

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final draft guidance**

**Therapeutics for people with COVID-19**

This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. Until the final guidance is published and implemented, treatment choices should continue to be guided by published UK-wide [NHS 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.

# 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 Sotrovimab is recommended as an option for treating COVID-19 in people aged 12 years and over and weighing at least 40 kg, 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](#) and
- nirmatrelvir plus ritonavir is contraindicated or unsuitable.

Sotrovimab is only recommended if the company provides it according to the commercial arrangement (see [section 2](#)).

1.3 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](#)).

1.4 These treatments are not recommended, within their marketing authorisations, for treating COVID-19:

- casirivimab plus imdevimab
- molnupiravir
- remdesivir

- tixagevimab plus cilgavimab.

See section 2 for the full marketing authorisation for each treatment.

### **Why the committee made these recommendations**

This evaluation reviews the clinical and cost effectiveness of:

- casirivimab plus imdevimab, molnupiravir, nirmatrelvir plus ritonavir, remdesivir, sotrovimab and tixagevimab plus cilgavimab for mild COVID-19
- casirivimab plus imdevimab, remdesivir and tocilizumab for severe COVID-19.

Most of the clinical evidence for these treatments is highly uncertain because it comes from studies done before the dominant Omicron variants of SARS-CoV-2 (the virus that causes COVID-19).

The cost-effectiveness estimates are highly dependent on how well each treatment works compared with standard care, and hospitalisation and mortality rates. Hospitalisation and mortality rates are lower with Omicron variants than earlier variants in the pandemic. These lower rates increase the cost-effectiveness estimates.

### **Mild COVID-19**

Clinical evidence suggests that:

- nirmatrelvir plus ritonavir and remdesivir are effective at treating mild COVID-19 compared with standard care
- sotrovimab is likely to be effective at treating mild COVID-19 compared with standard care but some of the evidence is uncertain
- molnupiravir has limited effectiveness at treating mild COVID-19 compared with standard care because it does not reduce hospitalisation and mortality rates.

Other evidence suggests that it is highly uncertain that casirivimab plus imdevimab and tixagevimab plus cilgavimab are effective against Omicron variants of COVID-19.

Nirmatrelvir plus ritonavir is recommended because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. The cost-effectiveness estimates for sotrovimab are also within what NICE considers an acceptable use of NHS resources, but only for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. So, sotrovimab is recommended in this group.

Remdesivir is not recommended because the likely cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources. Casirivimab plus imdevimab, molnupiravir and tixagevimab plus cilgavimab are not recommended because they are unlikely to be effective at treating COVID-19 and it is not possible to reliably estimate their cost effectiveness.

## **Severe COVID-19**

Clinical evidence suggests tocilizumab is effective at treating severe COVID-19 compared with standard care. It is highly uncertain that casirivimab plus imdevimab is effective against Omicron variants of COVID-19. Clinical evidence suggests that remdesivir has limited effectiveness at treating severe COVID-19 compared with standard care because it does not reduce mortality rates, but the evidence is uncertain.

Tocilizumab is recommended because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources.

Casirivimab plus imdevimab and remdesivir are not recommended because they are unlikely to be effective at treating severe COVID-19 and it is not possible to reliably estimate their cost effectiveness.

## **2 Information about the treatments**

### **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, Roche Products) 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'.

## Dosage in the marketing authorisation

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

## Price

- 2.15 The list price for casirivimab plus imdevimab is currently confidential.
- 2.16 The list price for molnupiravir is currently confidential.
- 2.17 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.
- 2.18 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.

- 2.19 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). The company also has a commercial arrangement (simple discount patient access scheme). This makes sotrovimab 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.
- 2.20 The list price of tixagevimab plus cilgavimab is £800 per 300-mg dose and £1,600 per 600-mg dose (excluding VAT; prices provided by company). The company also has a commercial arrangement (simple discount patient access scheme). This makes tixagevimab and cilgavimab 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.
- 2.21 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.

### 3 Committee discussion

The [evaluation committee](#) considered evidence from several sources. See the [committee papers](#) for full details of the evidence.

This evaluation reviews:

- casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (neutralising monoclonal antibodies), and molnupiravir, nirmatrelvir plus ritonavir and remdesivir (antivirals), in the mild COVID-19 setting

- casirivimab plus imdevimab (neutralising monoclonal antibody), remdesivir (antiviral) and tocilizumab (anti-inflammatory) in the severe COVID-19 setting (with and without supplementary oxygen).

## 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. In severe disease, 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 fluctuate and can last several months or years which severely impact a person's physical and mental health, and potentially affect their ability to work, attend school or do their usual activities. During draft guidance consultation, consultees highlighted the treatment gap for children. At the second evaluation committee meeting (referred to as second meeting from now on) one clinical expert explained that COVID-19 rarely makes children unwell. But there is a small proportion of children with underlying conditions who have an increased risk of severe COVID-19 comparable with adults with underlying conditions. Many people are at increased risk of hospitalisation or death from COVID-19, including people who are immunosuppressed (who have, for example, 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 their immune system cannot control the virus. Patient experts explained that the increased risk of hospitalisation and death has led to some people changing their 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 and that there is an unmet need in this population.

### **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. The properties of each variant can differ, 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. The committee understood that 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.

3.3 At the time of first evaluation committee meeting (referred to as first meeting from here on), the dominant variant of concern in the UK was the Omicron (B.1.1.529) sublineage BA.5. The Omicron variant (B.1.1.529) 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. At the second meeting, the committee saw the updated Omicron variant data published in the [UK Health Security Agency's \(UKHSA's\) technical briefing 49](#). Based on all the UK sequenced samples between 26 December 2022 to 1 January 2023, BQ.1 was the dominant 'designated variant'. BQ.1 was not

expected to increase the risk of severe COVID-19 compared with BA.5. The committee understood from this data that the BQ.1 subvariants account for a large proportion of the currently circulating variants in the UK. The committee noted the XBB.1.5 and CH.1.1 subvariants are some of the fastest growing variants in the UK. The clinical experts explained that people presenting at hospital with COVID-19 are mainly either unvaccinated or immunocompromised, or did not have an immune response to vaccines. They reported that 'viral persistence' from chronic infection is a concern in immunocompromised people because new variants or subvariants can develop if the viral infection persists. They also noted that offering a clinically ineffective treatment unable to clear the infection may increase the risk of future variants developing. The committee noted the changing nature of SARS-CoV-2, and context of the pandemic, affect the generalisability of the evidence for the treatments being evaluated. It agreed that the most appropriate approach would be to consider how relevant the clinical data are to the current endemic context of the disease at the time of this evaluation, but noted that the context and relevant variants are still changing at a fast pace.

## **Defining high risk**

### **Key definitions**

- 3.4 The committee noted that the marketing authorisations for the treatments, which lower the risk of progression to severe COVID-19 (casirivimab plus imdevimab, molnupiravir, nirmatrelvir plus ritonavir, remdesivir, sotrovimab and tixagevimab plus cilgavimab) 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 high risk and therefore treatment eligibility. PANORAMIC 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 aged over 50 years. It also allowed for clinical judgement of clinical vulnerability. The [independent advisory group report commissioned by the Department of Health and Social Care](#) (the McInnes report from here on) defined groups of people at highest risk for adverse COVID-19 outcomes, including hospitalisation and death. The [NHS interim commissioning policy on treatments for non-hospitalised patients with COVID-19](#) used the McInnes report to define high risk. The clinical experts noted that some treatments were available through the interim commissioning policy at the time of PANORAMIC enrolment. The interim commissioning policy's and McInnes report's high-risk definition would have influenced the risk level of people who enrolled in PANORAMIC. At the first meeting, the committee considered this in its evaluation of the clinical evidence. The committee considered the different definitions of risk and concluded that PANORAMIC included people who had a lower risk of severe COVID-19 compared with the McInnes high-risk definition.

## **Other key risk groups**

3.5 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 of adverse outcomes from COVID-19 infection compared with the general population, particularly if they are having rituximab.

- They cited an 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.

At the second meeting, the committee noted the draft guidance consultation comments highlighted the need for separate ‘high risk’ and ‘highest risk’ groups, or a separate high-risk group contraindicated to nirmatrelvir plus ritonavir. The committee saw examples on how the risk group could be split based on [Patel et al. 2022](#). The clinical experts explained that there is a small group of children who are also at high risk of severe COVID-19 and may not be able to access treatment. The committee noted that the McInnes report has made additional consideration for people 12 years and over in its definition of high risk. The committee concluded that it would expect clinicians to offer treatments using the McInnes high-risk criteria when applicable across all age groups, in line with product marketing authorisations.

### **Age as an independent risk factor**

3.6 PANORAMIC allowed enrolment of people aged 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. They cited 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 years 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. At the first meeting the committee concluded that more evidence was needed on the impact of age to justify including it as an independent factor that increases risk at similar levels to other risk factors defined in the McInnes report. This should include evidence, adjusted for these risk factors, from a vaccinated population who are infected with the Omicron variant. At the second meeting, the committee noted the additional evidence provided by consultees which showed a statistical relationship between age and comorbidities. The committee acknowledged that age is a risk factor for progression to severe COVID-19. The committee considered that the relationship between age and comorbidities can be important in explaining risk of severe disease. The committee concluded that age over 70 years is likely to be confounded by underlying conditions which could also contribute to increased risk of severe disease. The committee also noted that additional evidence is needed to model age over 70 years as an independent subgroup for the mild COVID-19 setting. It said the evidence should include age-adjusted hospitalisation and mortality rates for the untreated population and relative treatment effects. The committee concluded 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.

## High-risk definition conclusion

3.7 The assessment group (AG) explained the approach used to model high-risk groups in its economic model (see [section 3.22](#)). At the first meeting, it assumed that people had general population survival, with a starting age of 56.6 years and the same hospitalisation rate as PANORAMIC. Therefore, no individual high-risk subgroups were modelled based on specific baseline characteristics, and these characteristics were explored in sensitivity analyses that represented the entire group eligible for treatment. The clinical experts acknowledged the difficulties of defining high risk by separate subgroups. The committee recognised that the decision problem for this evaluation 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 [sections 3.21 to 3.22](#)). At the second meeting, the committee repeated these limitations of modelling separate high-risk groups and concluded that a single definition of high risk should be used. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. For example, additional functionality, clinical or cost inputs and treatment-effectiveness assumptions would be required to make differential subgroup recommendations and this would not be practical or aligned with the decision problem. The committee did not see additional evidence to justify splitting the high-risk group. The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19, and this did not include age as an independent risk factor. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. 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, from PANORAMIC, was included in the

marketing authorisations for each of the treatments (see [section 3.4](#)). However, it concluded that the definition of risk in the McInnes report is the most robust definition. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected.

## Current clinical management of COVID-19

### Treatments for mild COVID-19

3.8 Current clinical management of mild COVID-19 (includes hospital-onset COVID-19) in people who have a high risk for progression to severe COVID-19 includes treatments commissioned through an NHS interim commissioning policy (see [section 3.4](#)). In November 2022, the policy was:

- first-line treatment: nirmatrelvir plus ritonavir (antiviral)
- second-line treatment: remdesivir (antiviral)
- third-line treatment: molnupiravir (antiviral; not for hospital-onset COVID-19)
- sotrovimab (neutralising monoclonal antibody) to be considered when the above antivirals are contraindicated or unsuitable after a multidisciplinary assessment
- 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 as soon as possible 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 or intravenously. Neutralising monoclonal antibodies also aim to do this by binding to specific viral proteins to block viral infection. They are administered as injections or

infusions (intravenously, intramuscularly or subcutaneously, depending on the treatment).

### Treatments for severe COVID-19

3.9 For people hospitalised with severe COVID-19, anti-inflammatories are used along with antivirals and neutralising monoclonal antibodies, based on the NHS interim clinical commissioning policies for secondary care. 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, but is generally as follows:

- People admitted to hospital with COVID-19 who do not need oxygen: remdesivir is an option through the [NHS interim clinical commissioning policy on remdesivir](#) for people who are significantly immunocompromised.
- People admitted to hospital with COVID-19 who need low-flow oxygen or non-invasive mechanical ventilation:
  - dexamethasone is standard care
  - remdesivir or tocilizumab are offered, subject to eligibility criteria, through the [NHS interim clinical commissioning policies for secondary care](#).
- People admitted to hospital with COVID-19 who need high-flow oxygen:
  - baricitinib or tocilizumab are offered, subject to eligibility criteria, through the NHS interim clinical commissioning policies for secondary care.

## Clinical effectiveness

### Assessment group's indirect comparison approach

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

The mild COVID-19 setting included these clinical endpoints:

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

The severe COVID-19 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 their 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. Standard 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 mean and the upper and lower confidence limits of each efficacy estimate. This provided scenarios showing 'mean efficacy', 'lower efficacy' and 'higher efficacy' estimates. The AG cautioned the committee that the lower and higher efficacy scenarios 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. At draft guidance consultation, consultees highlighted the lower efficacy scenarios were arbitrary and a probabilistic sensitivity analysis would be a better way to capture the uncertainty. The committee noted that the heterogeneity in the trial populations and the generalisability issues across the trials made the uncertainty challenging to parameterise. Therefore, the appropriate type of uncertainty would not have been captured in the probabilistic sensitivity analysis. Consultees also noted that the mortality assumptions meant that treatment in hospital had a higher mortality risk compared with standard care. In response, the AG updated this assumption and capped the mortality rate to equal 1 for the low-efficacy scenario. Consultees noted the systematic reviews which informed the NMAs did not adhere to established reviewing methods and missed 2 key clinical trials (SOLIDARITY and ACTT-1). The AG addressed this concern and provided scenarios for the committee which included the company-provided NMA including SOLIDARITY and a scenario in which time to discharge for remdesivir was informed by ACTT-1. The AG also included the updated COVID-19 NMA results for molnupiravir, casirivimab plus imdevimab, and tocilizumab in the economic model.

## Observational evidence

3.11 The committee also considered the latest data from [OpenSAFELY](#) (non-randomised observational evidence from 40% of English GP practices). The OpenSAFELY database links with other national databases including the Office for National Statistics (ONS), inpatient hospital records, renal registries and Covid Medicines Delivery Units (CMDUs). The dataset is granular, updated regularly and reflective of the McInnes high-risk group during the Omicron wave in the UK. The committee acknowledged that this analysis of OpenSAFELY was done well and made efforts to account for confounding bias when possible. The analysis was done in a dynamic environment with changing treatment practices and linkages with various data sources which can increase risk of confounding bias. The committee noted the results of [Hill and Mirchandani \(2022\)](#) that compared the outcomes of a randomised controlled trial with non-randomised studies on COVID-19 treatments. The authors questioned the validity of non-randomised studies when their outcomes contradict the outcomes from a randomised controlled trial. The authors cautioned against using non-randomised evidence independent of randomised evidence for regulatory decisions. The committee was willing to accept the OpenSAFELY data on relative treatment effectiveness as supplementary evidence to the trial evidence and for modelling estimates for hospitalisation rates. The committee cautioned against solely relying on non-randomised evidence when making conclusions on treatment effect.

## Generalisability of trial evidence to current endemic context

3.12 The committee acknowledged that most trials informing the clinical efficacy data pre-dated the Omicron variant, 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](#)). The clinical experts and the committee considered it appropriate to consider how the clinical evidence would generalise to the endemic setting. It considered the main generalisability concerns to be:

- changes in population immunity through natural immunity and vaccination
- changes in the pathogenicity of the virus
- increased effectiveness of supportive care as knowledge of the virus evolved
- other differences that were specific to the context of a pandemic setting.

The absolute changes in these settings were considered in the economic modelling when possible. However, the committee considered the relative risks from these trials would also lack generalisability because there would be interaction between some of these concerns and treatment effect in the trial. This would likely favour the treatments compared with standard care, because the trials were done when key outcomes of hospitalisation and mortality were significantly higher. Therefore, the committee considered that mean-efficacy scenarios from these trials likely reflect the highest clinical effectiveness or ‘ceiling efficacy’ of the treatment. The committee concluded that changes in best supportive care and higher vaccination rates mean that any limited relative treatment effects seen during the pandemic setting would have less effect in an endemic setting. This is because any limited benefit in the pandemic setting would likely be further limited or potentially have no difference in treatment effect compared with standard care (hazard ratios [HRs] would tend towards 1) in an endemic setting.

3.13 The committee recognised that the treatment effects need to be considered separately as follows:

- **Antivirals (molnupiravir, nirmatrelvir plus ritonavir, remdesivir) – mild COVID-19 setting:** Evidence on remdesivir was collected before the Delta wave and before the widely vaccinated and naturally immune population. Evidence on nirmatrelvir plus ritonavir was more recent and captured the Delta wave. Evidence on molnupiravir was the most

recent in a largely vaccinated and naturally immune population, coming from PANORAMIC that recruited participants while the Omicron variant was circulating. The committee highlighted that the PANORAMIC study population had lower risk of severe disease than the McInnes defined high-risk population ([section 3.7](#)).

- **Antiviral (remdesivir) – severe COVID-19 setting:** The committee considered the additional evidence on remdesivir from SOLIDARITY provided by the company during draft guidance consultation. It understood that inclusion of SOLIDARITY in the NMA resulted in a statistically significant but smaller mortality benefit for remdesivir compared with standard care. The committee noted that SOLIDARITY was done before the Delta and Omicron waves, and widespread vaccination. It also noted key study limitations highlighted in the trial publication, including that standard care differed within and across countries. The committee understood that standard care including dexamethasone use, and the hospital practices of escalation to mechanical ventilation as part of standard care, varied in hospitals when SOLIDARITY was done. The committee also noted that the standard care arm in the economic model is modelled on the dexamethasone arm of the RECOVERY trial which enrolled people hospitalised with COVID-19 in the UK. The committee considered the inclusion of SOLIDARITY in the NMA important and appropriate for remdesivir. Because of the generalisability issues arising from trial limitations, the applicability of the mean-efficacy estimate from SOLIDARITY to the current NHS setting is highly uncertain and likely to be the ceiling efficacy estimate (see [section 3.12](#)). The committee remained cautious about the treatment effect of remdesivir shown in observational evidence submitted by the company during the draft guidance consultation when the original SOLIDARITY evidence already showed limited mortality benefit. The committee concluded that SOLIDARITY was an early study in the pandemic and there was no clinical evidence available for remdesivir in the context of the current endemic setting with a widely vaccinated and naturally immune

population and the Omicron variant. The committee concluded that significant uncertainty remained in terms of generalisability of the trial evidence for remdesivir.

- **Anti-inflammatory (tocilizumab):** Clinical trial evidence on tocilizumab was collected before the Omicron wave. The committee considered the corroborating clinical evidence from multiple trials with evidence on outcomes pooled from multiple studies. The key trial, REMAP-CAP, included multiple UK sites and RECOVERY was reflective of standard care in NHS clinical practice and was considered more generalisable to the endemic setting than the SOLIDARITY standard care. The committee also considered the relative treatment benefit of tocilizumab largely generalisable because the mechanism of action regulates hyperinflammation, which it did not expect would change based on variants, vaccination or natural immunity.
- **Neutralising monoclonal antibodies (casirivimab plus imdevimab, sotrovimab, tixagevimab plus cilgavimab):** For sotrovimab and casirivimab plus imdevimab (mild COVID-19 setting) the clinical trial evidence was collected before the Delta and Omicron waves. For tixagevimab plus cilgavimab (mild COVID-19 setting) and casirivimab plus imdevimab (severe COVID-19 setting) the collected evidence partly covered the timeline of the Delta wave but was before the Omicron wave. The committee noted that considerable uncertainty remained about the relative treatment effects on hospitalisation and mortality rates. This is because of generalisability of trial evidence to the endemic setting with a widely vaccinated population with additional and natural immunity, as well as the particular sensitivity of these antibodies to changes in variants.

## In vitro evidence

3.14 In vitro (laboratory) evidence may provide additional information on whether there is a realistic clinical possibility that a treatment retains efficacy against currently circulating variants. In vitro neutralisation assays can be used to assess if treatments can neutralise new variants, which

can then be used to infer whether they retain clinical effectiveness over time as the virus evolves. An advantage of in vitro evidence is that it can be generated much faster than clinical trial evidence. A large body of in vitro evidence suggests that specific COVID-19 treatments may no longer show neutralisation activity against some circulating Omicron variants. In the first meeting, the committee could not comment on the validity of in vitro data and welcomed comments in response to consultation. Because of this, NICE commissioned an 'in vitro expert advisory group' made up of experts in infectious disease, virology, vaccine epidemiology, immunology and pharmacology (see the in vitro expert advisory group report in the [committee papers](#)). The group developed a decision framework to link in vitro neutralisation data to clinical outcomes and helped the committee use the framework to interpret the in vitro evidence. The committee understood this framework and also noted the latest in vitro evidence.

- 3.15 The in vitro evidence considered by the committee was against newly circulating variants and was available shortly before the second meeting. Because the COVID-19 landscape is rapidly evolving, a systematic review of the in vitro data was not possible. Guided by the in vitro expert advisory group, the committee identified 5 in vitro studies that investigated the effectiveness of the neutralising monoclonal antibodies on currently circulating variants (BQ.1.1 and XBB). One in vitro study ([Imai et al. 2023](#)) also investigated the effectiveness of the antivirals against BQ.1.1 and XBB. The in vitro studies showed that some antiviral treatments retain the ability to neutralise a range of SARS-CoV-2 variants and subvariants, including those circulating at the time of this evaluation and are rapidly increasing. The committee also considered the in vitro evidence that was systematically collected and summarised by multiple organisations including the 'Stanford Coronavirus Resistance Database'. For further details on the in vitro evidence, see the in vitro slides in the committee papers.

## **Generalisability of clinical effectiveness**

- 3.16 By using the framework and the evidence the committee concluded that the clinical effectiveness of the anti-inflammatories (tocilizumab) are not variant-specific because of their mechanism of action. The committee concluded there was no in vitro evidence showing reduced clinical efficacy of the antivirals (molnupiravir, nirmatrelvir plus ritonavir, remdesivir) across the variants tested. However, as discussed in the first meeting and based on the in vitro expert advisory group framework, the committee confirmed that the neutralising monoclonal antibodies (casirivimab plus imdevimab, sotrovimab, tixagevimab plus cilgavimab) bind to spike proteins which are changing with each new variant and subvariant. The committee concluded that neutralising monoclonal antibodies may lose the ability to neutralise the virus over time, potentially as a result of the virus evolving to evade the treatments in use.
- 3.17 At the second meeting, the committee noted that BQ.1 and BQ.1.1 were the currently circulating Omicron subvariants (see [section 3.2](#)) in the UK. These are different to BA.5 which was prevalent at the time of the first meeting. As noted in [section 3.16](#), the clinical effectiveness of neutralising monoclonal antibodies (casirivimab plus imdevimab, sotrovimab, tixagevimab plus cilgavimab) is likely to vary by variant. At the second meeting, the committee carefully considered in vitro evidence for these treatments against the dominant variants. The committee understood that in vitro studies differ by how they are done and their quality. The clinical experts agreed with the in vitro expert advisory group's framework and explained that evidence showing no or limited neutralisation activity against a specific variant means there is unlikely to be any plausible clinical activity against that variant. The committee acknowledged that there was the possibility for casirivimab plus imdevimab and tixagevimab plus cilgavimab to regain activity against future variants but considered that the likelihood of this was low. The committee noted a recent update from the European Medicines Agency's emergency task force, which cautioned that neutralising monoclonal antibodies currently authorised for COVID-19 are unlikely to be effective against emerging strains of

SARS-CoV-2. Taking account of study differences, clinical expert conclusions and the framework (see [sections 3.14 to 3.16](#)) the committee concluded that casirivimab plus imdevimab and tixagevimab plus cilgavimab were unlikely to retain sufficient neutralisation activity against most variants circulating at the time of this evaluation. Also, this was the most useful estimate of effect against future variants. The committee concluded the clinical effectiveness of both casirivimab plus imdevimab and tixagevimab plus cilgavimab is highly uncertain in terms of reducing hospitalisation or mortality rates.

- 3.18 The committee noted that in vitro evidence on sotrovimab's neutralisation activity was inconsistent between the studies with some evidence suggesting partial reduction in neutralisation activity. The clinical experts explained that partial reductions in neutralisation are difficult to interpret without additional clinical evidence such as in vivo (in animals) or pharmacodynamic and pharmacokinetic data. They explained that in such cases the in vitro data are only pieces of the puzzle rather than an individual indication of the potential clinical efficacy. The committee considered additional evidence ([Addetia et al. 2023](#)) on sotrovimab. The company explained that, unlike the other neutralising monoclonal antibodies, sotrovimab's effectiveness against the virus depends on the expression levels of ACE2 to which the SARS-CoV-2 receptor binds. If the cell line used in the in vitro study over-expresses ACE2 then sotrovimab may appear not to neutralise the virus in laboratory studies. The results from these in vitro studies may underestimate sotrovimab's neutralising ability against the real virus. The committee considered this added uncertainty to the interpretations of the in vitro evidence for sotrovimab. The committee compared in vitro evidence on subvariant BA.5 (dominant during first meeting) with [OpenSAFELY](#) data collected when BA.5 was circulating. The OpenSAFELY data suggested that sotrovimab's clinical effectiveness was consistent during the Omicron wave whereas the in vitro evidence showed conflicting data that sotrovimab had reduced neutralisation abilities against BA.5. Using the in vitro expert advisory

group's framework and the evidence, the committee concluded that sotrovimab's clinical effectiveness is likely reduced against BA.5 but uncertainty remains about sotrovimab's clinical effectiveness against BQ.1 and BQ.1.1. The committee concluded the in vitro evidence for sotrovimab was ambiguous and the clinical effectiveness was uncertain. The committee noted that in some cases, when reduced neutralisation is seen from in vitro evidence, increasing the dosage of the treatment could result in increased neutralisation activity. The committee could not comment on whether increasing dosages outside of marketing authorisations impacts clinical effectiveness of neutralising monoclonal antibodies. This is because the risk–benefit profiles of increased doses have not been assessed by the Medicines and Healthcare Regulatory products Agency (MHRA) and NICE must appraise treatments within their licensed doses. The committee considered it was unclear how much reduced neutralising effect impacts clinical efficacy and therefore how that uncertainty could be characterised in the different clinical efficacy scenario analyses. The committee noted that the effectiveness of neutralising monoclonal antibodies will need continuous monitoring for each variant and subvariant.

### **Relative treatment effects for mild COVID-19**

3.19 For the mild COVID-19 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](#)). 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. 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). The committee considered that the heterogeneity of trial outputs and generalisability contributed greater uncertainty to the decision problem.

- **Discussion on 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 (EPIC-HR) done in an unvaccinated population in an earlier wave of the pandemic. The committee concluded that OpenSAFELY data provided support for the continuous hospitalisation and mortality benefit of nirmatrelvir plus ritonavir seen from the older trial. The committee was mindful not to make conclusions about relative treatment effects based solely on non-randomised evidence from OpenSAFELY. The committee noted the subgroup analysis from the recent EPIC-SR trial that included people who were vaccinated with at least one risk factor for severe COVID-19. The committee acknowledged the EPIC-SR enrolment was stopped early and the results were preliminary and published only on the company's website rather than a peer-reviewed journal. However, the committee noted the preliminary outcomes showed non-significant reduction in hospitalisation rates in this vaccinated high-risk subgroup adding to the existing generalisability concerns for EPIC-HR. It still considered there to be substantial uncertainty because of generalisability concerns with the mean-efficacy estimate. Therefore, the committee considered the range between the mean- and lower-efficacy estimates for nirmatrelvir plus ritonavir from the trial to be more suited to the current endemic setting, despite the limitations with this approach (see [section 3.10](#)). It noted that PANORAMIC was also recruiting a nirmatrelvir plus ritonavir treatment arm that could answer questions about effectiveness for people who have high risk but are not defined in the McInnes high-risk group.
- **Discussion on 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 uncertain because of the population differences. The committee noted the results of the OpenSAFELY data, which included a McInnes-defined high-risk population for molnupiravir, support the limited hospitalisation and mortality benefits observed in PANORAMIC and from the overall NMA. The committee noted that any benefit for hospitalisation or mortality is likely to be minimal when the HRs are close to 1, and stronger clinical evidence is needed to justify a difference in relative clinical effects. The committee concluded that it could not be certain of molnupiravir's clinical efficacy in terms of hospitalisation and mortality rates when the potential benefit is minimal.

- **Discussion on remdesivir:** The committee noted the statistically significant reduced risk of hospitalisation from the evidence synthesis based on the PINETREE trial (a double-blind, randomised controlled trial of remdesivir in the mild COVID-19 [non-hospital] setting, [Gottlieb et al. 2022](#)). The committee also acknowledged the lack of evidence of any survival benefit for remdesivir with no events in either arm. It considered all efficacy estimates for remdesivir in the mild COVID-19 setting because of the uncertainty.

**Discussion on sotrovimab:** The committee noted the evidence on sotrovimab was from 1 randomised trial (COMET-ICE) which reported a statistically significant reduction in all-cause hospitalisation or death. It commented that the trial was done before the Delta wave. The committee commented that OpenSAFELY data supported the continuous hospitalisation and mortality benefit of sotrovimab seen in COMET-ICE, although generalisability concerns remained with the trial evidence. The committee noted that OpenSAFELY showed no evidence of a difference in all-cause hospitalisation or death between

the sotrovimab and nirmatrelvir plus ritonavir groups when the BA.2 and BA.5 subvariants were prevalent. It also noted that sotrovimab showed a lower risk of severe outcomes compared with molnupiravir in the overall and the advanced renal disease groups over the Omicron wave. The committee understood that sotrovimab was used as an alternative treatment in some people with high risk of severe disease when nirmatrelvir plus ritonavir was contraindicated. The committee acknowledged that observational OpenSAFELY evidence supported the clinical efficacy seen in COMET-ICE but was mindful not to make conclusions about relative treatment effect solely based on non-randomised evidence. The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing BQ.1 and BQ.1.1 subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab.

### Relative treatment effects for severe COVID-19

3.20 For people presenting to hospital with COVID-19, 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 for severe COVID-19. This includes when to use respiratory support, anticoagulation treatments and corticosteroids.

- **Discussion on remdesivir:** The clinical experts considered that remdesivir is currently used in some people with lower oxygen needs but its use is not 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 in the pandemic. The committee considered the individual evidence from SOLIDARITY as well as the updated NMA with the SOLIDARITY results. In

SOLIDARITY 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 having oxygen. The updated NMA for remdesivir shows an HR of 0.85 (95% CI 0.76 to 0.95) for mortality versus standard care. The committee noted that it was not possible to make a decision based on the confidence intervals of data from SOLIDARITY and the pooled NMA analysis. This is because the precision around the confidential interval is reflective of population characteristics and standard care practices earlier on in the pandemic. The committee said these were important considerations for severe COVID-19, for which standard of care has considerably changed since the start of the pandemic when SOLIDARITY was done. It said this would have a considerable impact on the limited relative mortality benefit seen for remdesivir (see [section 3.13](#)). The committee therefore interpreted the available evidence with caution and considered a threshold analysis using the mortality rate ratios of 0.85 to 1.00. The committee was more certain that the relative mortality rate ratio would tend towards 1.00 because of generalisability concerns (see section 3.13). The committee noted that any mortality benefit is likely to be minimal when the HRs are close to 1, and stronger clinical evidence is needed to justify a difference in relative clinical effects. The committee concluded that it could not be certain of remdesivir's clinical efficacy in terms of mortality benefit when the potential benefit is minimal. The committee concluded there was insufficient evidence to show meaningful difference in mortality benefit versus standard care.

- **Discussion on tocilizumab:** For the anti-inflammatory immunomodulator treatment, tocilizumab, the committee noted statistically significant clinical-effectiveness results. The clinical expert considered that tocilizumab should be used with caution in clinical practice and noted uncertainty with relative effect in the changing context of COVID-19. The committee noted that the virus is changing and there is bound to be some uncertainty in the clinical evidence.

Tocilizumab acts on the complications caused by the virus, rather than attempting to neutralise the virus itself. Tocilizumab's mechanism of action is more robust to change than the neutralising monoclonal antibodies. The committee concluded that it was more confident in the mean-efficacy results because of tocilizumab's mechanism of action and clinical trial evidence base (see section 3.13).

## Economic model

### Model structure and key drivers of cost effectiveness

3.21 The economic model for this appraisal was developed by the AG and informed by a previous publication ([Rafia et al. 2022](#)) that evaluated COVID-19 treatment in a pre-hospital setting. The AG used a decision tree model structure for treatments in the mild COVID-19 (non-hospital) setting that joined with a partitioned survival model in the severe COVID-19 (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 3.10](#)). The AG fitted parametric distributions to long COVID data from the ONS. Consultees highlighted that the long COVID duration was underestimated and should be higher than the 108.6 weeks used by the AG. In response the AG updated the model which estimates that 30% of people will still have symptoms at 2 years, 10% at 5 years and 3% at 10 years. The AG assumed that 100% of people in the severe COVID-19 setting and 10% in the mild COVID-19 setting would have long COVID. Consultees noted that the proportion should be reduced for the severe COVID-19 setting and increased for the mild COVID-19 setting. The AG

considered its original assumption to be conservative and therefore appropriate because alternative evidence was not available at the time of the second meeting. 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 mild COVID-19 setting was the baseline rate of hospitalisation. This is because it determined how many people were included in the high-cost and low-utility hospital setting.
- The key drivers of the outputs in the severe COVID-19 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 relative treatment effect, and 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 appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19.

## Hospitalisation rates

3.22 The rate of hospitalisation is a key driver of model outputs (see [section 3.21](#)) 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, for the first meeting the AG used a hospitalisation rate of 0.77% from PANORAMIC in its base case to generate the decision-making ICERs. PANORAMIC was reflective of the

current COVID-19 landscape, including the Omicron variant. However draft consultation comments further highlighted that PANORAMIC would have excluded people at higher risk who were eligible for treatment through NHS interim clinical commissioning policies (see [section 3.4](#)). Consultees provided a range of hospitalisation rates identified through targeted reviews. The committee saw overall hospitalisation rates defined by the McInnes high-risk definition including: OpenSAFELY 2.41% (untreated but eligible using McInnes definition), 1.37% (untreated but eligible group without contraindications to nirmatrelvir plus ritonavir) and 2.82% (DISCOVER-NOW database, UK observational study of people covered in the McInnes report). Hospitalisation rates also varied across different conditions, including between 4.15% and 4.4% for advanced renal kidney diseases and 15.9% (study of people with primary and secondary immunodeficiency [[Shields et al. 2022](#)]). In the first meeting the clinical experts agreed, given the committee's preferred definition of high risk (see [section 3.7](#)), that 0.77% could be an underestimation because the highest risk group may have been underrepresented in PANORAMIC (see section 3.4). 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 people who have had a transplant and people having chemotherapy. The committee acknowledged significant uncertainty in estimating the hospitalisation rate for the population who have high risk of progression 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 2.82% from the DISCOVER-NOW database. The committee concluded that the hospitalisation rate for the McInnes high-risk group is between 2.41% and 2.82% based on OpenSAFELY and DISCOVER-NOW. For people contraindicated to nirmatrelvir plus ritonavir the hospitalisation rate is assumed to be about 4% as an upper limit using advanced renal disease as proxy from OpenSAFELY.

## Time to discharge

3.23 The amount of time spent in hospital is a key driver of cost effectiveness because of hospitalisation costs. Evidence on each treatment showed a relative reduction in time spent in hospital. One consultee highlighted during draft guidance consultation that the time to discharge data from ACTT-1 should have been included for remdesivir. In response the AG included the time to discharge data for remdesivir which resulted in a large reduction in the cost-effectiveness estimates. The AG had previously noted the time to discharge evidence was collected during the early stages of the pandemic, which could lead to substantial generalisability concerns because the context of care has changed in the endemic setting. 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 committee also noted that clinical experts in both meetings explained that people hospitalised with COVID-19 have very different symptoms at present (the time of this evaluation) compared with early stages of the pandemic. Also that the population is heterogeneous (see [sections 3.2 and 3.3](#)). 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. At the first meeting the committee considered these scenarios to be plausible but conservative if treatments had effects outside of hospitalisation and mortality. The committee was not presented with additional evidence on time to discharge or clinical improvement and was uncertain about the treatment benefit in the endemic setting. The committee concluded it was reasonable to remove these treatment effects.

## Utility values

### Utility value assumptions

3.24 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 mild COVID-19 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 compared with standard care and disadvantaged 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 severe COVID-19 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 *Clostridioides 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**

3.25 In the first meeting 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. During draft guidance consultation a consultee said the AG's base-case long COVID cost underestimates the true burden of long COVID and provided an alternative higher cost from [Vos-Vromans et al. 2017](#). The AG accepted this new evidence and inflated the cost to £2,267 per year (to reflect 2021/2022). The committee agreed with the updated base-case value.

### **Administration costs**

3.26 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 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. During draft guidance consultation, consultees did not agree with the administration costs used in the AG base case. Some consultees said additional pharmacist per hour costs (about £352.49) should be added for assessment of nirmatrelvir plus ritonavir interactions with other treatments. For treatments like molnupiravir with limited contraindications either no oral administration costs should be assumed or 10% of the current administration cost (about £41) should be charged. Other consultees argued that the prescribing cost for nirmatrelvir plus ritonavir should be lower and between £75 to £117 because e-consultations and telephone triage options factor in the assessment of contraindications by clinicians already familiar with doing them. The AG explained that changes in administration costs can be evaluated by looking at differences in net monetary benefit. The committee considered the differences in administration costs in relation to the net monetary benefit outcomes, noting the uncertainty about future delivery models.

### **Hospitalisation costs**

3.27 The AG used unit costs per hospital bed-day from the NHS National Schedule of NHS costs. During AG report consultation, the AG updated the costs for ordinal scales 3, 4 and 5 based on stakeholder suggestions. During draft guidance consultation, consultees said the approach to costing ordinal scales 4 and 5 underestimated the true cost. The AG agreed with the changes suggested and updated the costs. The final codes were as follows:

- ordinal scale 3: weighted average of DZ11R to DZ11V (Lobar, Atypical or Viral Pneumonia, without Interventions) for a regular day or night admission
- ordinal scale 4: weighted average cost of DZ19R to DZ19V (lobar, atypical or viral pneumonia, without interventions) for non-elective long stay (see the AG report in the [committee papers](#) for further adjustments that were applied)
- ordinal scale 5: weighted average cost of DZ19N to DZ19Q (lobar, atypical or viral pneumonia, with single intervention) for non-elective long stay (see the AG report in the committee papers for further adjustments that were applied)
- ordinal scale 6: using XC07Z (Adult Critical Care, 0 Organs Supported)
- ordinal scale 7: weighted average cost for adult critical care, 1 or more organs supported (XC01Z to XC06Z).

The committee acknowledged the changes implemented by the AG and agreed with the AG's final approach.

## **Cost-effectiveness estimates**

### **Treatments for mild COVID-19**

3.28 For the mild COVID-19 setting, ICERs and net monetary benefits were calculated for casirivimab plus imdevimab, molnupiravir, nirmatrelvir plus ritonavir, remdesivir, sotrovimab and tixagevimab plus cilgavimab. The committee looked at the pairwise ICERs compared with standard care presented by the AG:

The ICERs for casirivimab plus imdevimab, molnupiravir, sotrovimab, and tixagevimab plus cilgavimab compared with standard care cannot be reported here because of confidential prices and commercial discounts. The committee reviewed results for the low-, mean- and high-efficacy scenarios (see [section 3.10](#)). The committee noted its preferred assumptions to include combinations of the following:

- hospitalisation rates between 2.41% and 2.82%, and 4.00% for people contraindicated to nirmatrelvir plus ritonavir
- mean and low efficacy relative treatment effects (noting the limitations of the scenarios in section 3.10).

The committee noted substantial uncertainty with the relative treatment effects of casirivimab plus imdevimab, tixagevimab plus cilgavimab and molnupiravir. The committee concluded casirivimab plus imdevimab, tixagevimab plus cilgavimab and molnupiravir all have limited and uncertain clinical effectiveness in terms of reducing hospitalisation or mortality rates and therefore the ICERs were considered very uncertain (see [section 3.17](#)).

The ICERs for the treatments compared with standard care using a) mean and b) low efficacy treatment effect and a 2.41% hospitalisation rate were:

- remdesivir: a) £108,499 per QALY gained; b) £440,514 per QALY gained
- nirmatrelvir plus ritonavir: a) £7,892 per QALY gained; b) £14,039 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, for people with high risk of severe COVID-19, as defined by the McInnes criteria. This includes people in hospital for reasons other than COVID-19 but who are at high risk of progressing to severe COVID-19. The equivalent ICER for sotrovimab was above £20,000 per QALY gained, even when considering alternative lower administration costs.

The committee also considered the mean- and low-efficacy scenarios using a hospitalisation rate of 0.77% from PANORAMIC which more closely approximated the marketing authorisation population for nirmatrelvir plus ritonavir. The ICERs were above £20,000 per QALY

gained and nirmatrelvir plus ritonavir was likely not a cost-effective use of NHS resources in this broader lower risk population.

To explore cost effectiveness for people contraindicated to nirmatrelvir plus ritonavir the committee looked at a scenario in which the hospitalisation rate was set to 4.00%. The ICERs for remdesivir versus standard care were above £20,000 per QALY gained. For sotrovimab, the low-efficacy ICER versus standard care was above £20,000 per QALY gained. However, assuming the efficacy was between mean and low efficacy and with a lower administration cost (£410, equivalent to the cost used for providing an oral antiviral), the ICER was within the range normally considered an acceptable use of NHS resources. The committee concluded that remdesivir is not a cost-effective use of NHS resources. It concluded that sotrovimab is a cost-effective use of NHS resources, but only for people for whom nirmatrelvir plus ritonavir is contraindicated or otherwise unsuitable.

### **Severe COVID-19 and without supplemental oxygen**

3.29 For the severe COVID-19 setting without supplemental oxygen, ICERs were calculated for casirivimab plus imdevimab. Similar to the mild COVID-19 setting, pairwise ICERs versus standard care were presented. The committee reviewed results for the low- and mean-efficacy scenarios (see [section 3.10](#)). The committee noted its preferred assumptions to include HRs of 1 for time to discharge and clinical improvement at 28 days

The ICERs for casirivimab plus imdevimab cannot be reported here because of confidential prices. The committee did not consider casirivimab plus imdevimab to be clinically effective (see [section 3.17](#)) and therefore the ICERs were considered very uncertain.

The committee was aware that the AG presented ICERs for remdesivir in severe COVID-19 setting without supplemental oxygen. However, the committee did not consider that this setting was within the marketing authorisation for remdesivir (see [section 2](#)). It had separately considered

remdesivir for people with mild COVID-19 who do not need supplemental oxygen and who have an increased risk of progression to severe COVID-19 (see section 3.28).

## Severe COVID-19 and supplemental oxygen

3.30 For the severe COVID-19 with supplemental oxygen setting, ICERs were calculated for casirivimab plus imdevimab, remdesivir and tocilizumab. Pairwise ICERs compared with standard care were presented. The committee reviewed results for the low- and mean-efficacy scenarios (see [section 3.10](#)). The committee noted its preferred assumptions to be the same as for the severe COVID-19 setting without supplemental oxygen (see [section 3.29](#)).

The ICERs for casirivimab plus imdevimab and tocilizumab cannot be reported here because of confidential prices. The committee did not consider casirivimab plus imdevimab to be clinically effective (see [section 3.17](#)) and therefore the ICERs were considered very uncertain and inconclusive. The ICERs for tocilizumab compared with standard care were below £20,000 per QALY gained for the mean-efficacy scenario. The committee considered tocilizumab likely to be a cost-effective use of NHS resources compared with standard care.

For remdesivir, the committee considered the threshold analysis of mortality rate ratios between 0.85 and 1.00. The committee concluded there was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (see [section 3.20](#)). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness.

## Other factors

### Uncaptured benefits

3.31 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 or cost savings 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
- ability to alter selective pressure on the virus and generation of future variants
- 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
- value of treatment options available as insurance for people who are shielding.

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 NICE's manual on health technology evaluations](#). 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

3.32 The committee considered potential equality issues, including:

- **Disability – people contraindicated to nirmatrelvir plus ritonavir:**

The committee 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. The committee considered whether, by recommending nirmatrelvir plus ritonavir, without recommending an alternative for people contraindicated to 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 took this into account and considered a higher hospitalisation rate of 4% for the McInnes defined high-risk group who were also contraindicated to nirmatrelvir plus ritonavir (see [section 3.28](#)). For the alternative treatments assuming the higher hospitalisation rate meant that sotrovimab was considered a cost-effective use of NHS resources, for people contraindicated to nirmatrelvir plus ritonavir (see section 3.28).

- **Disability – optimised recommendation on nirmatrelvir plus ritonavir:** The committee noted the marketing authorisation for nirmatrelvir plus ritonavir is broader and included people at lower risk of severe COVID-19 compared with the optimised recommendation (see [section 1](#)) which uses the narrower McInnes high-risk definition. The committee acknowledged that the optimised recommendation may exclude some people in certain high-risk groups who were included in the marketing authorisation and who have disability, which is a protected characteristic (see [section 3.4](#)). The committee considered whether, by recommending nirmatrelvir plus ritonavir only within an optimised McInnes defined high-risk, it would be indirectly discriminating against people in these groups. The committee carefully considered these issues and concluded that there was not sufficient evidence to expand the high-risk group definition and modelling uncertainties (see [section 3.7](#)) would mean the ICERs for this broader high-risk group would be highly uncertain. The committee considered this could indirectly discriminate but would be a proportionate means of achieving the legitimate aim of maximising public health.

- **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. 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. It noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address this issue.
- **Age:** Some stakeholders considered age was an independent relevant risk factor (see [section 3.6](#)). 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.
- **Treatment for children:** The committee noted that the summary of product characteristics for nirmatrelvir plus ritonavir in the mild COVID-19 setting and tocilizumab in the severe COVID-19 setting do not recommend these treatments in people under 18 years. In the mild COVID-19 setting the committee has recommended sotrovimab for

people for whom nirmatrelvir plus ritonavir is unsuitable. Sotrovimab's marketing authorisation includes adolescents (aged 12 years and over), so this would be an option for them, if they have a high-risk of progression to severe COVID-19 as defined by the McInnes report. For younger children the only option in this setting is remdesivir. However, the ICERs were very high and not considered a cost-effective use of NHS resources. By only recommending tocilizumab in the severe COVID-19 setting there is a risk of indirectly discriminating against children and young people. However, the alternative treatments had substantially higher ICERs and were not considered a cost-effective use of NHS resources.

- **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 acute hospital treatment, 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

3.33 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. It noted that the issues raised 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, because 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 to tocilizumab and for younger children were substantially higher than what is considered a cost-effective use of resources.

## Conclusion

**Table 1 Overview of recommendations**

Setting	Recommended	Not recommended
Mild COVID-19 (in people who have high risk of progression to severe disease, this setting also includes hospital-onset COVID-19)	<ul style="list-style-type: none"> <li>nirmatrelvir plus ritonavir</li> <li>sotrovimab (only if nirmatrelvir plus ritonavir is contraindicated or unsuitable)</li> </ul>	<ul style="list-style-type: none"> <li>casirivimab plus imdevimab</li> <li>molnupiravir</li> <li>remdesivir</li> <li>tixagevimab plus cilgavimab</li> </ul>
Severe COVID-19 (without supplemental oxygen)	<ul style="list-style-type: none"> <li>no technologies recommended</li> </ul>	<ul style="list-style-type: none"> <li>casirivimab plus imdevimab</li> </ul>
Severe COVID-19 (with supplemental oxygen)	<ul style="list-style-type: none"> <li>tocilizumab</li> </ul>	<ul style="list-style-type: none"> <li>casirivimab plus imdevimab</li> <li>remdesivir</li> </ul>

## 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, sotrovimab or tocilizumab are the right treatments, they should be available for use, in line with NICE's recommendations.
- 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

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