of the changing COVID-19 landscape (see [section 3.2](#)). In future COVID-19 evaluations, higher QALY gains could be captured if the model includes the impact of treatments on the following outcomes:

- impact on incidence and duration of long COVID
- virological outcomes
- transmission to healthcare professionals

- enabling other NHS healthcare services to proceed (for example, routine operations and reducing impact on waiting lists)
- access to treatment within the window of clinical effectiveness

The committee considered that some of these benefits fall outside of the NICE reference case or there is limited evidence to support them. The committee noted community treatments may not limit transmission of the virus, because it mostly spreads when people are asymptomatic. The committee considered the advice in section 6.2.36 of the [NICE health technology evaluations: the manual](#). The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained.

Equality issues

3.24 The committee considered potential equality issues, including:

- Disability: The committee noted some people cannot be offered nirmatrelvir plus ritonavir because the recommendation in this guidance (see [section 1](#)) uses a definition of high risk from the McInnes report. This may exclude some people in certain risk groups who were included in the marketing authorisation and who have disability, which is a protected characteristic (see [section 3.3](#)). The committee considered whether, by recommending nirmatrelvir plus ritonavir, it would be indirectly discriminating against people in these groups. Indirect discrimination means producing guidance that appears to apply to all but has a disproportionate adverse impact on those with a protected characteristic. The committee considered this could indirectly discriminate but would be a proportionate means of achieving the legitimate aim of maximising public health. This is because it did not consider nirmatrelvir plus ritonavir would be cost effective in lower-risk populations. The committee also noted nirmatrelvir plus ritonavir was contraindicated for concomitant use with many medicinal products. The

committee evaluated alternative treatments for people who cannot take nirmatrelvir plus ritonavir. These alternative treatments had substantially higher ICERs and were not considered a cost-effective use of NHS resources (see [section 3.20](#)).

- **Race:** The committee was aware that people from minority ethnic family backgrounds were more likely to be diagnosed with COVID-19. Also, the risk of dying from COVID-19 was disproportionately higher in people from Black, Asian and other minority ethnic family backgrounds. The committee further noted that nirmatrelvir plus ritonavir was contraindicated in people with hepatic and renal impairments. The prevalence of certain comorbidities including renal impairment are known to be higher in people from these family backgrounds. Differences in prevalence cannot usually be resolved in a technology appraisal, although the committee did not consider that family background has a significant impact on access to treatment. Therefore, this issue of prevalence cannot be resolved by the recommendation. However, the committee noted that certain minority ethnic populations suffered worse health outcomes. The committee concluded that it would consider these issues in its decision making.
- **Age:** Some stakeholders considered age was an independent relevant risk factor (see [section 3.5](#)). The committee was mindful of excluding age from its recommendations because it is a protected characteristic. The committee noted the McInnes report did not include age as an independent risk factor. The committee did not consider there was enough evidence to support a relationship between specific age cut-off points alone (for example, adjusted for comorbidities) and a high risk of progression to severe COVID-19. It also could not adequately consider the impact of these changes in its cost-effectiveness analysis. A similar approach to recommendations has been taken for NICE technology appraisal guidance on treatments for cardiovascular conditions even though a strong link with age had been established in this disease area.
- **Pregnancy and or maternity:** The committee notes that the summary of product characteristics for tocilizumab states it should not be used

during pregnancy unless clearly necessary. By recommending tocilizumab there is a risk of indirectly discriminating against people who are pregnant. The committee considered that in the context of the acute hospital setting, no other alternative treatments for treating hyperinflammation were included in the scope of this appraisal. It considered that clinicians should use independent judgement when considering the risk factors of tocilizumab in people who are pregnant.

Addressing health inequalities

3.25 The committee noted the equalities issues outlined in [section 3.24](#), and considered flexibility as part of the [principles that guide the development of NICE guidance and standards](#). This emphasises the importance of considering the distribution of health resources fairly within society as a whole, and factors other than relative costs and benefits alone. The committee acknowledged and considered the contraindications of nirmatrelvir plus ritonavir and tocilizumab. It noted that this could affect some people with protected characteristics disproportionately which would contribute to health inequality. The committee said that in theory it would be willing to accept an ICER slightly more than what is usually acceptable if it addressed such health inequalities. However, it noted that departing from NICE's usual range needs to be done with caution, as it risks displacing funding from more cost-effective treatments elsewhere in the NHS, with an overall net loss of health gain. Even considering greater flexibility, the ICERs of alternative treatments were substantially higher than what is considered a cost-effective use of resources.

Conclusion

Table 1 Overview of recommendations

Setting	Recommended	Not recommended
Non hospital setting (mild COVID-19)	<ul style="list-style-type: none"> nirmatrelvir plus ritonavir 	<ul style="list-style-type: none"> casirivimab plus imdevimab molnupiravir sotrovimab remdesivir tixagevimab plus cilgavimab
Hospital setting (without supplemental oxygen)	<ul style="list-style-type: none"> no technologies recommended 	<ul style="list-style-type: none"> casirivimab plus imdevimab remdesivir
Hospital setting (with supplemental oxygen)	<ul style="list-style-type: none"> tocilizumab baricitinib 	<ul style="list-style-type: none"> casirivimab plus imdevimab remdesivir

4 Implementation

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation 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 guidance 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 draft guidance.
- 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 COVID-19 and the doctor responsible for their care thinks that nirmatrelvir plus ritonavir or tocilizumab are the right treatments, they should be available for use, in line with NICE’s

recommendations. This will also be the case for baricitinib, subject to it receiving a Great Britain marketing authorisation for this indication.

- 4.4 In Scotland, the advice will have the same status for health board consideration as other Scottish Medicines Consortium advice on new medicines.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal evaluation committees are standing advisory committees of NICE. This topic was considered by members from across the 4 committees.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The [minutes of each evaluation committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien

Chair, Technology appraisal evaluation committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Anuja Chatterjee

Technical lead

Adam Brooke

Technical adviser

Louise Jafferally

Project manager

ISBN: [to be added at publication]