NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Therapeutics for people with COVID-19 [ID4038]

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Final Scope, final Stakeholder list and Research Protocol

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

Assessment Report

Commercial in Confidence stripped version for consultation

Produced by: School of Health and Related Research (ScHARR), The University of Sheffield

STRICTLY CONFIDENTIAL

Baricitinib, casirivimab/imdevimab, lenzilumab, molnupiravir, nirmatrelvir/ritonavir, remdesivir, sotrovimab, and tocilizumab, for the treatment of COVID-19. An economic evaluation

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

Paul Dark is the National Deputy Medical Director of a National Institute for Health and Care Research Clinical Research Network. He is a Local Principal Investigator for both the RECOVERY and REMAP-CAP platform trials, NIHR Urgent Public Health (UPH) pandemic research Advisory Group Lead Link for REMAP-CAP and specialist member of NIHR UPH Advisory Group. His NHS host hospital Research and Innovation Department has been contracted and paid to provide advice on the use of tocilizumab for Roche and sotrovimab for GlaxoSmithKline both in COVID-19. He supported the activity as a named NHS expert employed by the Northern Care Alliance NHS Foundation Trust (Salford Care Organisation) but received no personal payments. There are no other conflicts of interest within this project team.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Keywords: COVID-19; cost-benefit analysis economic evaluation; cost-effectiveness; cost-utility analysis

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). Over six million deaths worldwide have been associated with COVID-19.

Objective. To assess the cost-effectiveness of eight treatments used for the treatment of COVID-19 in hospital or used in the community in patients with COVID-19 at high-risk of hospitalisation.

Perspective: Treatments provided in UK hospital and community settings.

Methods: Clinical effectiveness estimates were taken from the COVID-NMA initiative and the metaEvidence initiative. A mathematical model was constructed to explore how the estimated efficacy for interventions used in hospital and for those at high-risk in the community impacted on patient health, measured in quality-adjusted life years (QALYs) gained. The costs associated with treatment, including those of hospital care, were also estimated and used to form a cost per QALY gained value which was compared with thresholds published by the National Institute for Health and Care Excellence (NICE). Estimates of cost-effectiveness compared against current standard of care (SoC) were produced and a full incremental analysis performed.

Results: The treatments were estimated to be clinically effective although not all reached statistical significance. All treatments in the hospital setting were estimated to plausibly have a cost per QALY gained value below NICE's threshold when compared with SoC. This conclusion held for interventions used in the community although cost per QALY values were higher than in the hospital setting. Full incremental analyses indicated that baricitinib may be the most cost-effective treatment in a hospital setting and that nirmatrelvir with ritonavir (at an estimated price) may be the most cost-effective treatment in the community setting. However, there is considerable uncertainty in the results of the full incremental analyses due to heterogeneity in the pivotal studies and imprecision in estimates due to the small number of observed events and some treatments may have cost per QALY values greater than NICE's published thresholds.

Limitations: The decision problem has evolved in terms of improved SoC, vaccination status, history of being infected with SARS-CoV-2, and the prevalent SARS-CoV-2 variant. As such, studies do not reflect the current conditions. Therefore, many assumptions were required that limit the accuracy of the estimates of clinical- and cost-effectiveness. No head-to-head studies of interventions were identified for use in the model. Placeholder costs were used for some interventions and patient access schemes were not incorporated.

Conclusions: The results produced should be informative to decision makers, although conclusions regarding the most clinical—and cost-effective intervention in these settings should be tentative given the heterogeneity between studies, the evolving nature of the decision problem and the uncertainty in the costs of interventions.

Future work: Research assessing the relative clinical effectiveness of interventions within head-to-head studies would be beneficial. Contemporary information related to the probability of hospital admission and death for patients at high-risk in the community would improve the precision of the estimates generated as would ascertaining the average age of this population. Value of information analyses may efficiently direct future research.

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See the NIHR Journals Library website for further project information.

TABLES

FIGURES

Plain English Summary

COVID-19 is an infectious disease that can cause death and long-term ill-health. Treatments exist that can be provided in hospital to reduce the number of deaths from COVID-19. Treatments also exist which can be provided in the community for people at high-risk of needing to be admitted to hospital to reduce the number of admissions and to reduce the number of deaths from COVID-19. However, the value for money of these treatments have not been estimated. We took the clinical effectiveness of eight treatments from published literature sources and built a model that estimated the value for money of each treatment compared with care without these treatments. The results of the model showed that many treatments in a hospital setting had estimates of cost-effectiveness that would normally be seen to be good value for money using the thresholds published by the National Institute of Health and Care Excellence as did some treatments in a community setting. Comparing treatments directly was difficult as the studies which reported on the clinical effectiveness were different in many ways. These differences included 1) the treatments used in current care at the time the study was conducted, as better drugs are now used than when COVID-19 was first identified, 2) the proportion of people who have had vaccinations or who had previously had COVID-19 or the virus that causes COVID-19, and 3) the variant of the virus causing COVID-19. Because of these differences, and the unknown price of some interventions, we could not confidently say which treatment helped patients the most or which treatment represented the best value for money.

Scientific Summary

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). At the time of writing (June 2022) there had been over 540 million confirmed cases and over six million deaths worldwide associated with COVID-19. For the UK, these values are over 22 million cases and 175,000 deaths.

In addition to the widespread vaccination programme, treatments exist that can help people who have been hospitalised due to COVID-19 (casirivimab and imdevimab (henceforth casirivimab/imdevimab), tocilizumab, remdesivir, baricitinib, baricitinib and remdesivir, and lenzilumab) or be used in patients who have COVID-19 and are at high-risk of needing hospitalisation (casirivimab/imdevimab, molnupiravir, nirmatrelvir and ritonavir (henceforth nirmatrelvir/ritonavir), remdesivir, and sotrovimab). For reasons related to urgency, these treatments, unlike interventions in other disease areas, have not received positive guidance from the National Institute of Health and Care Excellence before being routinely used. As the pandemic subsides there is more need for a formal evaluation of the clinical and cost-effectiveness of these treatments.

Objectives

The objective of this study is to summarise the current knowledge related to the clinical efficacy of the interventions and to conduct an economic evaluation that estimates the cost-effectiveness of each intervention against standard of care (SoC), as of June 2022, and to perform a full incremental analysis, whilst noting the caveats in the comparison of all interventions simultaneously.

Methods

Given the timescale of the project, where there was less than three months between the publication of the final scope and the report deadline, a literature review following best practice was not possible. Instead, a pragmatic, alternative approach was undertaken where evidence was taken from two living systematic reviews (supported by the COVID-NMA initiative and the metaEvidence initiative). For interventions related to use in hospitals, data were extracted on time to death, clinical improvement, and time to discharge. For interventions which are used in the community for patients at high-risk of hospitalisation, data were extracted on the risks of hospitalisation or death, and the risks of death. These measures of efficacy were assumed transportable to June 2022 despite changes in background conditions which include the SoC, the percentage of people who have been vaccinated and a change in the dominant SARS-CoV-2 variant.

A mathematical model was constructed that used the data from the living systematic reviews to simulate the experiences of patients in hospital, and requirement for supplemental oxygen, until discharge or

death in hospital. Due to the (conditional) marketing authorisations of the interventions, the model was developed such that results could be produced for the supplemental oxygen group and the non-supplemental oxygen group separately. The model structure utilised an eight-point ordinal scale that was used in clinical trials to categorise patients during their admissions. Outputs from this model included the costs associated with interventions and care, and the quality-adjusted life-years (QALYs) gained by the patient both within the hospital episode and after discharge, incorporating decrements in health-related quality of life associated with the lasting impact of COVID-19. For interventions used in the hospital, these values allowed a cost per QALY gained to be calculated for each treatment compared with SoC, and for a full incremental analysis to be conducted.

The costs of each intervention were taken from public sources where available. However, tocilizumab and baricitinib have confidential patient access schemes agreed, which discount the price of the intervention, and are not considered in this document, but were provided to the NICE Appraisal Committee in a separate confidential appendix. The price of some treatments (casirivimab/imdevimab, molnupiravir and nirmatrelvir/ritonavir) were unknown at the time of writing and placeholder prices were used in the report.

For patients at high-risk of hospitalisation treated in the community, a decision tree was put before the hospital model, to simulate the reduced need for hospitalisation associated with early treatment. The total costs and QALYs associated with treatment options were estimated to allow an evaluation of the cost per QALY of each treatment against SoC and for a full incremental analysis to be undertaken. The modelling did not assess the logistics of treatment in the community, but the External Assessment Group notes that this could be a large factor in deciding which treatments could be preferred, as oral treatments could be more acceptable to patients and healthcare systems than treatments that are given intravenously or subcutaneously.

Three scenarios were run changing the efficacy of interventions. The mean efficacy estimate used the mean of each distribution extracted from the living systematic reviews, the high efficacy estimate used the most favourable limits of the 95% CIs and the low efficacy estimate used the least favourable limits of the 95% CIs.

Three scenario analyses were run that explored: the impact of changing the assumed average duration of health impact associated with COVID-19 (henceforth denoted long COVID); the proportion that are admitted to hospital of people in the community with COVID-19 at high risk of hospitalisation; and the average age of people with COVID-19 at high risk of hospitalisation.

Results were presented in terms of incremental cost-effectiveness ratios (ICERs) measured in cost per QALYs gained.

Results

All treatments used for hospitalised patients, had a median hazard ratio (HR) for death below 1, indicating a benefit, although all confidence intervals (CIs) crossed unity apart from those for tocilizumab and baricitinib. The overlapping CIs, and heterogeneous studies meant that no firm conclusions could be made regarding the relative efficacy of these treatments. There was less data relating to the relative risks (RRs) of clinical improvement at 28 days and the HRs for the time to discharge, although these were generally close to unity and had CIs that crossed unity. No clear conclusions could be made on the relative efficacy of treatments for these two measures.

All treatments used in the community had favourable median RRs for hospitalisation and death at 28 days, although due to wide CIs no firm conclusions could be made regarding the relative efficacy of these treatments. The median RR associated with death at 28 days were favourable for all interventions, except for remdesivir where the median estimate was unity. The CIs were wide and spanned 1 for all treatments except for molnupiravir and nirmatrelvir/ritonavir. As such, no clear conclusions relating to the relative efficacy of the interventions could be made regarding avoiding death at 28 days.

For hospitalised patients requiring supplemental oxygen, all treatments except lenzilumab, had estimated ICERs compared with SoC below £10,000 in both the mean efficacy and high efficacy scenarios; the value for lenzilumab was below £20,000. However, in the low efficacy scenario only baricitinib and tocilizumab generated more QALYs than SoC and had estimated ICERs under £20,000.

For hospitalised patients not requiring supplemental oxygen, all treatments except lenzilumab had estimated ICERs compared with SoC below £10,000 in both the mean efficacy and high efficacy scenarios; the corresponding ICER for lenzilumab was below £25,000. However, in the low efficacy scenario only baricitinib generated more QALYs than SoC and the estimated ICER for baricitinib compared with SoC was under £5,000.

For interventions used in the community, the estimated ICERs compared with SoC were more varied. For all interventions except molnupiravir and nirmatrelvir/ritonavir, the ICERs compared with SoC were in excess of £65,000 in the mean efficacy scenario. In the high efficacy scenario, all interventions except molnupiravir and nirmatrelvir/ritonavir had ICERs compared with SoC above £20,000. In the low efficacy scenario, all interventions except molnupiravir and nirmatrelvir/ritonavir produced less QALYs than SoC. In the mean efficacy scenario and the high efficacy scenario both molnupiravir and nirmatrelvir/ritonavir had ICERs below £15,000. In the low efficacy scenario, the ICER for

nirmatrelvir/ritonavir compared with SoC was below £10,000, although the ICER for molnupiravir was greater than £65,000.

The efficiency frontiers based on the full incremental analyses differed based on setting and efficacy scenario. For patients in hospital requiring supplemental oxygen, baricitinib was the intervention that produced most QALYs and had an ICER below £10,000 compared with the previous intervention on the efficiency frontier in both the mean efficacy scenario and the low efficacy scenario. In the high efficacy scenario, baricitinib and remdesivir were the interventions on the efficiency frontier with most QALYs and had ICERs compared with the previous intervention on the efficiency frontier below £20,000.

For patients not requiring supplemental oxygen, baricitinib was the intervention that produced most QALYs and had a cost per QALY below £5000 compared with the previous intervention on the efficiency frontier in both the mean efficacy and low efficacy scenarios. In the high efficacy scenario, baricitinib and remdesivir were the interventions on the efficiency frontier with most QALYs and had ICERs compared with the previous intervention on the efficiency frontier below £15,000.

For patients at high-risk of hospitalisation treated in the community, nirmatrelvir/ritonavir was the intervention that produced most QALYs and had a cost per QALY below £10,000 compared with the previous intervention on the efficiency frontier in all of the efficacy scenarios explored.

However, the comparative results are highly uncertain due to the wide CIs associated with each intervention and the heterogeneity associated with the pivotal studies. An additional uncertainty was the unconfirmed prices of nirmatrelvir/ritonavir and molnupiravir at the time of writing and the use of list prices where patient access schemes are available.

In the scenario analyses, the proportion of people with COVID-19 in the community at high-risk of hospitalisation who are hospitalised when treated with SoC had a large impact on the ICERs with treatments becoming more cost-effective as the admission proportion increased. The average age of people in the community with COVID-19 at high-risk of hospitalisation also had a marked impact on the ICERs with younger people making the drugs more cost-effective. The assumed duration of long COVID had a lower impact on the ICERs than the previous scenarios, although shorter durations of long COVID were associated with the treatments becoming more cost-effective.

Conclusions

There is considerable uncertainty in the efficacy of treatments compared to SoC due to the small number of observed events in studies, which result in wide CIs for HRs and RRs. Additionally, the SoC, the

percentage of people who have had a vaccination, and the dominant SARS-CoV-2 variant could all vary between pivotal studies. Some treatments (tocilizumab and baricitinib in the hospitalised setting and molnupiravir and nirmatrelvir/ritonavir in the community setting) were estimated to have a statistically significant benefit related to death due to COVID-19, however, this may also have been shown for other treatments if the pivotal studies had had larger sample sizes.

Multiple treatments have been shown to be cost-effective against SoC for patients in hospital, and for patients at high-risk of hospitalisation in the community. Full incremental analyses have been conducted, which indicated in the mean efficacy analyses that baricitinib was the most cost-effective treatment in hospital if a cost per QALY of £10,000 was deemed acceptable, and that nirmatrelvir/ritonavir was the most cost-effective treatment in the community setting if a cost per QALY of £5000 was deemed acceptable. However, the results are uncertain due to the wide CIs, the heterogeneity between pivotal studies, and the unconfirmed prices of nirmatrelvir/ritonavir and molnupiravir. In some scenarios, baricitinib and remdesivir were the most cost-effective if a cost per QALY of £20,000 was deemed acceptable. Furthermore, some treatments have patients access schemes which have not been incorporated in the analyses and the prices of some interventions are currently unknown.

Word Count 1877

CONTENTS

ABBREVIATIONS

Abbreviation	Description
ACTT-1	Adaptive COVID-19 treatment trial
AUC	Area under the curve
BNF	British national formulary
CI	confidence interval
COVID-19	Coronavirus disease 2019
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External assessment group
ECMO	Extracorporeal membrane oxygenation
eMIT	electronic market information tool
EQ-5D-5L	EQ-5D 5-level
HDU	High dependency unit
HFO	High flow oxygen
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IPD	Individual patient-level data
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
KM	Kaplan-Meier
LFO	Low flow oxygen
MAV	Medical attended visits
NHS	National health service
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NMA	Network meta-analyses
NMB	Net monetary benefit
ONS	Office for National Statistics
OS	Overall survival
PANORAMIC	Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community clinical study
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RECOVERY	Randomised Evaluation of COVid-19 thERapY
REES	Remdesivir Effectiveness Evaluation Study
RR	Relative risk
SAE	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMR	Standardised mortality ratio
SoC	Standard of care
WHO	World health organization
WTP	Willingness to pay

1. BACKGROUND

1.1 Description of the underlying health problem

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). At the time of writing (June 2022) there had been more than 540 million cases of COVID-19 worldwide and more than 6 million deaths; in the UK these values were more than 22 million cases and over 175,000 deaths.[1] In the UK, there have been waves of infections (peaking in late December 2021 and early January 2022), and waves of death (peaking in January 2021).[1]

The ratio of notified infections to death in the UK has changed markedly over time, being approximately 5 to 1 in April 2020, 45 to 1 in January 2021; and 700 to 1 in January 2022 (authors' calculations based on worldometer data[1]). Factors associated with the change in ratio include:

- better ascertainment of COVID-19 cases, which previously may have been left unobserved particularly early in the pandemic especially when mild or asymptomatic;
- increasing level of protection in the population, both acquired from previous SARS-CoV-2 infection and vaccine-induced;
- improved levels of treatment, such as the use of dexamethasone;
- the likelihood of more fragile people dying in earlier waves; and
- the potential change in variants of SARS-CoV-2.

Should the risk of death following COVID-19 remain at low levels and SARS-CoV-2 becomes endemic in society, then treatments for patients with COVID-19 may no longer be treated differently to interventions for other conditions such as breast cancer or heart disease. If this were the case, then it could be considered logical and acceptable that pharmacological treatment for COVID-19 would be appraised by the National Institute for Health and Care Excellence (NICE) using its standard methods.[2]

1.2 The NICE scope

In April 2022, NICE issued a final scope[3] for the assessment of therapeutics for people with COVID-19; the NICE website also hosts the final protocol written by the External Assessment Group (EAG).[4] The remit of the final scope was to appraise the clinical and cost-effectiveness of eight interventions for treating (i) people with mild COVID-19 at high-risk of progressing to severe COVID-19 and (ii) people with severe COVID-19. The comparators included established clinical management in clinical practice with or without corticosteroids and appropriate respiratory support, and other interventions. The components of the decision

problem are discussed more fully in Section 1.4. The deadline for the EAG report was the 30th of June 2022, allowing less than three months for the estimates of the clinical effectiveness of each intervention to be made, for the mathematical models to be adapted and run, the results to be interpreted and the report to be written.

1.3 Description of current service provision

Patients with severe COVID-19 are typically hospitalised with the intensity of treatment dependent on the severity of the condition. Patients may be treated in intensive care units (ICUs), be provided with high-flow oxygen or low-flow oxygen, and be treated with interventions, including those in the NICE scope and with corticosteroids.

1.4 The Decision Problem

This section has been sub-divided into sections detailing the population, interventions, comparators, outcome measures, and subgroups.

1.4.1 Population

The population considered within the EAG report has been divided into two broad groups. The first group consists of people who have been hospitalised due to COVID-19 and the second group consists of people who are at high-risk of requiring hospital care due to COVID-19. Patients who were hospitalised for reasons other than COVID-19 and contracted COVID-19 in hospital and were at high-risk of requiring hospital care for COVID-19 in itself were categorised within the second group. For brevity, all patients not hospitalised due to COVID-19 who are at high-risk of hospitalisation will be termed 'non-hospitalised patients' noting the aforementioned caveat regarding patients who contract COVID-19 in hospital, whereas patients who have been hospitalised directly because of COVID-19 are referred to as 'hospitalised patients'.

Following discussions with NICE, the definition for patients at high-risk was aligned to that considered within the Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community (PANORAMIC) clinical study,[5] with the exception that being aged 50 years or over was not considered to be a high-risk factor.

The aim of treatment differs between each group. For patients hospitalised due to severe or critical COVID-19, the aim of treatment is to reduce the immunoinflammatory response of the body and prevent clinical deterioration. For non-hospitalised patients, the aim of treatment is to prevent viral replication and damp inflammation, thus reduce the probability of the development of severe symptoms that could lead to hospitalisation and death.

1.4.2 Interventions

The interventions listed within the NICE scope[3], excluding anakinra which was withdrawn from the appraisal are shown in Table 1 to Table 3 based on marketing authorisation in the UK at the time of writing. Table 1 contains the interventions with marketing authorisation in the UK, Table 2 contains the interventions with conditional marketing authorisation in the UK, and Table 3 contains the interventions with no marketing authorisation in the UK. Each table contains the generic name of the intervention, its branded name and the company manufacturing it, the class of intervention, the mode of administration and recommended dose. Table 1 provides the indication for the drug, whilst Table 2 and Table 3 provide the population in key studies for the intervention.

Multiple interventions are indicated for the prevention of severe COVID-19. Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or saturation of peripheral oxygen <90% on room air and would require hospitalisation.[6]

1.4.3 Comparators

The comparators within the decision problem include all of the interventions contained in Table 1 to Table 3, when used in the same position as a particular intervention and additionally standard of care (SoC) which would be dependent on the severity of the patient's illness. SoC is defined as any treatment widely accepted by the National Health Service (NHS) as SoC, which is routinely funded by the NHS with no strong rationale to appraise it, for example supplemental oxygen and dexamethasone. SoC has evolved throughout the COVID-19 pandemic, which means that randomised controlled trials (RCTs) conducted comparing interventions against SoC may not be directly comparable as SoC has improved over time.

Table 1: Interventions with marketing authorisation in the UK as of the 28th of June 2022

Generic treatment name (branded name and company)	Class	Mode of administration, (recommended dose)	Indication relevant to the decision problem
Casirivimab/imdevimab (Ronapreve, Regeneron and Roche)	mAb	IV/SC (600mg of both drugs administered together as one infusion. An SC injection is permitted if an IV approach would lead to a delay)	Treatment of acute COVID-19 infection
Molnupiravir (Lagevrio, Ridgeback Biotherapeutics and Merck Sharp & Dohme)	Antiviral	Oral (800mg twice daily for 5 days)	Treatment of mild to moderate COVID-19 in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness
Tocilizumab (RoActemra, Roche)	Immunomodulator	SC/IV (8 mg/kg administered once IV with 0.9% sodium chloride over one hour) One additional infusion of tocilizumab 8 mg/kg may be administered. The interval between the two infusions should be at least 8 hours	Treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation

IV - intravenous, mAb – monoclonal antibody, SC – subcutaneous

Table 2: Interventions with conditional marketing authorisation in the UK as of the 28th of June 2022

Generic treatment name (branded name and company)	Class	Mode of administration, (recommended dose)	Therapeutic indication in the SmPC relevant to the decision problem
Nirmatrelvir/ritonavir (Paxlovid, Pfizer)	Antiviral	Oral (300mg (nirmatrelvir) and 100mg (ritonavir) twice daily for 5 days)	Treatment of COVID-9 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID 19
Remdesivir (Veklury, Gilead)	Antiviral	IV (200 mg loading dose on day 1 for all patients, then dependent on patient characteristics). • For adults and adolescents with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment): 100 mg daily IV for five to ten days) • For Adult patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19: IV (100 mg daily IV for three days)	Treatment of COVID-19 in: • adults and adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) or • adults with pneumonia not requiring supplemental oxygen
Sotrovimab (Xevudy, GlaxoSmithKline and Vir Biotechnology)	mAb	IV (500mg over 30 minutes)	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

IV - intravenous, mAb - monoclonal antibody, SC – subcutaneous, SmPC – summary of product characteristics

Table 3: Interventions with no marketing authorisation in the UK as of the 28th of June 2022

Generic treatment name (branded name and company)	**Class**	**Mode of administration, (recommended dose)**	**Population in key studies if no marketing authorisation or conditional marketing authorisation exists**
Baricitinib (Olumiant, Eli Lilly)	Immunomodulator	Oral (4mg daily, the optimal duration is currently unclear)	Studied in clinical trials, as a monotherapy, in people with COVID-19
Baricitinib (Olumiant, Eli Lilly) and R**emdesivir** (Veklury, Gilead)	Immunomodulator and antiviral	As for the component drugs	Studied in clinical trials in people aged 18 years and older, hospitalised with COVID-19
Lenzilumab (unknown brand name, Humanigen)	Humanised mAb	IV (three 600mg doses delivered 8 hours apart)	Studied in a clinical trial as a monotherapy in people aged 18 years and older, hospitalised with COVID-19

IV – intravenous, mAb – monoclonal antibody

1.4.4 Outcome Measures

The NICE scope[7] lists nine possible outcomes to explore: mortality; requirement for respiratory support; time to recovery; hospitalisation (requirement and duration); time to return to normal activities; virological outcomes (viral shedding and viral load); post-COVID-19 symptoms; adverse effects of treatments; and health-related quality of life (HRQoL). All model outcomes, except virological outcomes were assessed.

The cost-effectiveness of the eight treatments were expressed in terms of incremental cost-effectiveness ratios (ICERs) which were reported in terms of cost per quality-adjusted life year (QALY) gained. A patient lifetime horizon was used to take differential mortality between treatments into account.

1.4.5 Subgroups

Due to time constraints, the only subgrouping considered was related to whether oxygen was required upon admission to hospital entry. This was considered important as the licensed indication and the clinical outcomes for some of the appraised interventions depend on the level of oxygen support required. The EAG is aware that other possible criteria for selecting subgroups include, but are not limited to: age; immune system competence; comorbidities; seroprevalence; vaccination status; and the predominant SARS-CoV-2 variant but did not have the time to explore the impact of these characteristics.

2. CLINICAL-EFFECTIVENESS

2.1 Methods for the Rapid Evidence Review

Given the timelines of the project, the EAG could not follow best practice for systematically reviewing the clinical evidence relevant to the decision problem. Following discussions with NICE, a pragmatic, alternative approach was undertaken relying on the use of data extracted by third-parties which are referred to as 'living systematic reviews'. The methods used, assumptions taken, and the summarised results are provided in this chapter.

2.1.1. Rationale for using living systematic reviews

COVID-19 clinical research has accelerated dramatically worldwide, with over 5000 registered trials investigating therapeutic interventions for COVID-19.[8] The need for rapid information on COVID-19 has resulted in a paradigm shift, especially in the communication of scientific results. Traditional systematic reviews can date quickly but 'living' systematic reviews search for evidence much more regularly than standard reviews and incorporate relevant new evidence as it becomes available. This is important in the context of COVID-19, in which the evidence-base is rapidly changing as new data emerge. The ability of a 'living' systematic review and network meta-analysis (NMA) to regularly update and incorporate relevant new evidence as it becomes available makes it the best type of evidence synthesis, in the opinion of the EAG, to inform this pragmatic rapid evaluation.

2.1.2. Selection criteria for the living systematic reviews

Several living systematic reviews that incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple COVID-19 treatments, have been robustly developed and published.[8-11] Two sources were selected as they provided detailed relevant outcome data from individual studies and up-to-date evidence synthesis to inform the model.

The first source is the COVID-NMA initiative,[9, 12] supported by the World Health Organization (WHO) and Cochrane which is a living systematic review of registered randomised trials, in which all available evidence related to COVID-19 is regularly collected, critically appraised, and synthesised using pairwise comparisons and NMA methods. The analyses are updated every two weeks and results can be accessed via a web interface (https://covid-nma.com/).

The second source is the metaEvidence initiative,[10] supported by the University Hospital of Lyon and the University of Lyon which is also a living meta-analysis and evidence synthesis of therapies for COVID-19 and is an emerging online resource that provides direct access to the efficacy and safety results reported in the studies for potential drugs for the treatment of COVID-19. The risk of bias,

synthesised by meta-analysis, is also reported. The analyses are updated within a target time of less than 24 hours and results can be accessed through a web interface at http://www.metaevidence.org/COVID19.aspx.

Other sources of evidence, which primarily informed living guidelines,[8, 11] were deemed to lack full transparency in the extracted outcome data from individual studies. As such, they precluded further synthesis and evaluation and could even threaten the validity of the evidence synthesis.

2.1.3. Assumption of transportability of relative treatment effects

A consequence of the need to use data from the living systematic reviews was that the scope for the EAG to undertake nuanced analyses was reduced. An assumption was needed that all relative treatment effects were transportable to different settings. This meant that the same treatment effects, either hazard ratios (HRs) or relative risks (RRs), were assumed applicable regardless of study characteristics which include: the age, perceived severity, vaccination status, and history of SARS-CoV-2 infection of patients; the SoC at that time; the geographical location; and the dosage of the intervention used. It is acknowledged that this assumption may be incorrect, which adds additional uncertainty to the clinical- and cost-effectiveness results.

2.1.4 Inclusion criteria and data extraction

Data for the interventions contained in Table 1, Table 2 and Table 3 were extracted. Key model outcomes such as time to death, clinical improvement at day 28 or day 60 (defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery) and incidence of serious adverse events (SAEs) were initially extracted from the COVID-NMA living systematic review[9]. Where relevant outcome data were not available, these data were extracted from the metaEvidence living systematic review.[10] All data extractions (undertaken between the 16th of March to the 18th of May and updated between the 25th to the 31st of May 2022) were undertaken by one reviewer (AS) and checked by a second reviewer (AP), with any discrepancies resolved by a third reviewer (KR). All evidence synthesis analyses were extracted from data reported on the COVID-NMA and metaEvidence web interface; Double checks of the extracted data against the original RCT publications for accuracy could not be undertaken within the deadlines of the project.

2.1.5 Adjustments made for changing SoC, SARS-CoV-2 variant, vaccination status and prior infection

The conditions under which each study was evaluated were heterogeneous. Across time SoC has changed markedly, most particularly with reference to the widespread use of corticosteroids such as dexamethasone, and change in SARS-CoV-2 variants. The vaccine roll-out in England has provided

protection that was not available to patients recruited to early studies, similarly, there is likely to be an increased level of protection associated with prior infection. Ideally there would be attempts to establish the impact of different circumstances on the observed clinical effectiveness of interventions in studies, although this was not possible within the timescales of the project. As such, the EAG had to make a simplistic assumption that none of the changes were treatment effect modifiers, and that given this, the relative benefits observed in the studies were transportable and could be applied to the estimated outcomes for patients with COVID-19 in England in Summer 2022.

2.2 Results of the Rapid Evidence Review

This section reports key results from the analyses described in Section 2.1. A brief description of each included RCT, reproduced from the COVID-NMA Initiative,[9] is presented in Appendix 1. A summary of the extracted data for each intervention and relevant outcomes from the living systematic reviews is also presented in Appendix 1. The assumed clinical effectiveness for each intervention in hospitalised patients is detailed in Table 4, and in Table 5 for patients at high-risk of hospitalisation treated in the community. The interventions are listed in order of current marketing authorisation and alphabetical order. The values reported in Table 4 and in Table 5 are used in the economic evaluation. Where data were not available for clinical improvement or time to discharge a value of 1.0 was used as the model results were not sensitive to these values within the observed range associated with other interventions.

Table 4: Summarised clinical effectiveness data in patients hospitalised due to COVID-19

Intervention	Estimated efficacy (95% CI)	Source of evidence (number of studies informing the estimate)
Time to death HR		
Casirivimab/imdevimab	0.81 (0.53 – 1.23)	COVID-NMA[9] (1 study)
Tocilizumab	0.77 (0.65 – 0.91)	COVID-NMA[9] (9 studies)
Remdesivir	0.77 (0.57 – 1.04)	COVID-NMA[9] (3 studies)
Baricitinib	0.61 (0.47 – 0.78)	COVID-NMA[9] (2 studies)
Baricitinib/remdesivir	0.65 (0.39 – 1.09)	COVID-NMA[9] (1 study)
Lenzilumab	0.72 (0.42 – 1.23)	COVID-NMA[9] (1 study)
Clinical improvement RR at 28 days		
Casirivimab/imdevimab	1.02 (0.99 – 1.04)	COVID-NMA[9] (1 study)
Tocilizumab	1.04 (1.00 – 1.09)	COVID-NMA[9] (17 studies)
Remdesivir	1.04 (0.99 – 1.10)	COVID-NMA[9] (3 studies)
Baricitinib	1.02 (1.00 – 1.05)	COVID-NMA[9] (2 studies)
Time to discharge HR		
Casirivimab/imdevimab	1.19 (1.08 – 1.31)	metaEvidence[10] (2 studies)
Tocilizumab	1.05 (0.88 – 1.25)	metaEvidence[10] (2 studies)

CI - confidence interval, HR - hazard ratio, RR - relative risk

Table 5: Summarised clinical effectiveness data for patients at high-risk of hospitalisation due to COVID-19

Intervention	Estimated efficacy (95% CI)	Source of evidence (number of studies informing the estimate)
Hospitalisation or death RR		
Casirivimab/imdevimab	0.28 (0.18 – 0.44)	COVID-NMA[9] (3 studies)
Molnupiravir	0.68 (0.50 – 0.94)	COVID-NMA[9] (3 studies)
Nirmatrelvir/ritonavir	0.13 (0.07 – 0.27)	COVID-NMA[9] (1 study)
Remdesivir	0.28 (0.10 – 0.74)	COVID-NMA[9] (1 study)
Sotrovimab	0.20 (0.08 – 0.48)	COVID-NMA[9] (1 study)
All-cause mortality RR at 28 days		
Casirivimab/imdevimab	0.51 (0.09 – 2.95)	COVID-NMA[9] (3 studies)
Molnupiravir	0.19 (0.04 – 0.86)	COVID-NMA[9] (4 studies)
Nirmatrelvir/ritonavir	0.04 (0.00 – 0.63)	COVID-NMA[9] (1 study)
Remdesivir	1.00 (0.02 – 50.23)*	COVID-NMA[9] (1 study)
Sotrovimab	0.20 (0.01 – 4.16)	COVID-NMA[9] (1 study)

CI - confidence interval, HR - hazard ratio, RR - relative risk

* There were no deaths reported in either arm. This estimate is calculated assuming a continuity factor of 0.5 deaths and 1 extra observation was added to each arm.

To aid interpretation of the clinical efficacy data for interventions used to treat patients in hospital, plots of i) the HR for death at 28 days, ii) the RR for clinical improvement at 28 days, iii) the HR associated with time to discharge, iv) the probability that the intervention, based on the distribution extracted for clinical efficacy, is associated with more deaths at 28 days, and v) the ranked position of each intervention in 1000 joint samples of efficacy for all are shown in Figure 1, Figure 2, Figure 3, Figure 4 and Figure 5 respectively. Figure 1, Figure 2, and Figure 3 consist of two horizontal lines for each intervention which sit on a vertical line. The vertical line shows the lower and upper 95% confidence intervals (CI) whilst the lower horizontal line provides the median value, and the upper horizontal line provides the mean value from the distribution. When the mean and the median values are close these become indistinguishable in the figures.

As seen in Figure 1, all treatments have a beneficial mean estimate for the HR associated with death. The CIs of each treatment overlap showing that there is considerable uncertainty in the ranked order of clinical effectiveness. A similar conclusion related to the ranking of interventions for clinical improvement can be drawn from Figure 2, and for the ranking of treatments in relation to time to discharge from Figure 3, although only two interventions reported data on this measure.

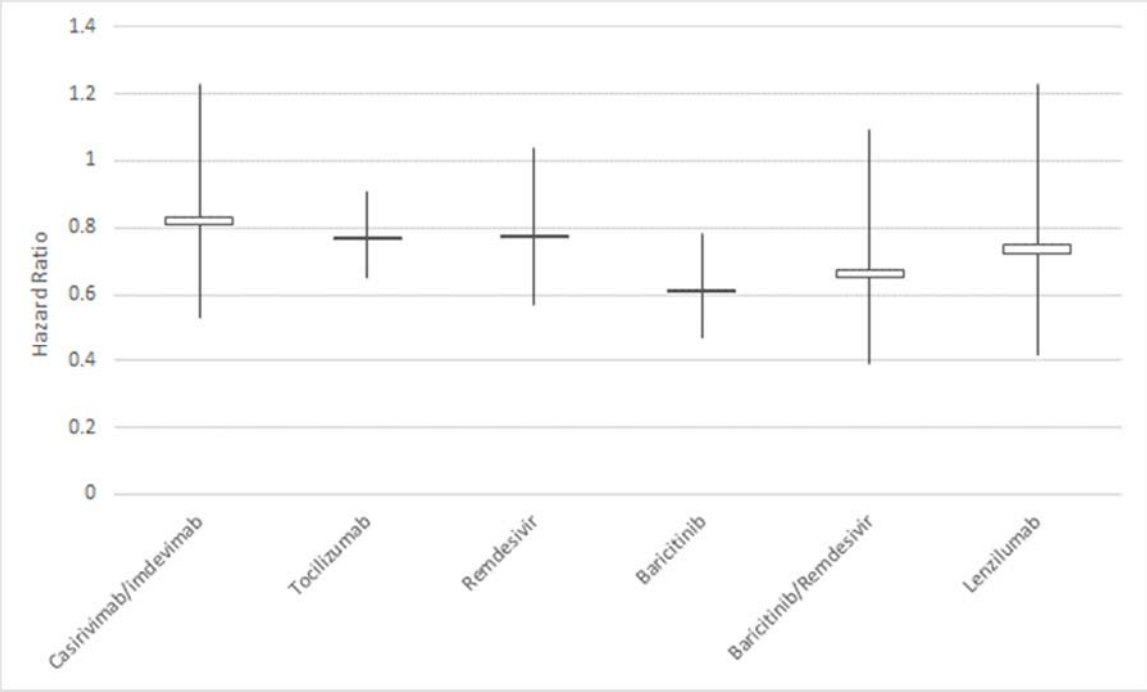

Figure 1: **The hazard ratio of avoiding death for interventions used to treat patients in hospital**

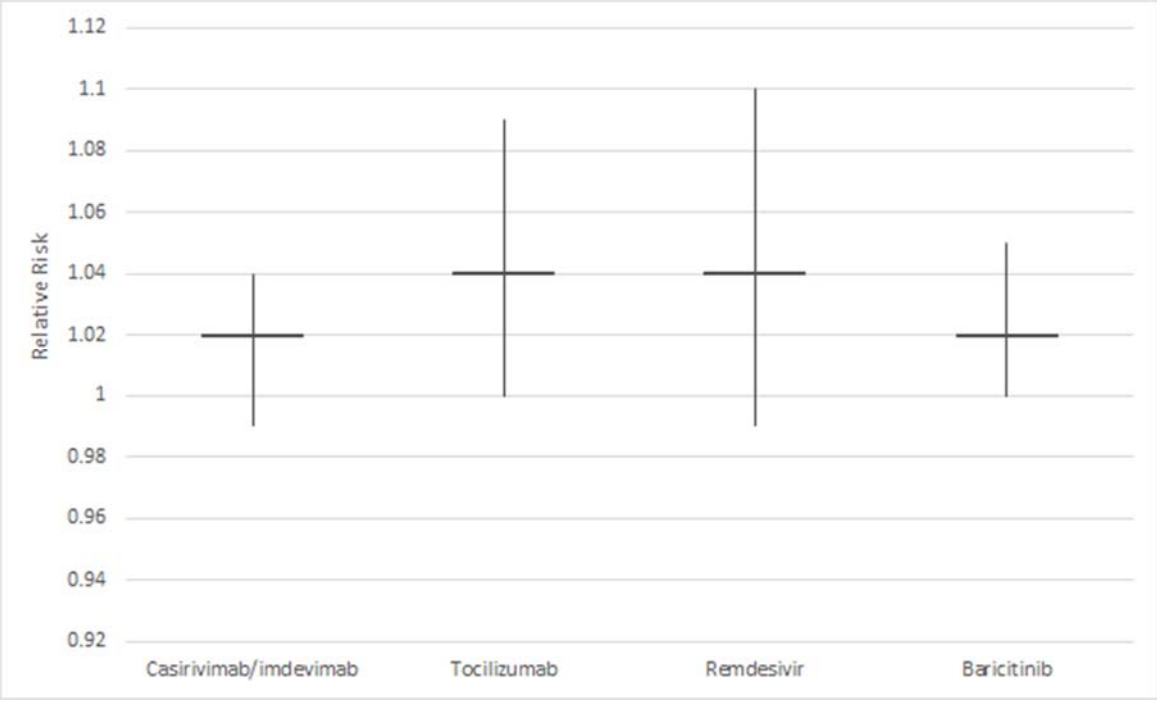

Figure 2: **The relative risk of clinical improvement at 28 days for interventions used to treat patients in hospital**

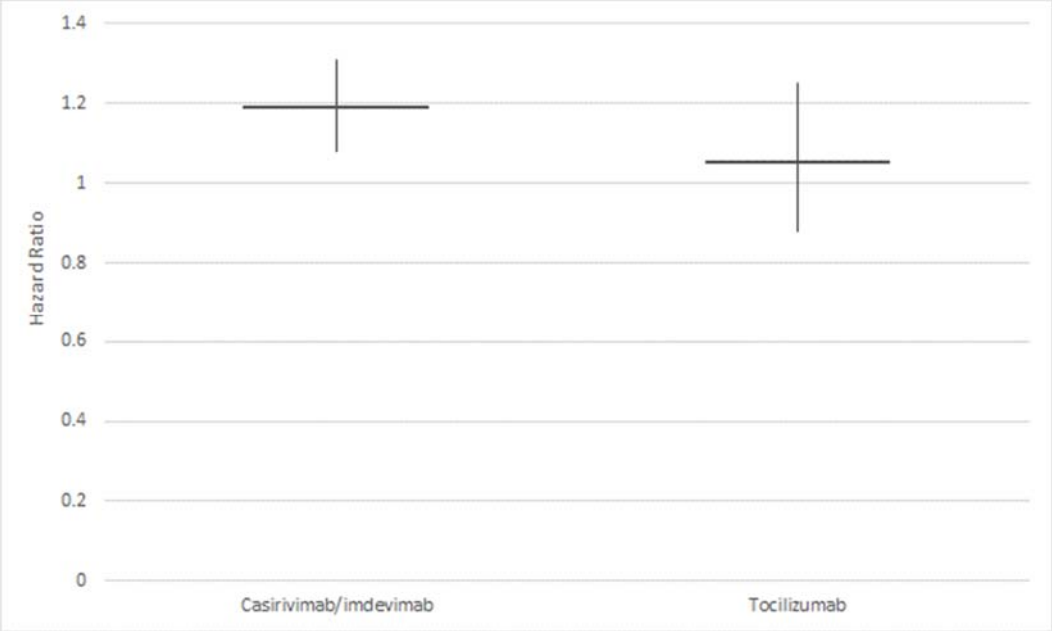

Figure 3: The hazard ratio of discharge for interventions used to treat patients in hospital

Figure 4 indicates the probability that each intervention is associated with greater deaths than SoC at 28 days. For tocilizumab and baricitinib, this probability is very low. For casirivimab/imdevimab and lenzilumab, the probability is in excess of 0.1.

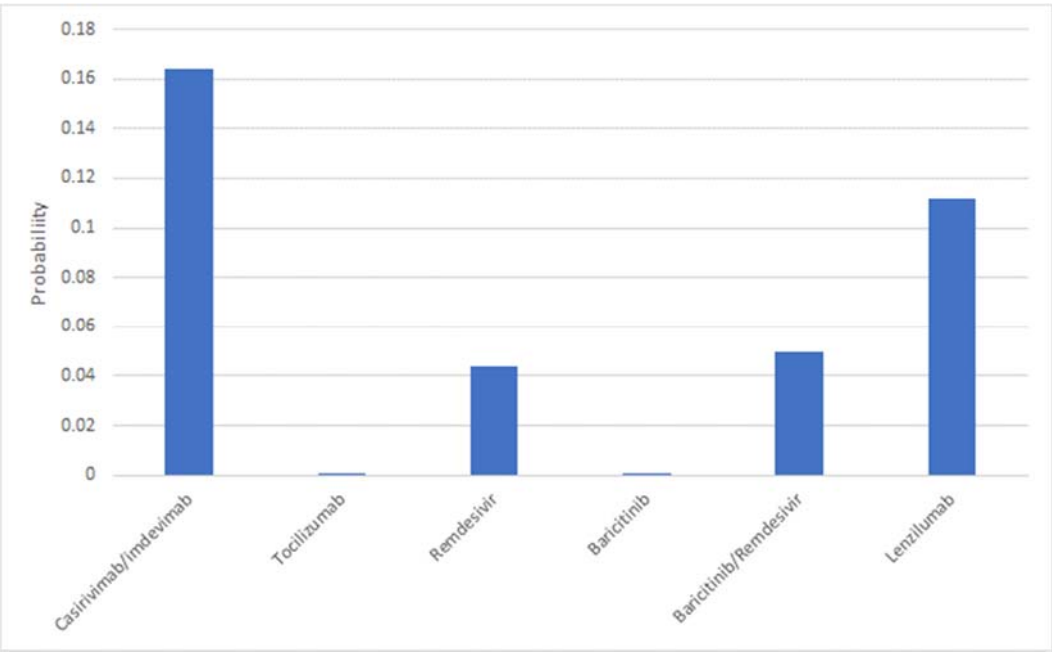

Figure 4: The probability that the intervention used in hospital is associated with increased mortality based on the lognormal distribution derived from the living systematic reviews

Figure 5 shows the large uncertainty in the ranking of each intervention in terms of efficacy, for example, baricitinib is the intervention with the greatest estimated probability of being ranked first, yet has similar probabilities of being ranked second, or of being third, fourth, fifth and sixth combined. To add additional uncertainty, the assumption that the efficacy estimate is transportable to different settings may be incorrect.

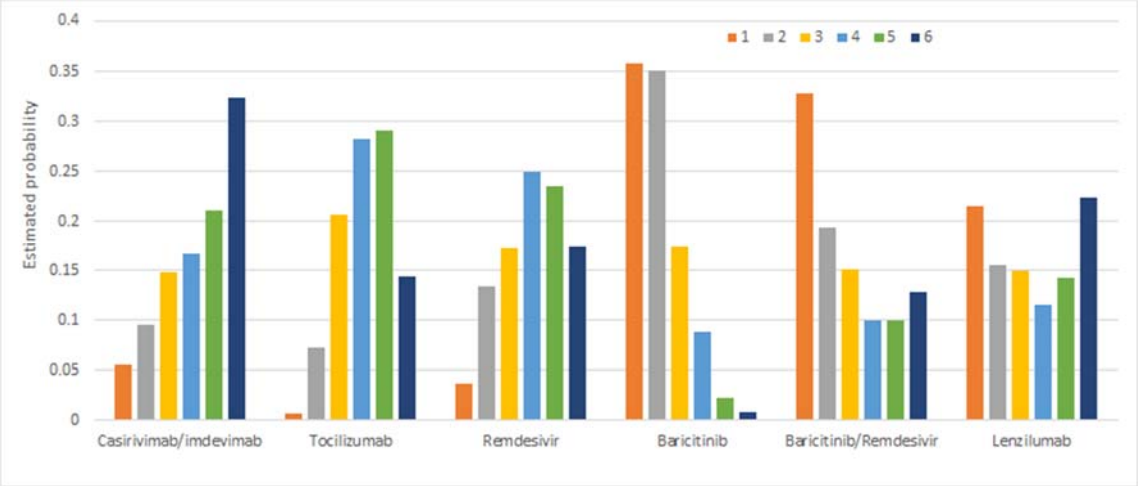

Figure 5: The estimated probability that each intervention is ranked first through to sixth for hazard ratio for mortality

To aid interpretation of the clinical efficacy data for interventions used to treat patients in the community, plots of i) the RR for avoiding hospitalisation or death at 28 days, ii) the RR for avoiding death at 28 days, iii) the probability that the intervention, based on the distribution extracted for clinical efficacy, is associated with more deaths at 28 days and iv) the ranked position of each intervention in 1000 joint samples of efficacy for all interventions are shown in Figure 6, Figure 7, Figure 8 and respectively. Figure 6 and Figure 7 consist of two horizontal lines for each intervention which sit on a vertical line. The vertical line shows the lower and upper 95% CIs whilst the lower horizontal line provides the median value, and the upper horizontal line provides the mean value from the distribution. When the mean and the median values are close these become indistinguishable in the figures.

From Figure 6, it can be seen that no CI crosses unity, although the width of the CIs differ, with that of nirmatrelvir/ritonavir having most precision, although the CI associated with this intervention overlaps with that of casirivimab/imdevimab, remdesivir, and sotrovimab indicating considerable uncertainty in the most clinically effective intervention.

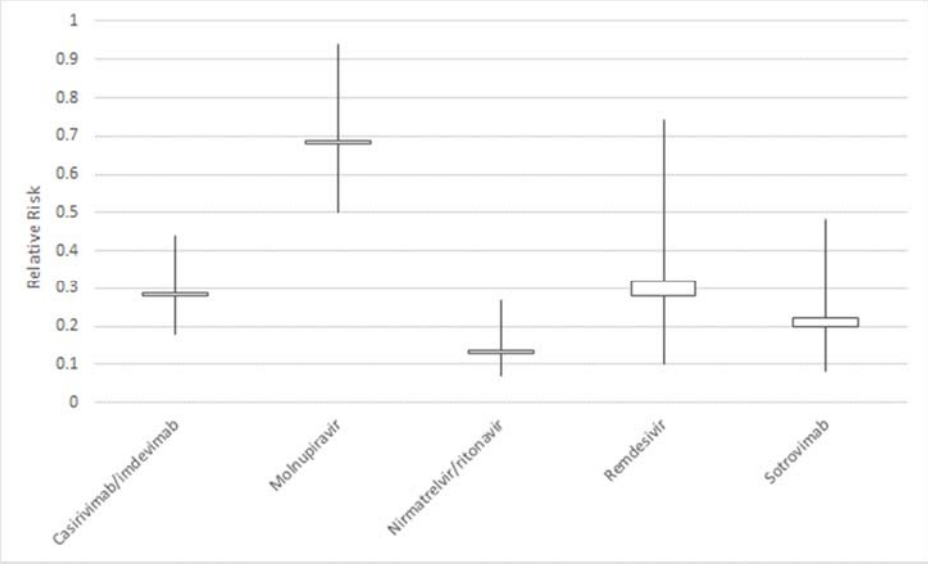

Figure 6: The relative risk of avoiding hospitalisation or death at 28 days for interventions used to treat patients in the community

For the avoidance of death at 28 days, Figure 7 indicates wide CIs for all treatments excluding molnupiravir and nirmatrelvir/ritonavir, in which the upper confidence limits do not exceed 1.0. The wide CIs are primarily related to the sample size and the small number of observed events in each arm.

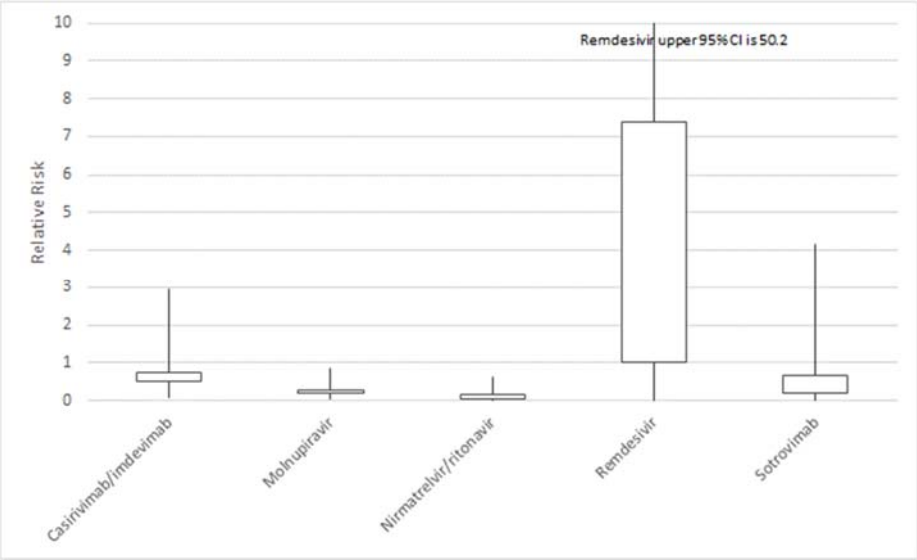

Figure 7: The relative risk of avoiding death at 28 days for interventions used to treat patients in the community

These wide CIs mean that there is a considerable probability (of more than 0.1) that all interventions except molnupiravir and nirmatrelvir/ritonavir could increase the risk of death, although this is a

frequentist interpretation of the distribution and does not consider any correlation between reduced hospitalisation rates and the reduced probability of death.

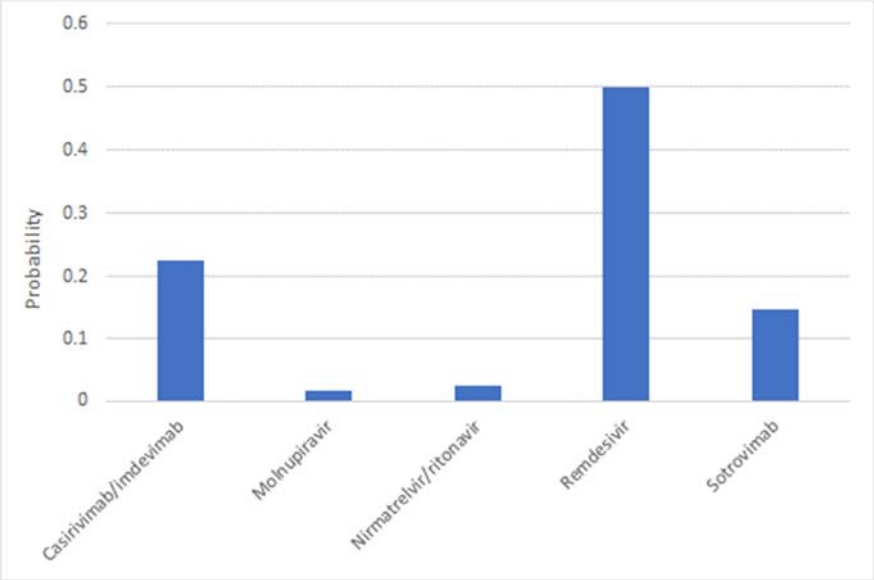

Figure 8: The probability that the intervention is associated with increased mortality based on the lognormal distribution derived from the living systematic reviews

Figure 9 shows large uncertainty in the ranking of each intervention in terms of efficacy, for example, whilst nirmatrelvir/ritonavir has a large estimated probability (greater than 60%) of being ranked first, it has a 19% chance of being ranked third or lower. To add additional uncertainty, the assumption that the efficacy estimate is transportable to different settings may be incorrect.

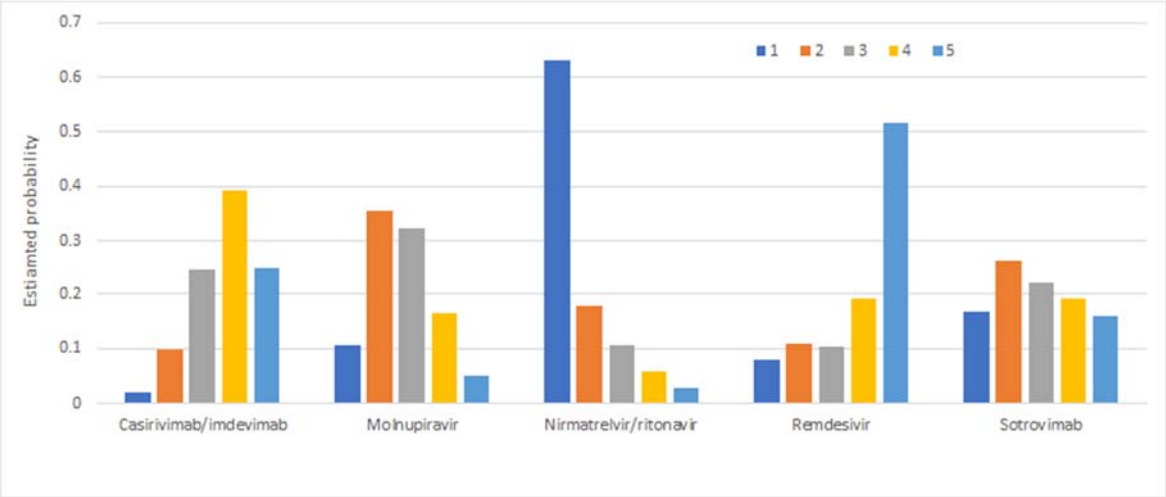

Figure 9: The estimated probability that each intervention is ranked first through to fifth for preventing mortality at 28 days

3. METHODS FOR THE COST-EFFECTIVENESS ANALYSIS

The model framework for assessing the cost-effectiveness of treatments for people hospitalised due to COVID-19 is an adaptation of the approach taken by Rafia *et al*.[13] This decision was made for two principal reasons. Firstly, that there is an overlap in the authors for both the Rafia *et al*. paper and this report, meaning that the model was available to the team reducing model construction time. Secondly, this model structure was used in a preliminary appraisal of remdesivir that was undertaken by a NICE panel meeting;[14] whilst no formal documents related to this meeting has been released an author of this report (MS) was on the panel and believes that no significant issues were raised relating to the model structure.

For non-hospitalised patients, the model structure was based on that outlined in an unpublished report by the NICE Decision Support Unit which provided an early economic evaluation of neutralising monoclonal antibodies and oral antivirals for treating COVID-19 prior to hospitalisation.[15] This consisted of a decision-tree approach where patients who ultimately required hospital admission were evaluated in the hospital-based structure, whereas those that didn't, remained in the community.

This section initially describes the model structures briefly, with later sections providing detail on the population of the parameters values used to generate the results within this report.

3.1 Model Structures

3.1.1 General model structure for hospitalised patients

The economic model was developed in Microsoft Excel and uses a partitioned survival approach (often referred to as area under the curve (AUC) approach) with three mutually exclusive health states; (a) discharged from hospital and alive, (b) hospitalised with or without COVID-19 and (c) death from any cause (COVID-19 or due to other causes).

Movements between health states are not explicitly modelled. Instead, the partitioned model estimates health state occupancy at each time interval. A simplified schematic of the model structure is shown in Figure 10. A daily cycle length is used until the end of parametric extrapolation, at day 70, after which a weekly cycle length is used. An initial daily cycle length was chosen to allow changes in treatment and/or hospitalisation and oxygen requirements that happen early in a patient's stay to be modelled at a granular level. A cohort partitioned survival approach was chosen due to the limited time and the absence of individual patient data (IPD). A limitation of this approach is that it is not possible to track individual patients in the model which may have allowed a better representation of the patient experience.

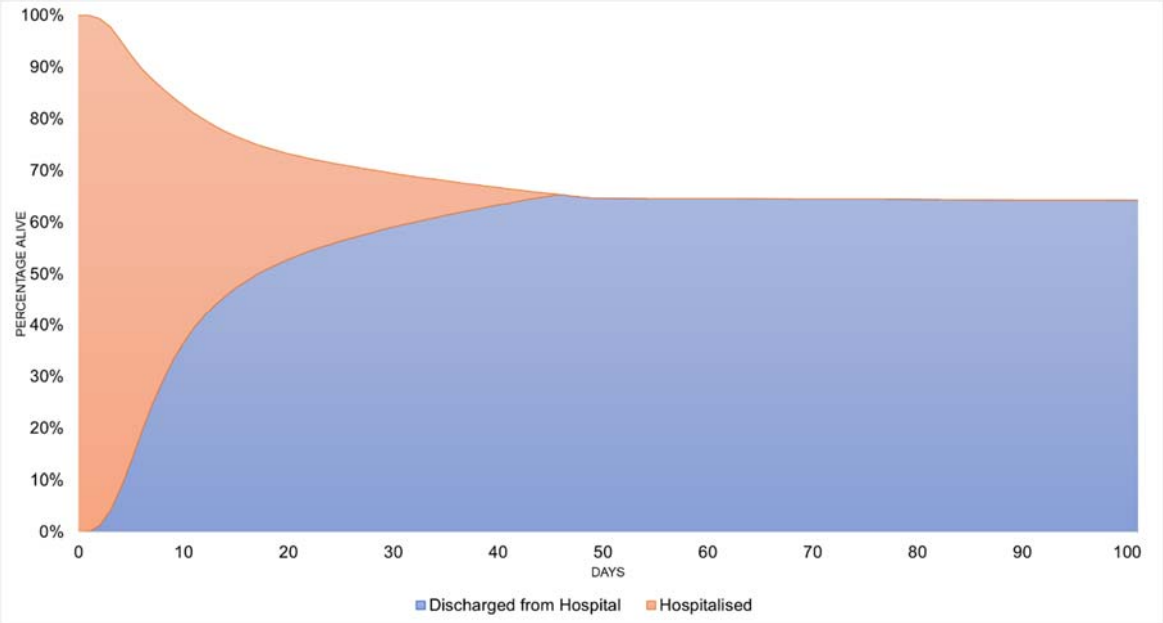

Figure 10: Simplified schematic of model structure (values are for illustration only)

Whilst in hospital, the 8-point ordinal scale of clinical status (an inverted version of the scale originally developed for severe influenza requiring hospitalisation as recommended by the World Health Organization (WHO)) used in the Adaptive COVID-19 Treatment Trial (ACTT-1) RCT,[16] and in the Remdesivir Effectiveness Evaluation Study (REES)[17] is used. This ordinal scale is described in Table 6 and is used in the model to (1) define the population at baseline in terms of oxygen requirements at the start of treatment, and (2) estimate changes in hospital/oxygen requirements during the hospital stay.

Table 6: Eight-points ordinal scale of clinical status used in ACTT-1[16]

	Clinical status
1	not hospitalised and no limitations of activities
2	not hospitalised, with limitation of activities, home oxygen requirement, or both
3	hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control or other nonmedical reasons)
4	hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions)
5	hospitalised, requiring any supplemental oxygen such as low-flow oxygen (LFO)
6	hospitalised, requiring non-invasive ventilation (NIV) or use of high-flow oxygen (HFO) devices
7	hospitalised, receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)
8	Death

When evaluating the interventions, patients enter the hospital model based on the marketing authorisation, where this has been granted, or in relation to the population in the key studies. A schematic of the positioning (or anticipated positioning when marketing authorisation has not been granted) of each intervention in Table 1 to Table 3 is provided in Table 7 with reference to the 8-point ordinal scale detailed in Table 6. Scale values of 1 or 2 describe patients with COVID-19 in the community whilst values 3 or higher describe patients in hospital. Only the latter group are relevant for the hospital model, although scale 3 does not require ongoing medical care.

Table 7: The positioning of treatments based on the 8-point ordinal scale

	Ordinal Scale						
Intervention	1	2	3	4	5	6	7
Cas and imd							
Molnupiravir	Δ	Δ	Δ				
Tocilizumab					†	†	†
Nirm and rit	Δ	Δ	Δ				
Remdesivir	⅄	⅄	⅄	⅄	⅄	⅄	⅄
Sotrovimab	Δ	Δ	Δ				
Baricitinib							
Bari and rem							
Lenzilumab							

Cas and imd – casirivimab/imdevimab; Nirm and rit – nirmatrelvir/ritonavir; Bari and rem – baricitinib and remdesivir

Δ – with one risk factor for developing severe illness, † - when receiving corticosteroids, ⅄- in patients with pneumonia

Interventions are permitted in cells shaded green and not permitted in cells shaded peach

Movements (improvement or worsening) between the different hospitalisation/oxygen requirements over time is modelled with each scale being associated with cost and HRQoL implications. During their hospital stay, patients are distributed according to their hospital/oxygen requirement derived from the placebo arm of the ACTT-1 study and additional assumptions where necessary. An illustration of movement between ordinal scales is shown in Figure 11 for patients who needed supplemental oxygen on hospital entry and when treated with SoC. The model assumes that all patients are discharged at 70 days. This may underestimate the costs and QALY losses associated with hospital care for the most efficacious drugs, although this is not expected to be a large limitation as the proportions of patients estimated to be in hospital at day 70 is relatively small.

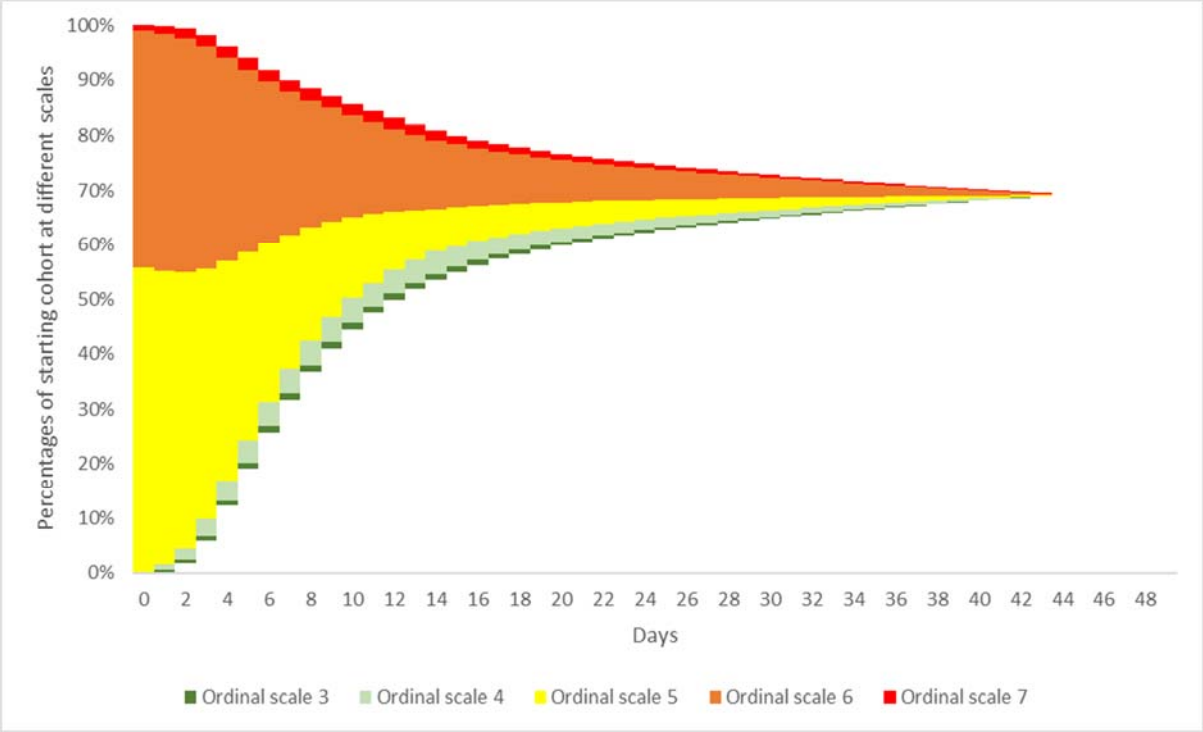

Figure 11: Illustration of ordinal scale occupancy during hospital stay of a cohort admitted to hospital requiring supplemental oxygen and receiving SoC treatment

Pivotal clinical trials/studies for treatments for COVID-19 used in this economic evaluation tend to follow patients and typically collect key clinical outcomes after 28 days of follow-up. It is, therefore, necessary to extrapolate beyond the duration of studies to capture the life expectancy and HRQoL following hospital discharge from COVID-19. Following discharge patients with COVID-19 are at an elevated risk of death,[18] emerging evidence suggest that some patients discharged with COVID-19 continue to experience symptoms and have a reduced quality of life,[19-28] may require re-admission due to COVID-19,[16, 29-33] and are at an elevated risk to experience multi-organ dysfunctions[18] (such as respiratory diseases, diabetes, cardiovascular, liver and kidney diseases) and may require long term management/monitoring.[34] Within the model, HRQoL reductions and additional costs associated with COVID-19 have been included; for brevity this has been termed 'long COVID'. In addition, the possibility of patients having an increased risk of death following COVID-19 has been modelled using a standardised mortality rate (SMR) applied to the mortality rates for an age- and sex-matched population.

Consequently, a seven-step approach is employed:

- Step 1: use of a parametric function (hazard spline model with 3 knots) fitted to the relevant outcomes (time to death and time to discharge) for all patients on the SoC arm in RECOVERY study[35] for the first 28 days, as used in Rafia *et al*.[13]

- Step 2: This parametric function is adjusted to reflect the outcomes at day 28 as reported in the literature to reflect the benefit of using corticosteroids, which represent the current SoC for patients in need of supplemental oxygen.[36] The model was calibrated as detailed in Section 3.6.2,
- Step 3: Treatment effect in the form of hazard ratios (HRs) or RRs for the interventions were applied to the SoC curves. Data were missing for some interventions with respect to the HR for discharge and the HR for clinical improvement (see Section 2.2). The EAG noted that given the values for other interventions, neither were large drivers of the cost-effectiveness results, and that there was no clear relationship between these and other variables. Therefore, as no values for interventions with data were markedly different from unity when compared with SOC, the EAG decided to use the values for SoC where data were missing,
- Step 4: As shown in Figure 11, ordinal scale occupancy in hospital is assumed to last until the distribution for overall survival (OS) and the distribution for time to discharge intersect. It was assumed in the model that none of the hospitalised cohort would remain in hospital after 70 days,
- Step 5: parametric extrapolation is employed to estimate the rates of death between day 28 until day 70 in the base case,
- Step 6: use of mortality rates from the general population, adjusted by an SMR for the assumed mean duration of long COVID to reflect the elevated risk of death in patients with COVID-19 discharged from hospital,
- Step 7: use of unadjusted mortality rate from the general population after the assumed mean duration of long COVID.

3.1.2 General model structure for non-hospitalised patients

The model structure used for assessing interventions that can be provided to patients with COVID-19 and at high-risk of hospitalisation is depicted in Figure 12. This is comprised a decision tree which simulates whether hospitalisation is required or not, and for those patients who are hospitalised, whether supplemental oxygen is required on admission.

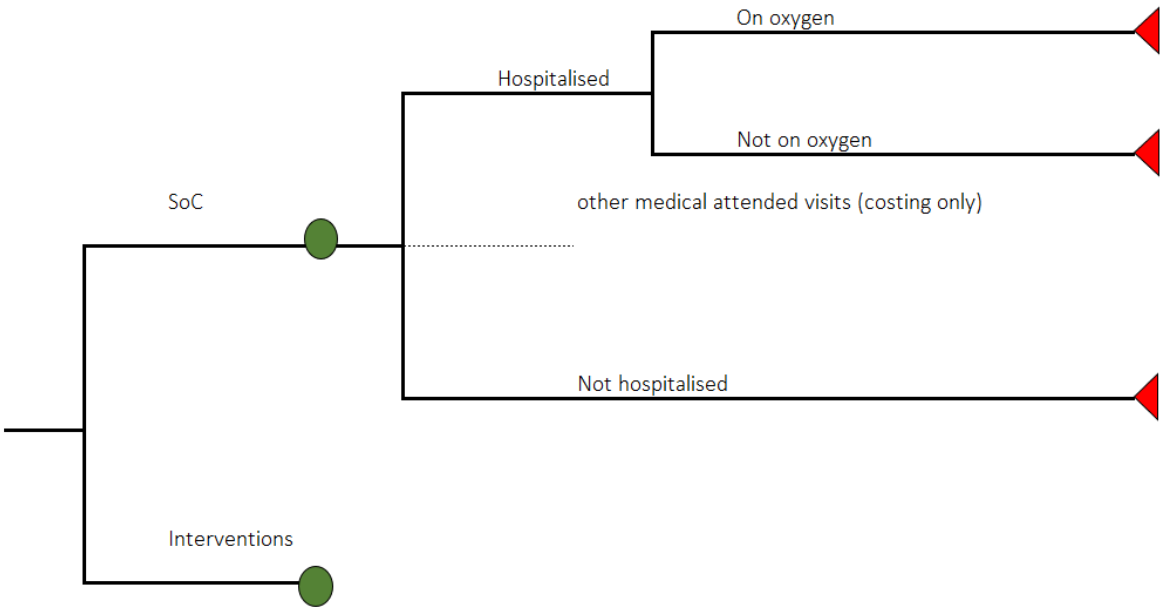

Figure 12: Structure of the decision tree used for the non-hospitalised cohort

Hospitalisation rates for patients on SoC were taken from Nyberg *et al.*[37] where recent risks of hospitalisations associated with the Omicron variant were reported. Hospital admission up to 14 days after positive test was approximately 0.9% (over 9,000 patients admitted from a reported million cases). This value differed from the rates reported in the UK Coronavirus dashboard, in this source there were two million positive cases in the past three months and a hundred thousand admissions (implying a rate of 5%). Clinical advice given to the EAG is that although the dashboard has a much larger sample size, the data is less nuanced and does not allow attributions of COVID-19 to admissions, and it may be the case that half of patients with COVID-19 in hospital, were not hospitalised due to COVID-19. Hence, the EAG adopted the 0.9% rate in its base case and increased it in sensitivity analyses (see Section 3.4).

Since interventions for this group of patients are indicated for those with high risk of hospitalisation, the underlying risk had to be inflated from the average. The EAG reviewed data presented in Hippisley-Cox *et al.*[38] where the QCovid3 model was used to calculate cause specific hazard ratios for COVID-19 hospital admissions after vaccination for subgroups with different comorbidities. Based on these data and clinical advice, the EAG applied a multiplier of 2 to the average hospitalisation rate for all patients to estimate the rate in people at high-risk of hospitalisation in the base case and increased it in sensitivity analyses (see Section 3.4). The proportion of hospitalised patients requiring supplemental oxygen was estimated from an ISARIC report[39] where the requiring oxygen of any level on admission was calculated at 81% (55% high flow oxygen, 16% non-invasive ventilation, and 10% invasive ventilation).

The model applies an RR to account for other medical attended visits (MAVs) (i.e., visits other than hospital admission) compared to admissions. This RR was estimated from data in Nyberg *et al.*[37] and was equal to 1.37 (1.23% MAV rate divided by 0.9% hospitalisation rate). Only costs were considered for MAVs and incorporated a visit to an accident and emergency department.

Two key clinical outcomes were extracted from the living systematic reviews: RRs for hospitalisation or death, and RRs for day 28 all-cause mortality, which are shown in Figure 6 and Figure 7 respectively. The RR for hospitalisation or death was assumed to apply for hospitalisations only due to the relatively low mortality rate compared to the admission rate. A separate RR was calculated for each intervention for deaths within hospital such that the overall RR for death at 28 days was consistent with the published estimate reported in Table 4 and Table 5. This methodology assumes that there were no deaths amongst non-hospitalised patients in the first 28 days of the model. The EAG believes that this limitation would have a negligible impact on the ICER.

For patients treated in the community it was assumed that there would be no further active treatment in hospital, and thus patients receive SoC only. This decision was based on the following factors: that the RRs for mortality for some of the interventions used in the community were substantially lower than the HRs for those treatments used in hospital where the midpoint efficacy was beneficial. For example, the RR for death for nirmatrelvir/ritonavir was 0.04 whilst the midpoint HR for death for baricitinib was 0.61, indicating that the residual effect of nirmatrelvir/ritonavir was larger than the impact of baricitinib, which was the most efficacious hospital intervention based on midpoint values. Furthermore, there is no evidence for the synergistic effects (or not) of using multiple interventions.

The modelling did not assess the logistics of treatment in the community, but the EAG notes that this could be a large factor in deciding which treatments could be preferred, as oral treatments could be more acceptable to patients and healthcare systems than treatments that are given intravenously or subcutaneously.

3.2 Clinical Parameters and Inputs Used in this Rapid Assessment

3.2.1 Baseline characteristics after discharge

Age and gender distribution are used in the economic model to estimate both the rate of mortality beyond the duration of clinical evidence and to estimate HRQoL beyond hospitalisation and for the non-hospitalised cohort. The baseline mean age for the modelled hospitalised cohort was calculated from weekly Office for National Statistics (ONS) data[40] reported in the middle of May 2022. For patients with COVID-19, these data included rates of hospital admissions per 100,000 people and number of deaths, by age bands. These values were multiplied by population data obtained from the

ONS[41] to estimate the absolute number of admissions and deaths by age band. The estimated number of discharged patients was calculated by subtracting the number of deaths from the number of admissions. Table 8 presents the estimated numbers and percentages calculated for admission, death and discharge conditional on age band.

Table 8: Hospital Admission and Death weekly numbers and percentages by age band compared to the whole population (mid May 2022)

Age band	Hospital Admission n(%)	Death n(%)	Discharge n(%)
0 to 14	196 (3.9%)	2 (0.3%)	194 (4.4%)
15 to 24	126 (2.5%)	0 (0.0%)	126 (2.9%)
25 to 44	478 (9.4%)	7 (1.0%)	471 (10.7%)
45 to 54	237 (4.7%)	6 (0.9%)	231 (5.3%)
55 to 64	545 (10.8%)	29 (4.3%)	516 (11.8%)
65 to 74	761 (15.0%)	97 (14.4%)	664 (15.1%)
75 to 84	983 (19.4%)	209 (31.0%)	774 (17.6%)
85+	1,737 (34.3%)	324 (48.1%)	1,413 (32.2%)
Overall	5,062 (100%)	674 (100%)	4,388 (100%)

If the midpoint of each age band represented the entire band, mean ages for admission, death and discharge are estimated at 70.6, 82.8 and 68.7 years respectively. For the non-hospitalised cohort, it was presumed that the average age would be lower than for the hospitalised group, as older age was believed to be associated with a greater risk of hospitalisation. Without data to accurately estimate the age for people with COVID-19 at high-risk of hospitalisation who do not get hospitalised, an arbitrary value of 65 years was assumed with sensitivity analyses using 60 and 70 years; patients who are hospitalised due to COVID-19 have the same characteristics as patients in the hospital model.

The distribution between sexes was taken from an Intensive Care National Audit & Research Centre report[42] which reported that 38.3% of patients admitted to hospital from May 2021, in a critically ill state due to confirmed COVID-19, were female.

3.2.2 Time to hospital death in patients initiating SoC (with or without corticosteroids)

The following steps were used to estimate the survival of patients admitted to hospital due to COVID-19 and receiving SoC based on current conditions such as vaccination status, SARS-CoV-2 variant, seropositivity and the widespread use of corticosteroids.

The Kaplan-Meier (KM) estimate for OS was taken from the control arm of the RECOVERY study,[35] and was digitised which allowed pseudo-IPD to be reconstructed based on the algorithm developed by Guyot et al (2012).[43] A spline model (hazard scale) with 3 knots was subsequently fitted to the pseudo-IPD using the R package flexsurv and employing a natural cubic spline function. This model was selected over standard parametric functions (such as the exponential, Weibull, Gompertz, Log-Normal, Log-Logistic, Gamma, Generalized Gamma) to increase the accuracy in the estimate and because parametric extrapolation beyond the observed period of the trial was limited to a maximum of 70 days. This distribution was then calibrated to the current data such that 73.5% of patients were alive for the population in need of oxygen and 86.0% of patients were alive for the population admitted with no need of supplemental oxygen at 28 days. These values were taken from a NICE rapid guideline[11] assuming that the outcomes for patients without corticosteroid use were generalisable to patients requiring supplemental oxygen and the outcomes for those patients corticosteroids were generalisable to patients not requiring supplemental oxygen. This decision was made as corticosteroids were only seen to be efficacious in patients not requiring supplemental oxygen. For illustration, Figure 13 shows the OS curves used in the model for SoC and remdesivir by oxygen requirement at hospital admission.

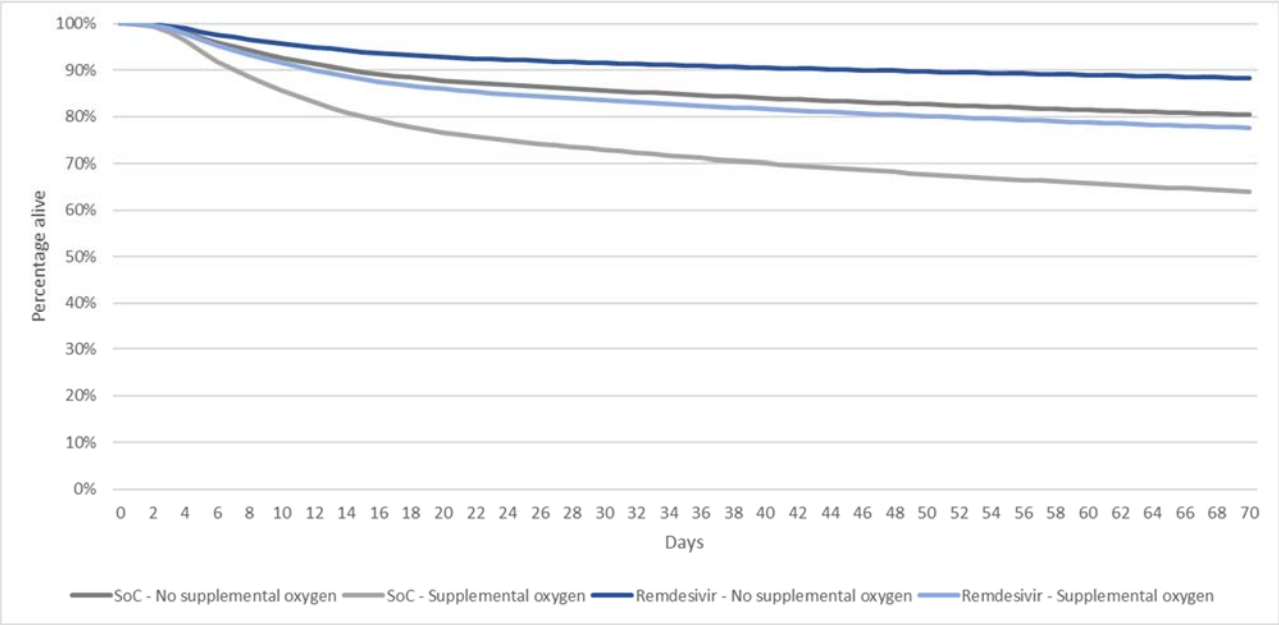

Figure 13: Illustration of OS curves used for the hospitalised cohort for SoC and remdesivir by oxygen requirement at entry

3.2.3 Time to discharge for patients initiating SoC

The KM estimate for time to discharge was taken from the control arm of the RECOVERY study,[35] and was digitised which allowed pseudo-IPD to be reconstructed based on the algorithm developed by Guyot et al (2012).[43] A spline model (hazard scale) with 3 knots was subsequently fitted to the pseudo-

IPD and was selected over standard parametric functions (such as the exponential, Weibull, Gompertz, Log-Normal, Log-Logistic, Gamma, Generalized Gamma) to increase the accuracy in the estimate and because parametric extrapolation beyond the observed period of the trial was limited to a maximum of 70 days. This distribution was then calibrated to the current data such that 64.0% of patients for the population in need of supplemental oxygen and 80.4% of patients with no need of supplemental oxygen were discharged at 28 days. These values were taken from a NICE rapid guideline[11] assuming that the outcomes for patients without corticosteroid use were generalisable to patients requiring supplemental oxygen and the outcomes for patients using corticosteroids were generalisable to patients not requiring supplemental oxygen. This decision was made as corticosteroids were only seen to be efficacious in patients not requiring supplemental oxygen. For illustration, Figure 14 shows the time to discharge curves used in the model for SoC and casirivimab/imdevimab by oxygen requirement at hospital admission.

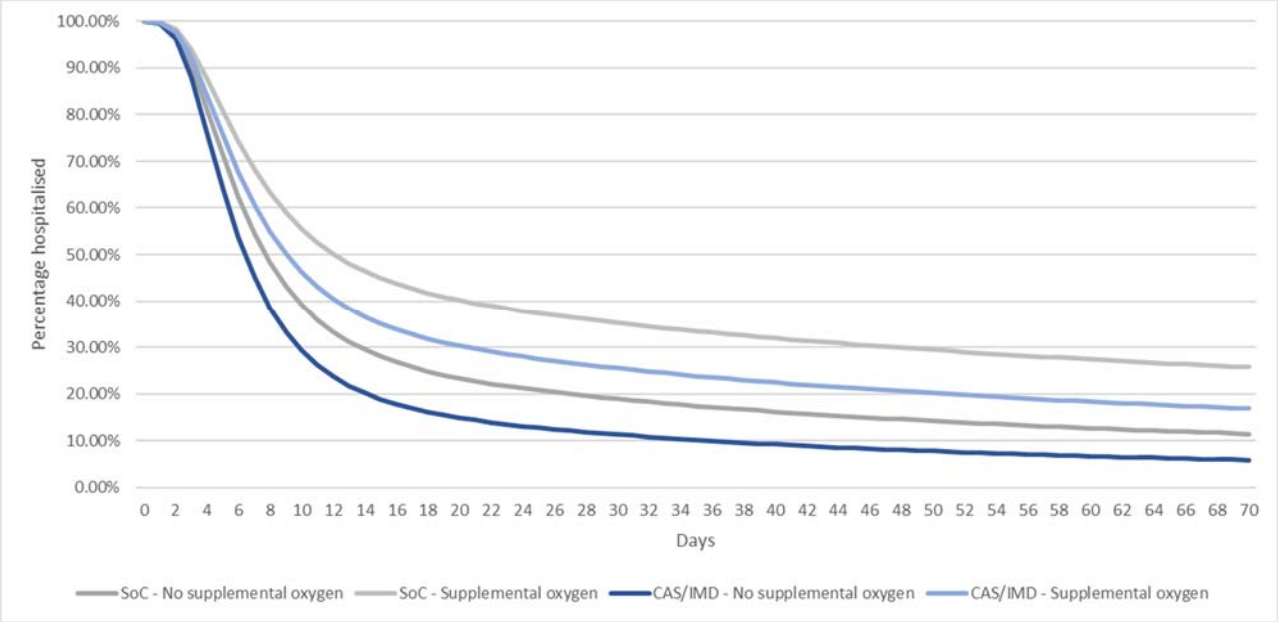

Figure 14: Illustration of time to discharge curves used for the hospitalised cohort for SoC and casirivimab/imdevimab by oxygen requirement at entry

3.2.4 Redistribution of patients according to supplemental oxygen/hospitalisation requirements

In order to estimate costs and QALYs during an average hospital stay, it was necessary to model how patients move between the 8-point ordinal scale as each scale has different consequences in terms of the costs of treatment and the HRQoL of the patient. Hospitalised patients with COVID-19 may receive supplemental oxygen, defined as LFO, HFO, and mechanical ventilation (MV). However, during their

hospital stay, patients may require more or less intensive management. Hospitalised patients are divided into five states, which correspond to ordinal scales 3 to 7.

3.2.4.1 Assumed distribution of patients on the 8-point ordinal scale on hospital entry

By definition, all patients admitted to hospital due to COVID-19 without the need for supplemental oxygen are in ordinal stage 4. For patients requiring supplemental oxygen, data from ACTT-1[16] which reported the distribution of ordinal score by treatment for placebo on admission to hospital were used. These data however do not reflect the distribution of current admissions as the percentage requiring IMV or ECMO (ordinal stage 7) was 46%, however a recent value suggests that this was only 1%.[42] The distribution from ACTT-1 was adjusted such that only 1% of patients resided in ordinal stage 7 with those patients reallocated from ordinal stage 7 being redistributed between ordinal stages 5 and 6, according to their relative weight in the ACTT-1 study. Table 9 and Table 10 show the proportions of patients across the ordinal health stages at baseline for those requiring supplemental oxygen and those not requiring supplemental oxygen respectively.

3.2.4.2 Distribution of hospitalised patients between the ordinal stages on SoC at day 14

Beigel *et al*. report data from the ACTT-1 study[16] for the placebo arm which detailed the ordinal stage distribution at baseline and 14 days later. Because of small numbers, which would have meant that movement between some stages was impossible, a continuity correction was added for all possible transitions, splitting 1 new observation at day 14 equally over the five ordinal scales.

However, ACTT-1 was an early study and there have been many changes such as a vaccination programme, increased use of corticosteroids and changes in SARS-CoV-2 variants. These changes have meant that the results from this study are no longer generalisable to the UK, particularly in terms of the proportion of patients who reach ordinal scale 7 and require IMV or ECMO. In ACTT-1, the EAG calculated that the percentage of patients' time spent in ordinal scale 7 was 48%, contrastingly, this value has been reported in May 2022 to be only 4.12%.[44] The ACTT-1 data was calibrated so that the percentage of time in ordinal stage 7 was equal to 4.12%, with the patients no longer allocated to ordinal scale 7 being allocated to ordinal stage 6 instead. The decision to allocate to ordinal stage 6 was to avoid a situation where the predicted outcomes for patients at stage 7 on hospital entry were better than those for patients admitted at ordinal stage 6. The estimated proportions of patients in hospital across the ordinal health stages at day 14 are shown in Table 9 and Table 10 for patients not requiring supplemental oxygen and those requiring it respectively.

Table 9: The distribution of hospitalised patients not requiring supplemental oxygen on entry to hospital and at day 14

Ordinal Health Scale	Assumed proportion on entry to hospital (day 0)	Assumed proportion of patients alive at day 14
3	0%	21%
4	100%	36%
5	0%	26%
6	0%	14%
7	0%	3%

Table 10: The distribution of hospitalised patients requiring supplemental oxygen on entry to hospital and at day 14

Ordinal Health Scale	Assumed proportion on entry to hospital (day 0)	Assumed proportion of hospitalised patients at day 14
3	0%	4%
4	0%	15%
5	56%	28%
6	43%	46%
7	1%	7%

3.2.4.3 Movement between ordinal scales between day 0 and day 14

We assumed that the distribution of patients changes linearly from the distribution at baseline to the proportions assumed at day 14; for simplicity these proportions were assumed to remain constant after day 14. Figure 15 provides the assumed splits between ordinal scales over a 28-day period.

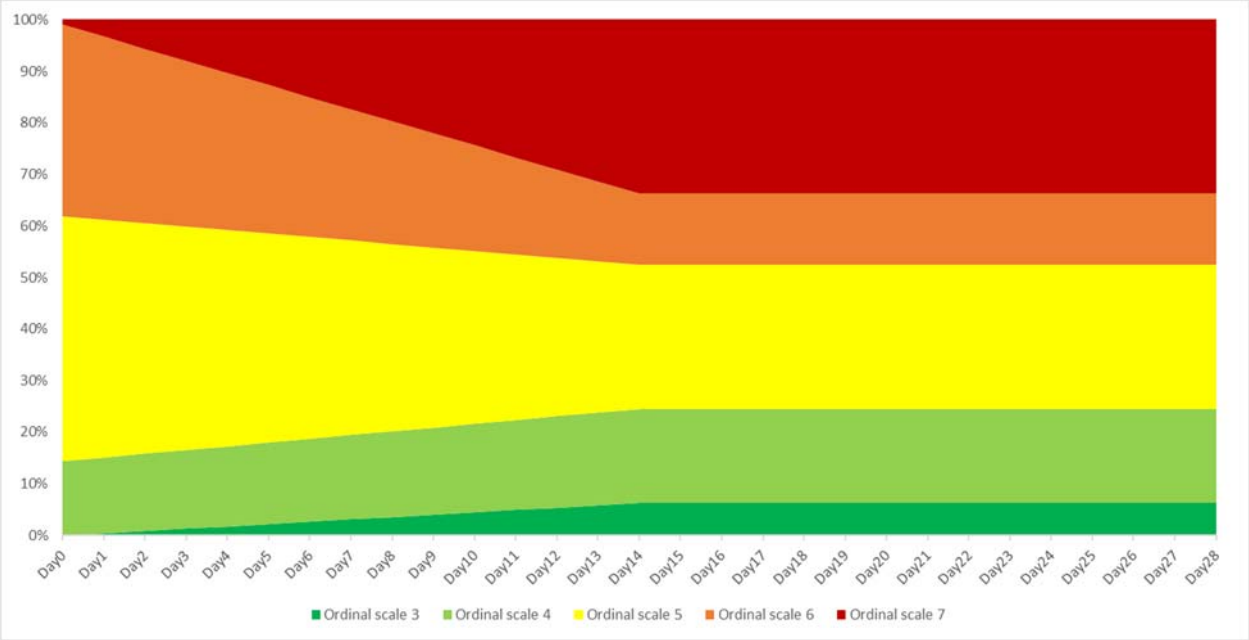

Figure 15: Linear assumptions for distribution across the five ordinal scales during hospital stay

3.2.5 Treatment effects for interventions compared with SoC

The treatment effects for interventions are summarised in Table 4 and Table 5. Where data were not available for clinical improvement or time to discharge a value of 1.0 was used as the model results were not sensitive to these values within the observed range associated with other interventions.

3.2.6 Duration of treatment/number of doses

The dosage information data were taken from the NICE COVID-19 rapid guideline.[11] Where either the dosage or the duration of treatment was not available, this information was taken from alternative sources. Table 11 summarises the dosage information used in the model.

Table 11: Dosing information of the interventions included in the model

Intervention	Dosing	Source
Casirivimab/imdevimab	600 mg of both drugs administered together once	Table 1
Molnupiravir	800 mg twice daily for 5 days*	NICE guideline[11] and Table 1
Tocilizumab	Single dose of 8 mg/kg with a maximum of 800 mg. Assumed 50% will receive the maximum dose with the rest getting 600 mg	NICE guideline, Table 1 and an assumption
Nirmatrelvir/ritonavir	300 mg of nirmatrelvir and 100 mg of ritonavir twice daily for 5 days*	NICE guideline and Table 2
Remdesivir	100 mg once daily for 3 days	NICE guideline
Sotrovimab	500 mg single infusion	Table 2
Baricitinib	4 mg once daily for 14 days or discharge whichever earlier	Table 3 and COVID-NMA Initiative
Lenzilumab	Three 600 mg doses delivered 8 hours apart	Table 3

*The dosing information was not used in the model as the overall course cost was derived from an Institute for Clinical & Economic Review report[45] as requested by NICE

3.2.7 Mortality rate assumed post-hospitalisation and for those people who did not require hospital admission

The unadjusted rate of mortality for the general population is taken from the England and Wales life table 2018-2020.[46] After discharge, patients hospitalised with COVID-19 were assumed to be at an elevated risk of death whilst they have long COVID. An SMR of 7.7 (7.2 – 8.3) was applied based on the RR reported by Ayoubkhani *et al.*[18] which was estimated from 47,780 patients treated for COVID-19 in NHS hospitals and discharged alive, using matched-controls and which had a median follow-up of 140 days. This SMR was also applied to patients at high-risk in the community for the period in which they were simulated to have long COVID.

3.2.8 Serious Adverse Events

Whilst the living systematic reviews allowed the relative risks related to SAEs to be extracted, on inspection these were not events related to the unwanted impacts of the interventions but were conditions related to severe COVID-19. As such, many interventions were associated with less SAEs than SoC, which is generally atypical for efficacious pharmacological treatments. As the model was explicitly tracking the severity of patients through the use of the 8-point ordinal scale the EAG decided to omit SAEs from the model.

3.2.9 Long Covid

The prevalence of long COVID within the wider community has been taken from an ONS report dated the 6th May 2022,[47] which in supplementary tables reports adjusted model estimates for long COVID of any severity and at any point since the last vaccine of: 8.7% of double-vaccinated patients and 8.0% of triple-vaccinated patients, who had the Omicron BA 1 variant; and 15.9% of double-vaccinated patients and 8.6% of triple-vaccinated patients, who had the Delta variant. Having noted the relatively wide CIs for the ONS estimates, the difference depending on vaccination status (with no data reported for unvaccinated patients) and the method it proposes to use for estimating the duration of long COVID (described below), the EAG assumed that 10% of patients in the community who were at high-risk of severe COVID-19 but did not need hospitalisation would experience long COVID. The EAG was not aware of any evidence on the impact of community treatment on the incidence of long COVID and thus it was assumed that this was independent of treatment.

The duration of long COVID-19 was estimated from an ONS publication dated the 1st of June 2022.[48] This stated that of people with self-reported long COVID, defined as "*symptoms continuing for more than four weeks after the first suspected coronavirus (COVID-19) infection that were not explained by something else*" 72% of people had been first infected by COVID-19 (or suspected they had) at least 12 weeks earlier, 42% were infected at least one year previously, and 19% at least two years previously. This publication also reports that 22% of people had suspected they were infected by COVID-19 less than 12 weeks previously; it was not clear to the EAG why the addition of the proportion of patients less than 12 weeks, and 12 weeks or more, did not add up to 100%, but only 94%.

Simple parametric distributions were fitted to the three reported estimates of at least 12 weeks duration (72% with long COVID at 12 weeks, 42% at 1 year, and 22% at 2 years). A Gamma distribution (shape = 100.547, scale 0.644), a Weibull distribution (shape =0.749, scale 57.268) and a lognormal distribution (mean = 3.468, standard deviation 1.562 (on the log scale) were observed to fit the data well. The mean survival times from these distributions were 64.7 weeks (Gamma), 68.3 weeks (Weibull) and 108.6 weeks (lognormal). The plots using the Gamma and lognormal distributions, which had the lowest and highest values are shown in Figure 16.

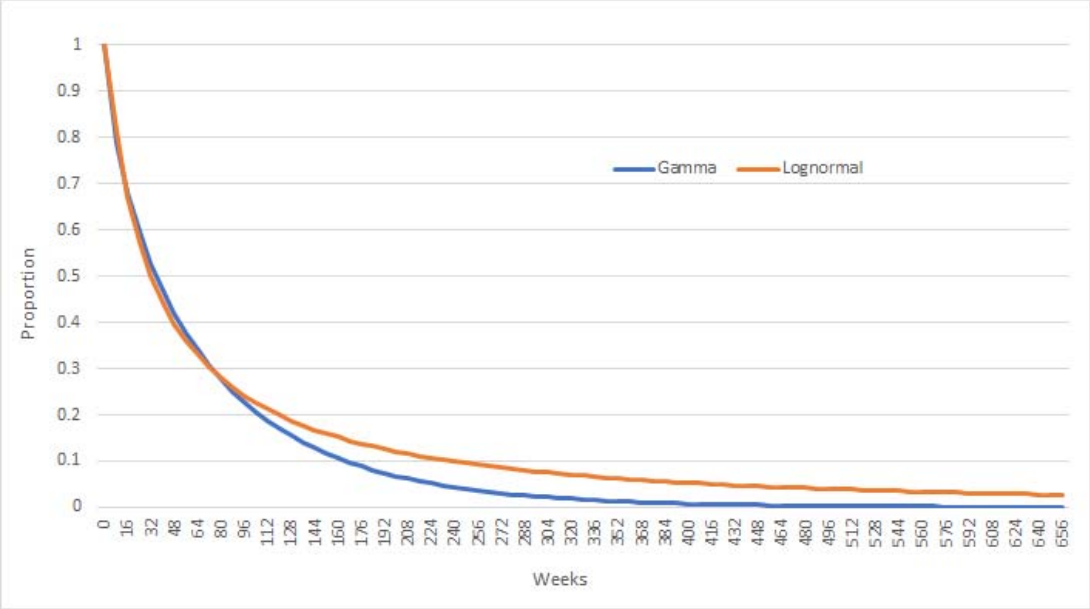

Figure 16: Assumed duration of long Covid

For its base case the EAG assumed the lognormal distribution was most appropriate, but undertook sensitivity analyses halving and doubling the mean duration, the range of which includes the mean from the Gamma distribution. The reason for this was that based on the previous ONS report, on which the EAG had conducted similar analyses, it was seen that the mean time with long COVID had increased, and the data is relatively immature and may be administratively censored. The EAG notes that its analyses are simplistic as formal survival analysis methods have not been used, and that it does not assume that all patients must have long COVID for at least 4 weeks, as used in some definitions but believes that the analyses undertaken are informative for decision making despite this limitation.

From Evans *et al*.[49] it is estimated that at approximately 6 months, 51.7% of patients with non-missing data (n=830) reported that they had not recovered from COVID-19; this value increases to 71.2% when patients stating they were not sure if they had recovered were included. The patients included in the study were hospitalised early in the pandemic (between March and November 2020) and it is unclear how generalisable this result is to patients hospitalised in 2022. The best-fitting gamma and log-normal distributions shown in Figure 16 estimate the proportions of patients not recovered from long COVID to be 57.8% and 55.3% at 26 weeks which is similar to the value reported in Evans *et al*.[49] Given the uncertainty in patients who stated they were not sure if they had recovered, a simplistic assumption was made that all patients hospitalised due to COVID-19 would suffer long COVID. The EAG was not aware of any evidence on the impact of hospital treatment on the incidence of long COVID and thus it was assumed that this independent of treatment.

3.3 Costs and Health-Related Quality of Life

3.3.1 Drug acquisition costs

Drug acquisition costs were supplied to the EAG by NICE. This included the list price for remdesivir, tocilizumab, baricitinib, lenzilumab, and sotrovimab. However, list prices were not available for molnupiravir, casirivimab/imdevimab, and nirmatrelvir/ritonavir. NICE requested that placeholder prices be used which were estimated from an Institute for Clinical & Economic Review report (dated March 2022) for molnupiravir and nirmatrelvir/ritonavir,[45] and that the price for sotrovimab was used for casirivimab/imdevimab. All analyses in this report are conducted at the list or placeholder prices, with analyses using the Patient Access Scheme (PAS) discounts for tocilizumab and baricitinib included in a confidential appendix. For corticosteroids, daily costs were assumed negligible compared to the in-hospital day cost and were not included for simplicity. Table 12 summarises the list prices used in the model with assumptions done when necessary.

Table 12: List prices of interventions used in the model

Intervention	List price	Notes
Casirivimab/imdevimab	£2209.00	As requested by NICE, the price of sotrovimab has been used as a placeholder
Molnupiravir	£579.74	The Institute for Clinical & Economic Review report[45] states $707 as the treatment course price. An exchange rate of $1 = £0.82 was assumed.
Tocilizumab	£512.00 £256.00	Price for 1 vial of 400 mg tocilizumab Price for 1 vial of 200 mg tocilizumab
Nirmatrelvir/ritonavir	£433.78	The Institute for Clinical & Economic Revie report[45] states $529 as the treatment course price. An exchange rate of $1 = £0.82 was assumed.
Remdesivir	£340.00	Price for 1 vial of 100 mg remdesivir
Sotrovimab	£2209.00	Price for 1 vial of 500 mg sotrovimab
Baricitinib	£805.56	Price for a pack of 28 tablets, each contains 4 mg baricitinib
Baricitinib and remdesivir	As component interventions	As component interventions
Lenzilumab	£7300.00	Price for 10 vials, each contains 92 mg of lenzilumab

3.3.2 Administration costs

It was assumed that the costs associated with treatment administration whilst in hospital would be incorporated in the unit costs associated with hospitalisation (see Section 3.3.3). Additional administration costs were assumed for intravenous treatment in the community, but for simplicity, not for oral or subcutaneous treatments. For each intravenous administration, a cost of £221 was incurred

which was that of NHS reference code SB12Z.[50] Within the analyses it has been assumed that there is likely to be a delay in patients receiving intravenous casirivimab/imdevimab and that a subcutaneous version would be used instead.

3.3.3 Unit costs associated with hospitalisation

The unit costs per hospital bed day are taken from the NHS National Schedule of NHS costs 2019-2020.[50] The NHS codes used are detailed in Table 13.

Table 13: The unit costs by ordinal scale used in the economic model and Utility values/decrement in HRQoL

Ordinal scale	Clinical status	Unit cost	Source	Utility decrement (unless stated)	Source
3	hospitalised, no longer requiring ongoing medical care	£378	National Schedule of NHS costs 2019 – 2020[50] For non-elective excess bed days: (Total cost of bed days / number of bed days) = £125,088,847 / 331,177	0.36	Wilcox et al (2017)[51]
4	hospitalised, not requiring supplemental oxygen	£390	Weighted average National Schedule of NHS costs 2019 – 2020[50]; Rehabilitation for respiratory disorders (VC40Z)		
5	hospitalised, LFO	£633	National Schedule of NHS costs 2019 – 2020[50]; Regular day or Night admission; Other respiratory disorders, single intervention, CC score 0-4 (DZ19K)	0.58	Hollmann et al (2013)[52]
6	hospitalised, HFO or NIV	£1096	National Schedule of NHS costs 2019 – 2020[50]; Adult Critical Care, 0 Organs Supported (XC07Z)		
7	hospitalised, receiving IVM or ECMO	£1703	Weighted average National Schedule of NHS costs 2019 – 2020[50]; Adult Critical care one or more organs supported (XC01Z-XC06Z)	Utility value of 0	assumption

HFO: high-flow oxygen; IVM: invasive mechanical ventilation; LFO: low-flow oxygen; NIV: non-invasive ventilation

3.3.4 Costs associated with COVID-19 for outpatients or following discharge

3.3.4.1 Monitoring costs

For simplicity, monitoring/follow-up was assumed to occur in the first year only. Following discharge, patients were assumed to undergo 2 chest X-rays and 6 GP e-consultations on average related to their COVID-19 as in Rafia *et al.*[13] A one-off cost of £384 was applied to all patients assuming the cost of a chest X-ray was £44 (taken from Stroke *et al.*[53] and inflated to 2019/2020 prices using NHSCII pay and prices indices[54]) and the cost associated with a GP e-consultation was £49.[54]

3.3.4.2 Costs associated with long COVID

The EAG assumed that management costs for long COVID was similar to the management of chronic fatigue syndrome. For time constraints, the EAG pragmatically searched for literature and found an economic evaluation study evaluating multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome in the Netherlands.[55] Healthcare resource use included GP care, mental healthcare specialist, paramedical care, medical specialist care, hospital care, medications, alternative healers, company physicians, and the evaluated interventions. The EAG substituted the company physician cost with GP care and noted the similarity in costs between arms when intervention costs were excluded. An average of the two costs was used, which resulted in an annual cost of €1195. After conversion using the average of the HMRC rates[56] published in January and December 2016, and inflation using NHS cost inflation index pay and prices indices,[54] an annual cost of £1013 was estimated for patients with long COVID.

3.3.5 Health-related quality of life

3.3.5.1 Unadjusted baseline utility value by age

Baseline utility values (prior to any decrements/adjustments) are taken from Ara and Brazier based on the age-sex utility values (EQ-5D) in the UK.[57]

3.3.5.2 HRQoL during the hospitalisation episode

Due to the nature of this rapid assessment, no formal systematic review of the literature was conducted to identify the most appropriate utility values. Hence, utility values (or decrements) were sourced from Rafia *et al.*[13] which estimated the cost-effectiveness of remdesivir.

3.3.5.3 HRQoL related to long COVID

A paper by Evans *et al.*[49] reported the impact on HRQoL following hospitalisation due to COVID-19. The EQ-5D 5 level (EQ-5D-5L) prior to hospitalisation was observed to be 0.84 but was 0.71 after hospitalisation, suggesting a utility impact of long COVID of 0.13. This value is not dissimilar to a reported utility loss in patients following severe sepsis.[58] It was assumed that this disutility would apply to all patients for their duration of long COVID.

3.4 Analyses undertaken

Probabilistic sensitivity analysis (PSA) is the most appropriate method for providing the most accurate estimation of the ICER, however this could not be undertaken within the deadlines of the project. This was because there was a need to calculate the proportion of patients treated in the community who are admitted to hospital, and die within this episode, as the model assumed that deaths due to COVID-19 only occurred in the hospital (see Section 3.1.2). This calculation added considerable computational time.

To circumvent this problem three 'deterministic' analyses were run, which were i) using the mean value for clinical effectiveness data, and the median for all other parameters, ii) using the most favourable limit of the 95% CI for clinical effectiveness data, and the median for all other parameters, and iii) using the least favourable limit of the 95% CI for clinical effectiveness data, and the median for all other parameters. For brevity, the analyses have been referred to as 'mean efficacy', 'high efficacy' and 'low efficacy' respectively. One exception was made in relation to the 'mean efficacy' which was for the use of remdesivir in a community setting. This was because there were no observed deaths in either arm, and using a mean HR of 7.36 was assumed to be overly punitive and a value of 1.00 was used instead. When operationalising these analyses, problems were encountered for the low efficacy values for three treatments for patients with COVID-19 at high-risk of hospitalisation in the community. This was because Excel generated a numerical error when the multiplier for RR of death for hospitalised patients treated with SoC was greater than 121 as, due to the number of decimal places used in Excel, the package was attempting to calculate the natural log of zero. As such, the EAG assumed that the upper limit of the 95% CIs for the RR of mortality at 28 days were 1.82 for casirivimab/imdevimab, 3.07 for remdesivir and 1.99 for sotrovimab, which were the values calculated when a multiplier of 121 was applied to the RR of death for hospitalised patients treated with SoC. The EAG notes that for all analyses no attempts of incorporating prior beliefs have been conducted and a frequentist approach using distributions derived from the raw data is used. The EAG comments that it may be clinically implausible that treatments which have a statistically significant beneficial HR relating to hospitalisation or death would be associated with increased RR of death at 28 days, but this limitation could not be addressed in the timescales of the project.

These analyses were supplemented by sensitivity analyses and are believed to provide the NICE appraisal committee with pertinent information relating to the true uncertainty in the decision problem, which will be much larger than any difference between the mean results from a PSA and from a deterministic analysis using the mean of the distribution. As the efficacy of treatments are assumed to be independent, then there is considerable uncertainty in the true treatment effect (see Figure 5 and

Figure 9) and it is plausible that one intervention had its 'low efficacy' value whilst another had its 'high efficacy' value.

Three sensitivity analyses were performed, which explored the impact of changing i) the duration of long COVID (ranging from half to double that of the base case), ii) changing the product of the rate of hospital admission in the community and the RR associated with people being at 'high risk' of hospitalisation from a value of 1.8% to 1.35% and 5.00% and iii) changing the average age of patients at high-risk of hospitalisation in the community from 65 years to 60 and 70 years.

The results presented provide the ICER, measured in terms of cost per QALY gained, for each intervention compared to SoC and also the efficiency frontier, which contains all interventions that are not dominated or extendedly dominated. For the efficiency frontier, the willingness to pay (WTP) at which the preferred treatment changes, presented in terms of cost per QALY thresholds, is provided.

For the sensitivity analysis, in order that a large number of results can be shown simultaneously, an incremental net monetary benefit, shortened to net monetary benefit (NMB) approach was taken comparing all interventions with SoC. Within this framework, the largest NMB is associated with the most cost-effective strategy at the stated cost-per-QALY threshold, and multiple strategies can be compared simultaneously, as the absolute difference in strategies in terms of cost, having monetarised health differences, can be easily determined. The formula for calculating NMB is the increase in QALYs associated with an intervention multiplied by a stated cost per QALY threshold minus the additional costs of associated with the intervention compared with the costs associated with SoC. If NMB is positive the intervention is cost-effective compared with SoC at the selected threshold; if the NMB is negative then the intervention is not cost-effective compared with SoC at the selected threshold. When multiple interventions are considered, the intervention with the greatest NMB would be interpreted as the most cost-effective intervention. For the analyses presented in this report, the cost per QALY threshold was set at £20,000 per QALY which is the lowest of NICE's published thresholds. NMBs were also provided in the base case results.

One limitation associated with the omission of PSA is that value of information analyses could not be conducted to assess the monetary implications of recommending an intervention that was not the most cost-effective and to put a ceiling on the expenditure of research addressing knowledge gaps. This is an area for future research.

3.5 The use of severity modifiers

The guidance from NICE is that if there is an absolute discounted QALY shortfall of less than 12 and that the proportional shortfall in discounted QALYs is less than 85% then no severity modifier should be applied in the decision problem, and that the ICER remains unchanged.

For patients admitted to hospital, the mean age was assumed to be 70.6 years and with 38.3% being female. Using these characteristics, the EAG calculated that the discounted QALYs associated with the general population would be approximately 9.05. Based on the results presented in Section 4, SoC is associated with estimated discounted QALYs of 4.65 for patients who require supplemental oxygen on admission and 5.84 for patients who do not require supplemental oxygen on admission. For those requiring supplemental oxygen, the absolute shortfall was 4.40 discounted QALYs and the proportional shortfall was 49%; these numbers are lower for those who do not require supplemental oxygen. As such, no severity modifier is applied for patients who are hospitalised due to COVID-19.

For patients at high-risk of hospitalisation in the community, the mean age in the base case was assumed to be 65 years. The 38.3% proportion of females used for hospitalised patients was assumed to be generalisable to patients at high-risk in the community. Using these characteristics, the EAG calculated that the discounted QALYs associated with the general population would be approximately 10.05. Based on the results presented in Section 4, the absolute shortfall in discounted QALYs for patients at high-risk of hospitalisation was less than 1, and the proportionate shortfall in discounted QALYs was 7%. Given these values, no severity modifier is applied for patients who are at high-risk of hospitalisation due to COVID-19.

4 COST-EFFECTIVENESS RESULTS

The cost-effectiveness results have been divided into three subsections. The first provides the results for hospitalised patients who require supplemental oxygen on admission, the second provides the results for hospitalised patients who do not require supplemental oxygen on admission with the third providing the results for patients at high-risk of hospitalisation in the community. Each of the three subsections are further divided to provide the results from the mean efficacy, high efficacy, and low efficacy scenarios.

The EAG stresses that, following NICE's recommendations, some prices are placeholders and that the PASs for tocilizumab and baricitinib are not included. This means that the results presented are not accurate representations of the true ICERs for some drugs. Results incorporating PASs, and NICE-suggested prices rather than the placeholders used in this report are contained in a confidential appendix.

4.1 Results for hospitalised patients who need supplemental oxygen on admission

4.1.1 Mean efficacy results for patients requiring supplemental oxygen on admission to hospital

The results of the mean efficacy analysis for patients requiring supplemental oxygen on admission to hospital are shown in Table 14. All interventions were estimated to have a cost per QALY gained compared to SoC below £20,000, with the majority less than £10,000. A full incremental analysis indicates an efficiency frontier of SOC for a WTP up to £3951, casirivimab/imdevimab for a WTP between £3951 and £6226, and baricitinib for a WTP over £6226.

Table 14: Mean efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	Cost per QALY Incremental Analyses (£)
SoC	12,116	4.65	-	-	-
Casirivimab/Imdevimab	13,570	5.02	3951	5905	3951
Tocilizumab	14,341	5.14	4535	7586	Extendedly Dominated
Remdesivir	15,229	5.12	6553	6386	Dominated
Baricitinib	16,619	5.51	5250	12,651	6226
Baricitinib/remdesivir	16,730	5.37	6406	9791	Dominated
Lenzilumab	21,889	5.19	17,880	1158	Dominated

† Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.1.2 High efficacy results for patients requiring supplemental oxygen on admission to hospital

The results of the high efficacy analysis for patients requiring supplemental oxygen on admission to hospital are shown in Table 15. All interventions were estimated to have a cost per QALY gained compared to SoC below £20,000, with the majority below £10,000. A full incremental analysis indicates an efficiency frontier of SoC for a WTP up to £1310, tocilizumab for a WTP between £1310 and £6456, casirivimab/imdevimab between £6456 and £17,781, and baricitinib and remdesivir for a WTP over £17,781. The costs associated with tocilizumab and casirivimab/imdevimab are lower than for other drugs due to the assumed higher rate of discharge of patients.

Table 15: High efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	Cost per QALY Incremental Analyses (£)
SoC	12,116	4.65	-	-	-
Tocilizumab	13,139	5.43	1310	14,590	1310
Casirivimab/Imdevimab	15,049	5.72	2724	18,597	6456
Remdesivir	18,251	5.62	6339	13,221	Extendedly Dominated
Baricitinib	18,966	5.87	5615	17,547	Extendedly Dominated
Baricitinib/remdesivir	21,329	6.08	6444	19,381	17,781
Lenzilumab	27,020	6.00	11,039	12,099	Dominated

[†] Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.1.3 Low efficacy results for patients requiring supplemental oxygen on admission to hospital

The results of the low efficacy analysis for patients requiring supplemental oxygen on admission to hospital are shown in Table 16. All interventions except for baricitinib and tocilizumab were dominated by SoC due to increased hazards of death associated with the upper limit of the 95% CI being above 1 (see Table 4). The ICERs for baricitinib and tocilizumab were both below £20,000. A full incremental analysis indicates an efficiency frontier of SoC for a WTP up to £4608 and baricitinib for a WTP over £4608.

Table 16: Low efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	Cost per QALY Incremental Analyses (£)
SoC	12,116	4.65	-	-	-
Casirivimab/Imdevimab	12,255	4.20	Dominated	-9083	Dominated
Baricitinib/remdesivir	12,595	4.47	Dominated	-4096	Dominated
Remdesivir	12,859	4.57	Dominated	-2368	Dominated
Baricitinib	14,296	5.12	4608	7279	4608
Tocilizumab	15,752	4.83	19,696	56	Dominated
Lenzilumab	17,979	4.20	Dominated	-14,830	Dominated

† Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.2 Results for hospitalised patients who do not need supplemental oxygen on admission

4.2.1 Mean efficacy results for patients requiring no supplemental oxygen on admission to hospital

The results of the mean efficacy analysis for patients not requiring supplemental oxygen on admission to hospital are shown in Table 17. With the exception of lenzilumab, all interventions were estimated to have a cost per QALY gained compared to SoC below £10,000, with the ICER for lenzilumab being greater than £20,000. A full incremental analysis indicates an efficiency frontier of SoC for a WTP up to £3053 and baricitinib for a WTP over £3053.

Table 17: Mean efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	Cost per QALY Incremental Analyses (£)
SoC	7068	5.84	-	-	-
Baricitinib	8611	6.34	3,053	8568	3053
Casirivimab/Imdevimab	8629	6.06	7,025	2884	Dominated
Remdesivir	8796	6.12	6,058	3976	Dominated
Baricitinib/remdesivir	9334	6.26	5,302	6280	Dominated
Lenzilumab	15,212	6.16	24,906	-1604	Dominated

† Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.2.2 High efficacy results for patients requiring no supplemental oxygen on admission to hospital

The results of the high efficacy analysis for patients not requiring supplemental oxygen on admission to hospital are shown in Table 18. All interventions were estimated to have a cost per QALY gained compared to SoC below £15,000. A full incremental analysis indicates an efficiency frontier of SoC for a WTP up to £2863, casirivimab/imdevimab between £2863 and £7646, baricitinib for a WTP between £7646 and £13,243, and baricitinib and remdesivir for a WTP over £13,243. The costs associated with casirivimab/imdevimab are lower than for other drugs due to the assumed higher rate of discharge of patients.

Table 18: High efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	Cost per QALY Incremental Analyses (£)
SoC	7068	5.84	-	-	-
Casirivimab/Imdevimab	8865	6.46	2863	10,761	2863
Baricitinib	9468	6.54	3396	11,734	7646
Remdesivir	9785	6.40	4787	8633	Dominated
Baricitinib/remdesivir	10,972	6.66	4759	12,502	13,243
Lenzilumab	16,991	6.61	12,763	5626	Dominated

[†] Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.2.3 Low efficacy results for patients requiring no supplemental oxygen on admission to hospital

The results of the low efficacy analysis for patients not requiring supplemental oxygen on admission to hospital are shown in Table 19. With the exception of baricitinib, all interventions were estimated to be dominated by SoC due to the 95% CI for these interventions being greater than 1 (see Table 4). A full incremental analysis indicates an efficiency frontier of SoC for a WTP up to £2820 and baricitinib for a WTP over £2820.

Table 19: Low efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	Cost per QALY Incremental Analyses (£)
SoC	7068	5.84	-	-	-
Baricitinib	7869	6.12	2820	4879	2820
Baricitinib/remdesivir	7929	5.72	Dominated	-3109	Dominated
Remdesivir	7969	5.79	Dominated	-1906	Dominated
Casirivimab/Imdevimab	8337	5.55	Dominated	-6156	Dominated
Lenzilumab	13,821	5.55	Dominated	-12,415	Dominated

† Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.3 Results for patients at high-risk of hospitalisation treated in the community

4.3.1 Mean efficacy results for patients at high-risk of hospitalisation

The results of the mean efficacy analysis for patients at high-risk of hospitalisation are shown in Table 20. Nirmatrelvir/ritonavir and molnupiravir were estimated to have a cost per QALY compared to SOC of below £15,000 with all other interventions having an ICER in excess of £60,000. A full incremental analysis indicates an efficiency frontier of SoC for a WTP up to £4439 and nirmatrelvir/ritonavir for a WTP over £4439.

Table 20: Mean efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	Cost per QALY Incremental Analyses (£)
SoC	413	10.05	-	-	-
Nirmatrelvir/ritonavir	670	10.11	4439	904	4439
Molnupiravir	1027	10.10	13,684	283	Dominated
Remdesivir	1923	10.07	88,320	-1,169	Dominated
Casirivimab/Imdevimab	2450	10.08	74,907	-1,493	Dominated
Sotrovimab	2662	10.09	65,922	-1,567	Dominated

† Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.3.2 High efficacy results for patients at high-risk of hospitalisation

The results of the high efficacy analysis for patients at high-risk of hospitalisation are shown in Table 21. Nirmatrelvir/ritonavir and molnupiravir were estimated to have a cost per QALY compared to SOC of below £15,000 with all other interventions having an ICER in excess of £20,000. A full incremental analysis indicates an efficiency frontier of SoC for a WTP up to £3895 and nirmatrelvir/ritonavir for a WTP over £3895.

Table 21: High efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	Cost per QALY Incremental Analyses (£)
SoC	413	10.05	-	-	-
Nirmatrelvir/ritonavir	675	10.12	3895	1087	3895
Molnupiravir	1001	10.11	9825	610	Dominated
Remdesivir	1934	10.12	23,051	-201	Dominated
Casirivimab/Imdevimab	2476	10.11	33,834	-844	Dominated
Sotrovimab	2674	10.12	33,840	-925	Dominated

[†] Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.3.3 Low efficacy results for patients at high-risk of hospitalisation

The results of the low efficacy analysis for patients at high-risk of hospitalisation are shown in Table 22. All interventions, except for nirmatrelvir/ritonavir and molnupiravir were estimated to be dominated by SoC. The ICER for nirmatrelvir/ritonavir compared with SoC was below £10,000 whereas that for molnupiravir was greater than £65,000. A full incremental analysis indicates an efficiency frontier of SoC for a WTP up to £7989 and nirmatrelvir/ritonavir for a WTP over £7989.

Table 22: Low efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	Cost per QALY Incremental Analyses (£)
SoC	413	10.05		£-	-
Nirmatrelvir/ritonavir	676	10.08	7989	395	7989
Molnupiravir	992	10.06	69,786	-413	Dominated
Remdesivir	1920	9.98	Dominated	-2,874	Dominated
Casirivimab/Imdevimab	2442	10.04	Dominated	-2,286	Dominated
Sotrovimab	2664	10.03	Dominated	-2,657	Dominated

† Assuming a threshold of £20,000 per QALY gained QALY – quality-adjusted life years; SoC – standard of care

4.4 Sensitivity Analysis Results

Three sets of sensitivity analyses were run that related to:

- Amending the assumed duration of long COVID from 108.6 weeks to 54.3 weeks and to 217.2 weeks
- Changing the product of the percentage of hospital admission due to COVID-19 in the community and the RR associated with people being at 'high risk' of hospitalisation from a value of 1.8% to values of 1.35% and 5.00%
- Changing the average age of patients at high-risk of hospitalisation in the community from 65 years to 60 and 70 years.

For reference, the NMBs of each intervention are shown in Figure 17, Figure 18 and Figure 19 for patients who are hospitalised and require supplemental oxygen, patients who are hospitalised but do not require supplemental oxygen, and patients with COVID-19 in the community who are at high-risk of hospitalisation respectively.

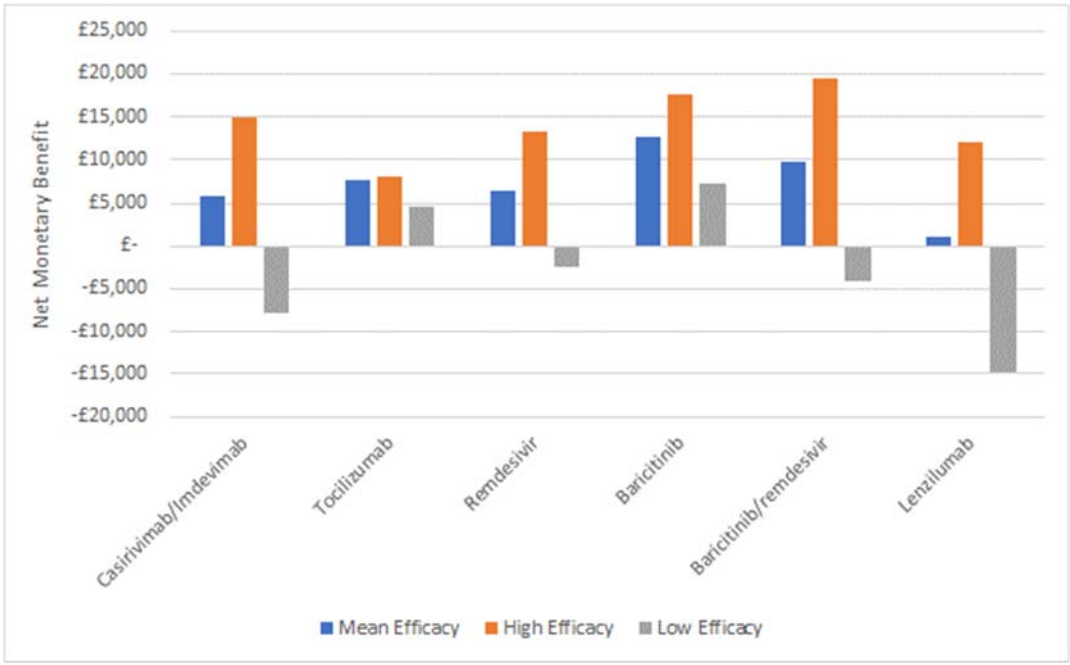

Figure 17: Base case net monetary benefits for patients admitted to hospital who require supplemental oxygen

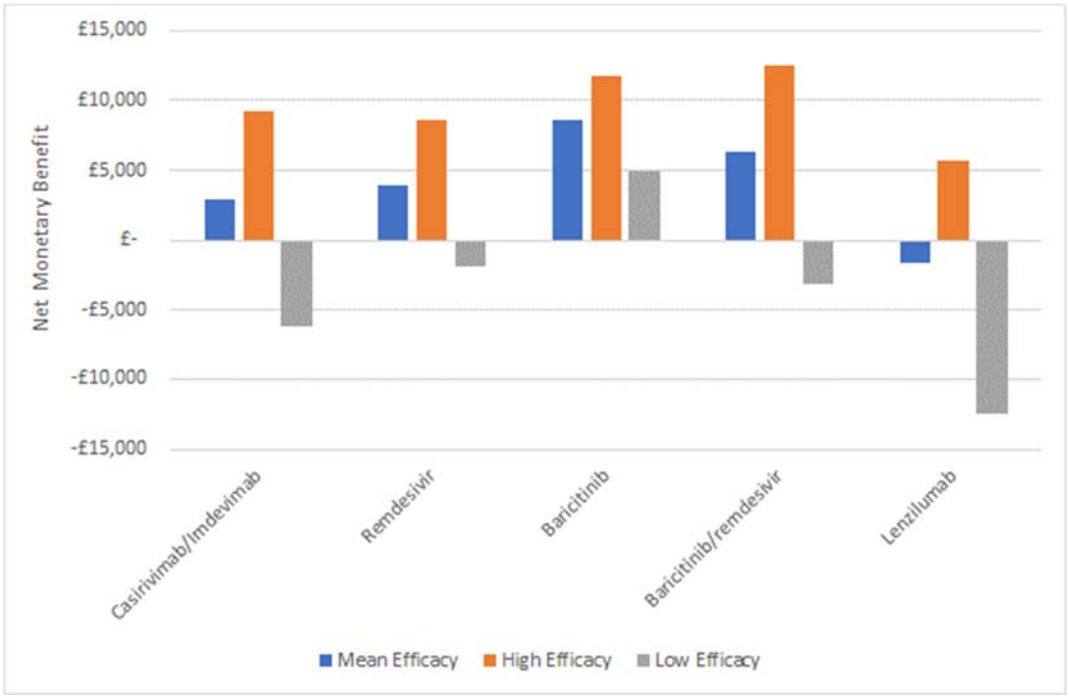

Figure 18: Base case net monetary benefits for patients admitted to hospital who do not require supplemental oxygen

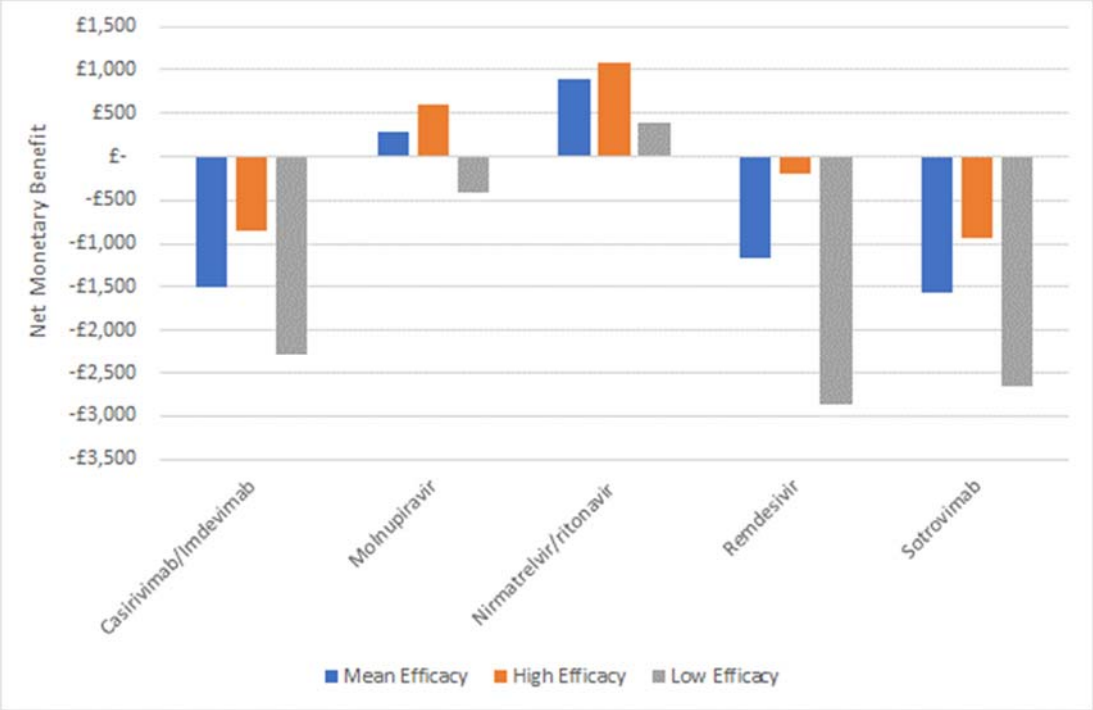

Figure 19: Base case net monetary benefits for patients with COVID-19 in the community and high-risk of hospitalisation

4.4.1 Amending the duration of long COVID

The NMB results when the duration of long COVID is doubled (to 217.2 weeks) and halved (to 54.3 weeks) are shown in Figure 20, Figure 21 and Figure 22 for people admitted to hospital requiring supplemental oxygen, those admitted to hospital with no need for supplemental oxygen, and those treated in the community at high-risk of hospitalisation respectively.

For patients in all settings, the absolute difference in NMB between scenarios where the duration of long COVID was halved and scenarios where the duration was doubled was markedly smaller than the absolute differences in NMB when using the high efficacy scenario and the low efficacy scenario (Figure 20, Figure 21 and Figure 22). This indicates that the duration of long COVID was of lesser importance in driving the ICER than the actual efficacy of the interventions. The interventions were more cost-effective when the duration of long COVID was shorter, as the interventions typically increased survival and more QALYs would be gained from patients who had long COVID for a shorter period.

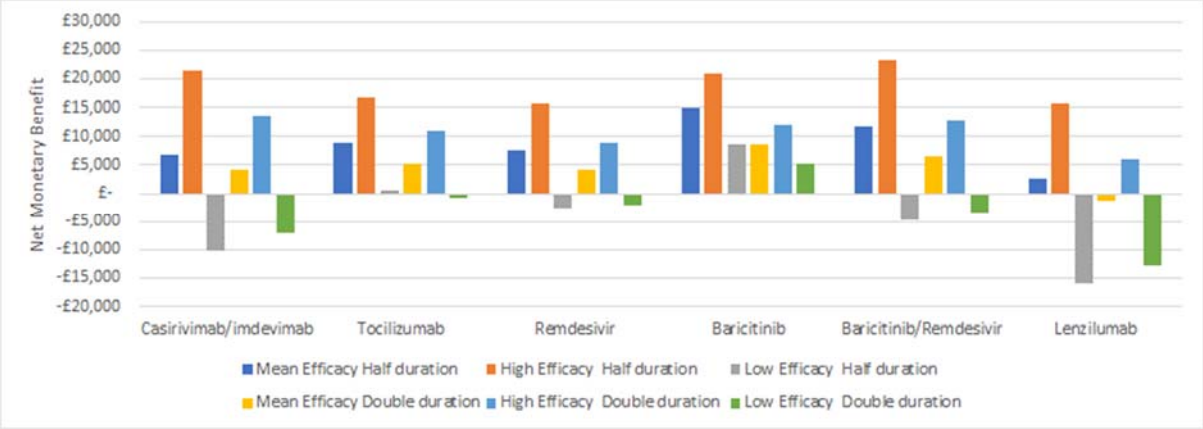

Figure 20: **The NMB results for patients admitted to hospital who require supplemental oxygen when the duration of long COVID is halved and doubled**

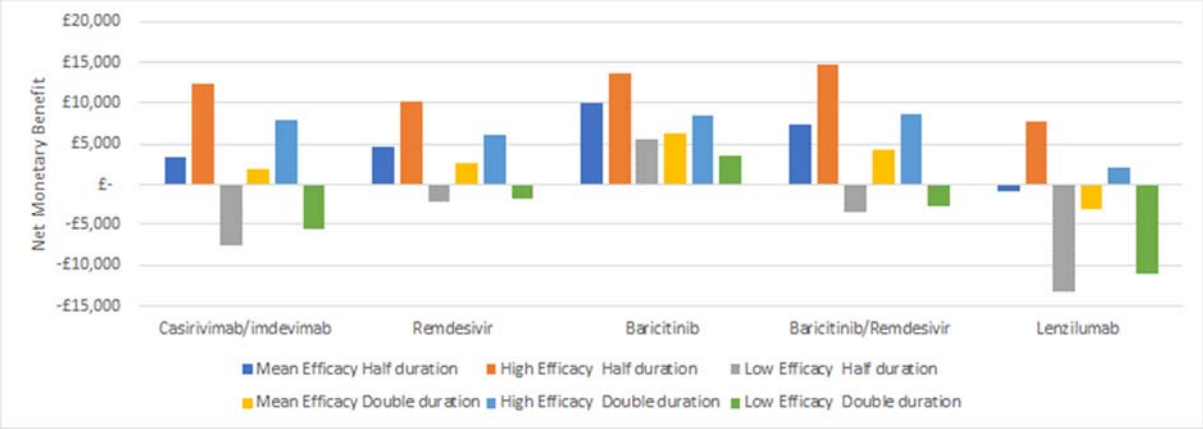

Figure 21: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the duration of long COVID is halved and doubled**

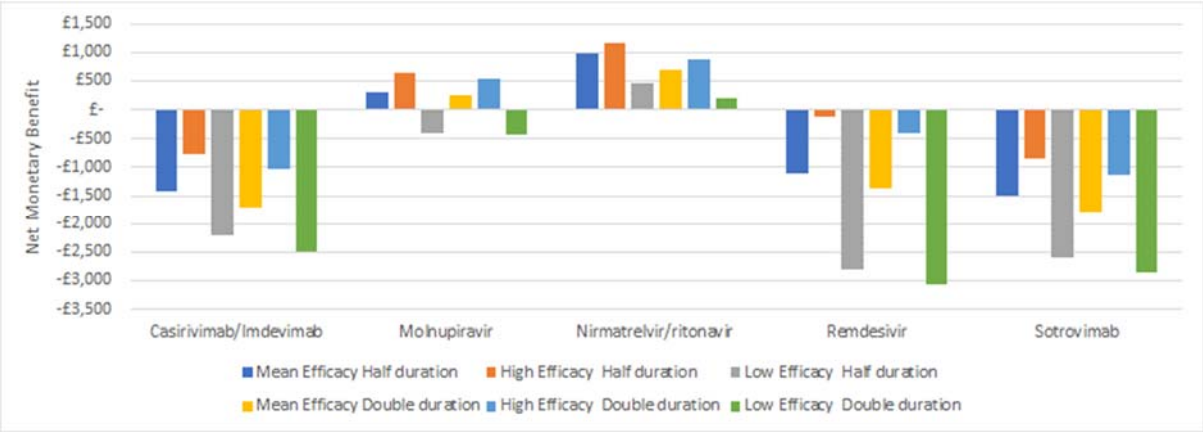

Figure 22: **The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the duration of long COVID is halved and doubled**

4.4.2 *Amending the hospital admission percentage for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC*

The NMB results when the hospitalisation admission percentage for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC was changed from 1.8% to 1.35% and 5.00% are shown in Figure 23. It is seen that in the mean efficacy scenario and the high efficacy scenarios the proportion of patients with COVID-19 at high-risk of being hospitalised being admitted to hospital makes a large difference to the NMB. All interventions had a positive NMB when the proportion of patients hospitalised was increased to 5.00% and the high efficacy scenario was used. This shows that the proportion of patients with COVID-19 at high-risk of hospitalisation is an important driver of the ICER with the interventions becoming more cost-effective as the admission proportion increases.

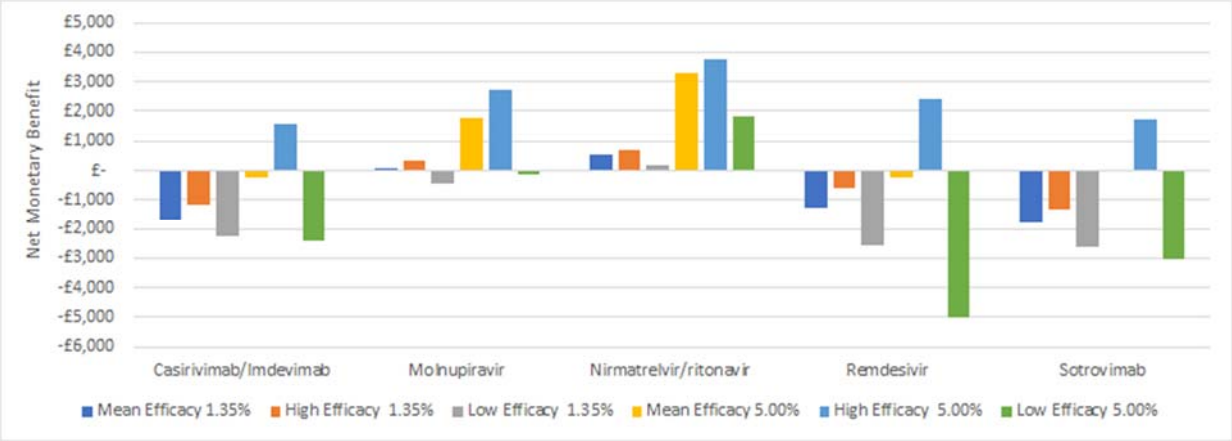

Figure 23: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the hospital admission percentage was changed

4.4.3 *Amending the age of people with COVID-19 in the community at high-risk of hospitalisation treated with SoC*

The NMB results when the age assumed for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC was changed from 65 years to 60 years and 70 years are shown in Figure 24. It is seen that the change in NMB between the ages of 60 and 70 years is not dissimilar from the changes in NMB when the different efficacy scenarios are used. As such, age is an important driver of the ICER for treatment of patients with COVID-19 at high-risk of hospitalisation in the community, with the drugs being more cost-effective as the age of patients decrease.

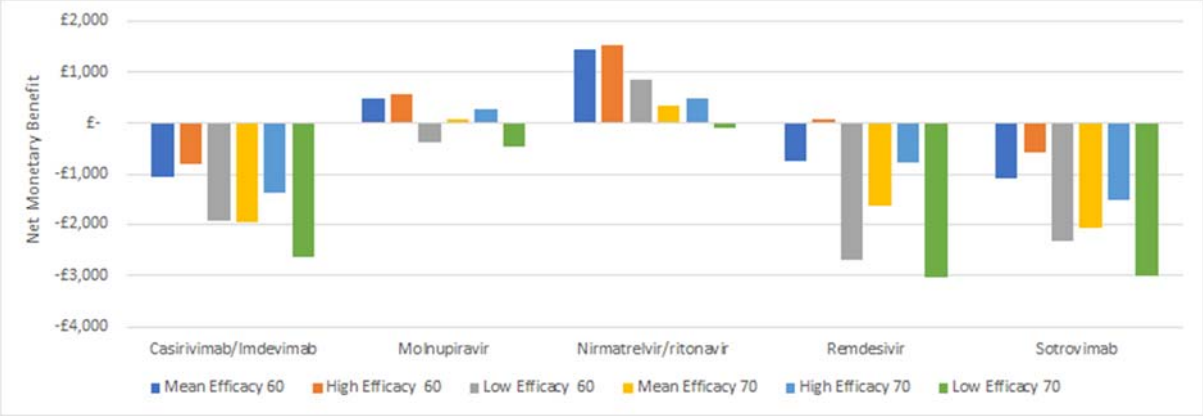

Figure 24: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the age was changed from 65 years to 60 years and 70 years

5 DISCUSSION AND CONCLUSIONS

5.1 Summary Of Clinical-Effectiveness data

For time reasons, the EAG used data from two living systematic reviews and had to assume that the reported efficacy of treatments was transportable to other settings. This assumption may not be correct due to: the evolving nature of SoC; the impact of vaccination; the impact of previous SARS-CoV-2 infection; and the predominant SARS-CoV-2 variant. In addition, patient age, ethnicity, sex and immune system competence may be treatment effect modifiers.

All treatments were associated with a midpoint beneficial effect on preventing mortality, with the exception of remdesivir for patients at high-risk in the community where there were no deaths in either arm. Noting the caveats associated with assuming transportability of treatment effects and the relatively wide CIs associated with preventing mortality, the EAG did not feel confident that it could robustly identify a treatment that was more efficacious than others.

5.2 Summary of Cost-Effectiveness analyses

For patients who have been hospitalised due to COVID-19, all treatments had scenarios where the ICER was below £20,000 compared with SoC, however, in the low efficacy scenario only baricitinib and tocilizumab had ICERs under £20,000 compared with SoC. For patients with COVID-19 in the community at high-risk of hospitalisation, nirmatrelvir/ritonavir and molnupiravir appeared to have the lowest ICERs, with the ICERs for the remaining drugs never falling below £20,000 compared with SoC in any efficacy scenario. In the mean efficacy scenario and the high efficacy scenario both molnupiravir and nirmatrelvir/ritonavir had ICERs below £15,000 compared with SoC.

In the mean efficacy analysis, baricitinib was the intervention that produced most QALYs and had an ICER below £10,000 compared with the previous intervention on the efficiency frontier for people admitted to hospital, independent of supplemental oxygen requirements. For people treated in the community with COVID-19 at high-risk of hospitalisation, nirmatrelvir/ritonavir produced most QALYs and had an ICER below £5,000 compared with the previous intervention on the efficiency frontier in the mean efficacy analysis. However, fully incremental analyses should be treated with caution due to the SoC, the percentage of people who have had a vaccination and the dominant SARS-CoV-2 variant which could vary between studies. Furthermore, the PASs for baricitinib and tocilizumab have not been incorporated in this document and some prices are placeholders at the request of NICE.

The analyses in this report are more favourable to remdesivir treatment in hospital than previous estimates reported by Rafia *et al*.[13] The primary reasons for this are differing assumptions in the models. In Rafia *et al*.[13] remdesivir was associated with an odds ratio for clinical improvement that indicated that remdesivir was harmful to a patient who did not die, compared with SoC and the proportion of patients in ordinal scale 7 receiving SoC was large (22% at day 14). In our analyses, remdesivir is now associated with improved outcomes for patients who do not die but also the proportion of patients in ordinal scale 7 who receive SoC was significantly reduced (9% at day 14). These changes result in a considerable saving in hospital costs, which results in a lower ICER in our work.

The analyses did not look at the logistical aspects of providing treatment. For patients in hospital this is unlikely to be a significant issue, however it could be for patients in the community if an IV treatment was preferred. Local decision makers would need to ascertain whether IV treatment for patients with COVID-19 is possible.

5.2.1 Strengths of the economic analysis include:

- The use of contemporary effectiveness data from living systematic reviews
- An attempt by the EAG to align the results of SoC produced by the model with data observed in mid-2022
- Uncertainty in the model inputs and assumptions has been explored in wide ranging sensitivity analyses
- The modelling attempts to capture movement between the 8-point ordinal scale to consider the costs and consequences of patient improvement and patient decline
- The modelling explicitly attempts to take the impact of the longer-term implications of COVID-19 into consideration

5.2.2 Limitations of the analysis include:

- The characteristics of the decision problem may have changed considerably since the pivotal trials for each intervention was conducted. Such changes include the introduction of a vaccination programme, new SARS-CoV-2 variants, history of prior SARS-CoV-2 infection, the level of supplemental oxygen requirement, and the widespread use of corticosteroids in SoC. The EAG assumed that none of these were treatment effect modifiers and that the treatment effects were transportable which may be incorrect.
- No head-to-head studies of interventions were identified that could be used in the modelling and the uncertainty regarding the most efficacious treatment is large.

- Some prices for interventions are placeholders only and that results included PASs could not be provided in a publicly available document
- Uncertainty remains in the underlying rates of hospitalisation in patients with COVID-19 at high-risk of hospitalisation under SoC
- Uncertainty remains in the underlying rates of death in patients hospitalised due to COVID-19 who receive SoC
- SoC only was assumed to be provided to patients in hospital if they had been treated with an intervention in the community
- Treatments used in hospital were not assumed to affect the proportion of discharged people with long COVID and that treatments used in the community were not assumed to affect the proportion of people not admitted to hospital with long COVID
- All patients were assumed to be discharged from hospital at day 70, which could favour the more efficacious treatments in reducing hospital costs
- No prior beliefs were incorporated relating to the clinical efficacy of the interventions
- No value of information analysis was conducted. This would allow funders to estimate the relative benefits of investing in future research
- No analysis was conducted on whether it is logistically possible to treat patients in the community with COVID-19 and a high-risk of hospitalisation with IV drugs

5.3 The use of patient and public involvement

There was no patient and public involvement in producing this report. This was not considered possible within the timescales of the project. However, the EAG is aware that at the NICE Technology Appraisal Committee that will discuss this topic, there will be patient and public involvement and representation and this may result in the EAG changing model parameters and generating revised results.

5.4 Equality, Diversity and Inclusion

As this report is secondary research, no patient participation was involved and the EAG did not need to consider the Equality, Diversity and Inclusion of participants. The primary research team was part of the ScHARR Technology Assessment Group contracted by the Department of Health, and this team is a diverse group representing a wide range of protected characteristics, consisting of a wide range of seniority, ages, ethnicity and religious beliefs and including both males and females. The clinical team represent experts within their field who have successfully worked with the ScHARR Technology Assessment Group on previous projects. The lead author is not the most senior member of the team.

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None.

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7 APPENDICES

Appendix 1: Summary of clinical studies used to inform the economic model

Table 23: Summary of study and patient characteristics of included studies with relevant outcomes to inform the economic model (all data extracted from https://covid-nma.com/,[9] unless specified otherwise)

Author, year	Design	Population	Severity	Sample size	Intervention	Comparator	Outcomes extracted	Follow-up	Funding	Overall risk of bias
Baricitinib										
Marconi et al. 2021[59] (status: published) COV-BARRIER (NCT04421027)	RCT, single blind	Patients with confirmed COVID-19 admitted to 101 centres in Argentina, Brazil, Germany, India, Italy, Japan, Mexico, Russia, South Korea, Spain, UK, and the USA	Mild to severe Mean age: NR but includes adults aged ≥18 years	1525	Baricitinib, 4 mg/day (n=764) (delivered orally)	Placebo (n=761)	Time to death; clinical improvement (28 day); serious adverse events	60 days	Private	Some concerns
Horby et al 2022[60] (status: preprint) RECOVERY (NCT04381936)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 159 centres in the UK.	Mild to critical Mean age: NR but includes	8156	Baricitinib, 4 mg/day (n=4148) (delivered orally)	Standard care (n=4008)	Clinical improvement (28 day)	28 days	Public/ non profit	Some concerns

			adults aged ≥2 years							
Ely et al. 2022[61] (status: published) COV-BARRIER (NCT04421027)	RCT, double blind	Patients with confirmed COVID-19 admitted to 18 centres in Argentina, Brazil, Mexico and the USA.	Critical Mean age: NR but includes adults aged ≥18 years	101	Baricitinib, 4 mg/day (n=51) (delivered by nasogastric tube or orally)	Placebo (n=50)	Time to death; clinical improvement (28 day); serious adverse events	60 days	Private	Low RoB
Kalil et al. 2020[62] (status: published) ACTT-2 (NCT04401579)	RCT, double blind	Patients with confirmed COVID-19 admitted to 67 centres in Denmark, Japan, Mexico, Singapore, South Korea, Spain, UK, and the USA.	Mild to critical Mean age: NR but includes adults aged ≥18 years	1033	Baricitinib, 4mg/day plus Remdesivir, 100 mg/day[a] (n=515) (baricitinib delivered by nasogastric tube or orally; remdesivir delivered intravenously)	Placebo plus Remdesivir, 100 mg/day[a] (n=518) (remdesivir delivered intravenously)	Time to death; serious adverse events	29 days	Public/ non profit	Low RoB
Casirivimab/imdevimab										

Horby et al. 2022[63] (status: published) RECOVERY-REGEN (NCT04381936)	RCT, unblinded	Hospitalised patients with suspected or confirmed COVID-19 at 127 centres in the UK	Mild to critical Mean age: NR but includes patients ≥12 years	9785	REGN-COV2, 8g (n=4839) (casirivimab, 4g and imdevimab 4g delivered intravenously)	Standard care (n=4946)	All-cause mortality (28 day); clinical improvement, (28 day); hospital discharge[b,c]	28 days	Mixed (Public/ Private)	Some concerns
Somersan-Karakaya et al., 2022[64] (status: preprint) (NCT04426695)	RCT, double blind	Hospitalised patients with confirmed COVID-19 at 103 centres across USA, Brazil, Chile, Mexico, Moldova, and Romania	Mild to moderate Mean age: NR but includes adults aged ≥18 years	1364 (3-arm trial)	REGN-COV2, 8g (n=455) (casirivimab, 4g and imdevimab 4g delivered intravenously)	Placebo (n=452)	Time to death; clinical improvement, (28 and 60 day); hospital discharge[b,d]	56 days	Mixed (Public/ Private)	Some concerns
O'Brien et al. 2022[65] (status: published) (NCT04452318)	RCT, double blind	Outpatients with confirmed COVID-19 (asymptomatic) treated at 112 centres in Moldova, Romania, and the USA.	Mild outpatients Mean age: NR but includes adults aged ≥18 years and adolescents	314	REGN-COV2, 1200 mg (n=156) (delivered subcutaneously once-off)	Placebo (n=158)	All-cause mortality (28 day); serious adverse events	226 days	Mixed (Public/ Private)	Some concerns

			aged ≥12 to <18 years							
Weinreich et al. 2021[66] (status: published) (NCT04425629)	RCT, double blind	Outpatients with COVID-19 (mild) treated at 82 centres in Mexico and the USA	Mild outpatients Mean age: NR but includes adults aged ≥18 years	1678 (Amended phase 3 portion only of trial)	REGN-COV2, 1200 mg (n=838) (delivered intravenously once-off)	Placebo (n=840)	All-cause mortality (28 day)	28 days	Mixed (Public/ Private)	Some concerns
				3029 (Original and amended phase 3 portion of trial)	REGN-COV2, 2400 mg (n=1529) (delivered intravenously once-off)	Placebo (n=1500)	All-cause mortality (28 day)			
Weinreich et al. 2020[67] (status: published) (NCT04425629)	RCT, blinding NR	Outpatients with COVID-19 (symptomatic-mild) treated at 27 centres in the USA	Mild outpatients Mean age: NR but includes	275	REGN-COV2, 2.4g/8.0g (n=182) (casirivimab, 2.4g and imdevimab 8g	Placebo (n=93)	Serious adverse events	29 days	Mixed (Public/ Private)	Low RoB

			adults aged ≥18 years		delivered intravenously)					
Lenzilumab										
Temesgen et al. 2021[68] (status: published) LIVE-AIR (NCT04351152)	RCT, double blind	Patients with confirmed COVID-19 admitted to 29 centres in Brazil and USA.	Moderate to severe Mean age: NR but includes adults aged ≥18 years	520	Lenzilumab, 1800 mg/day (n=261) (delivered intravenously)	Placebo (n=259)	Time to death; serious adverse events	28 days	Private	Some concerns
Molnupiravir										
Arribas et al. 2021[69] (status: published) MOVe-IN (NCT04575584)	RCT, double blind	Patients with suspected or confirmed COVID-19 admitted to 65 centres in Brazil, Chile, Colombia, France, Israel, Mexico, Philippines, Poland, Russia,	Mild to severe Mean age: NR but includes adults	304 (4 arm trial)	Molnupiravir, 1600 mg/day (n=76) (delivered orally)	Placebo (n=78)	Clinical improvement, (28 day); serious adverse events	28 days	Private	Some concerns

		South Africa, South Korea								
Caraco et al. 2021[70] (status : published) MOVe-OUT (NCT04575597)	RCT, double blind	Outpatients with confirmed COVID-19 (asymptomatic, mild) treated by 82 centres in 14 countries	Mild outpatients Mean age: NR (no further details provided)	302 (4 arm trial)	Molnupiravir, 1600 mg/day (n=76) (delivery method NR)	Placebo (n=74)	Serious adverse events	210 days	Private	Low RoB
Fischer et al. 2021[71] (status: published) (NCT04405570)	RCT, double blind	Outpatients with confirmed COVID-19 (mild) treated by 10 centres in the USA	Mild outpatients Mean age: NR but includes adults aged ≥18 years	202 (4 arm trial)	Molnupiravir, 1600 mg/day (n=55) (delivered orally)	Placebo (n=62)	Serious adverse events	28 days	Mixed (Public/ Private)	High RoB
Jayk Bernal et al. 2021[72] (status: published)	RCT, double blind	Outpatients with confirmed COVID-19 (mild-moderate) treated by 107 sites in 20 countries	Mild-moderate outpatients Mean age: NR (no further	1433	Molnupiravir, 1600 mg/day (n=716) (delivered orally)	Placebo (n=717)	Serious adverse events	28 days	Private	Low RoB

			details provided)							
Koudinya Tippabhotla et al. 2022[73] (status: preprint) (CTRI/2021/07 /034588)	RCT, unblinded	Outpatients with confirmed COVID-19 (mild) treated at 16 centres in India	Mild outpatients Mean age: NR but includes adults aged ≥18 years and ≤60 years	1220	Molnupiravir, 1600 mg/day (n=610) (delivered orally)	Standard care (n=610)	Clinical improvement, (28 day); serious adverse events	28 days	Private	Some concerns
Nirmatrelvir/ritonavir										
Hammond et al. 2022[74] (status: published) EPIC-HR (NCT04960202)	RCT, double blind	Outpatients with confirmed COVID-19 (mild) treated by 343 centres in 21 countries	Mild outpatients Mean age: NR but includes adults aged ≥18 years	2246	Nirmatrelvir, 600 mg/day plus ritonavir, 200 mg/day (n=1120) (delivered orally)	Placebo (n=1126)	All-cause mortality (28 day); serious adverse events	34 days	Private	Some concerns
Remdesivir										
Ader et al. 2022[75] (status: published)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 48	Mild to critical	857	Remdesivir 100 mg/day[a] (n=429)	Standard care (n=428)	Clinical improvement, (28 day);	90 days	Public/ non profit	Some concerns

DisCoVeRy (NCT04315948)		centres in France, Belgium, Portugal, Austria, and Luxembourg	Mean age: NR but includes adults aged ≥18 years		(delivered intravenously)		serious adverse events			
Biegel et al. 2020[76] (status: published) (NCT04280705)	RCT, double blind	Patients with confirmed COVID-19 admitted to 60 centres in 10 countries	Mild to critical Mean age: NR (no further details provided)	1062	Remdesivir 100 mg/day[a] (n=541) (delivered intravenously)	Placebo (n=521)	Time to death; serious adverse events	28 days	Public/ non profit	Some concerns
Mahajan et al. 2021[77] (status: published) (NR)	RCT, unblinded	Patients with confirmed COVID-19 admitted to a single centre in India	Moderate to severe Mean age: NR but includes adults aged between 18 and 60 years	82	Remdesivir 100 mg/day[a] (n=41) (delivered intravenously)	Standard care (n=41)	Clinical improvement, (28 day)	24 days	None	High RoB
Wang et al. 2020[78] (status: published)	RCT, double blind	Patients with confirmed COVID-	Severe	237	Remdesivir 100 mg/day [a] (n=158)	Placebo (n=79)	Time to death; clinical improvement,	28 days	Mixed (Public/ Private)	Some concerns

(NCT04257656)		19 admitted to 10 centres in China	Mean age: NR but includes adults aged ≥18 years		(delivered intravenously)		(28 day); serious adverse events			
Spinner et al. 2020[79] (status: published) (NCT04292730)	RCT, unblinded	Patients with COVID-19 admitted to 105 centres in the USA, Europe and Asia	Mild to severe Mean age: NR but includes patients ≥12 years	596	Remdesivir 100 mg/day [a] (5 & 10 arms days merged) (n=396) (delivered intravenously)	Standard care (n=200)	Time to death; clinical improvement, (28 day); serious adverse events	28 days	Private	Some concerns
				396	Remdesivir 100 mg/day [a] for 5 days (n=197) (delivered intravenously)	Remdesivir 100 mg/day [a] for 10 days (n=199) (delivered intravenously)	Time to death; clinical improvement, (28 day); serious adverse events			
Goldman et al. 2020[80] (status: published) (NCT04292899)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 55 centres across 5 countries.	Moderate to critical Mean age: NR but includes	402	Remdesivir 100 mg/day [a] for 5 days (n=200)	Remdesivir 100 mg/day [a] for 10 days (n=202)	Clinical improvement, (28 day); serious adverse events	40 days	Private	Some concerns

			patients ≥12 years		(delivered intravenously)	(delivered intravenously)				
Gottlieb et al. 2021[81] (status: published) PINETREE (NCT04501952)	RCT, double blind	Outpatients with confirmed COVID-19 (mild) treated at 64 centres in Denmark, Spain, UK and USA.	Mild outpatients Mean age: NR but includes patients ≥12 years	584	Remdesivir 100 mg/day [a] (n=292) (delivered intravenously)	Placebo (n=292)	All-cause mortality (28 day); serious adverse events	28 days	Private	Some concerns
Sotrovimab										
Self et al. 2021[82] (status: published paper) ACTIV-3 (NCT04501978)	RCT, double blind	Patients with confirmed COVID-19 admitted to 43 centres in Denmark, Poland, Switzerland, and USA	Mild-moderate Mean age: NR but includes adults aged ≥18 years	546 (3-arm trial)	Sotrovimab, 500 mg once-off (n=184) (delivered intravenously)	Placebo (n=183)	Time to death, Clinical improvement, (60 day); serious adverse events	90 days	Mixed (Public/ Private)	Low RoB
Gupta et al. 2022[83] (status: published) COMET-ICE (NCT04545060)	RCT, double blind	Outpatients with confirmed COVID-19 (mild) and at high risk for Covid-19 progression, treated by 57 centres in the	Mild outpatients Mean age: NR but includes	1057	Sotrovimab, 500 mg once-off (n=528) (delivered intravenously)	Placebo (n=529)	All-cause mortality (28 and 60 day); serious adverse events	168 days	Private	Some concerns

		USA, Canada, Brazil, Spain and Peru.	adults aged ≥18 years							
Tocilizumab										
ARCHITECTS, 2021 (status: unpublished) (NCT04412772)	RCT, double blind	Patients with confirmed COVID-19 admitted to a single centre in the USA	Critical Mean age: NR (no further details provided)	21	Tocilizumab 8 mg/kg once-off (n=10) (delivered intravenously)	Placebo (n=11)	Clinical improvement, (28 day); serious adverse events	90 days	Public/ non profit	Low RoB
Broman et al. 2022[84] (status: published) COVIDSTORM (NCT04577534)	RCT, unblinded	Patients with confirmed COVID-19 admitted to a single centre in Finland.	Moderate to-severe Mean age: NR but includes adults aged ≥18 years	88	Tocilizumab 400 to 800 mg once-off, depending on weight (n=59) (delivered intravenously)	Standard care (n=29)	Time to death; serious adverse events	90 days	No specific funding	Some concerns
COV-AID, 2021 (status: unpublished) (NCT04330638)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 16 centres in Belgium	Severe to critical Mean age: NR but includes	153	Tocilizumab 8 mg/kg once-off (n=81) (delivered intravenously)	Standard care (n=72)	Time to death; serious adverse events	90 days	Public/ non profit	Low RoB

			adults aged ≥18 years							
COVIDOSE-2, 2021 (status: unpublished) (NCT04479358)	RCT, unblinded	Patients with confirmed COVID-19 admitted to multiple centres in the USA	Moderate to severe Mean age: NR but includes adults aged ≥18 years	28	Tocilizumab 40 mg or 120 mg once-off (n=20) (delivery method NR)	Standard care (n=8)	Clinical improvement, (28 day); serious adverse events	28 days	Public/ non profit	Low RoB
COVITOZ-01, 2021 (status: unpublished) (NCT04435717)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to a single centre in Spain.	Mild to severe Mean age: NR but includes adults aged >18 years	26	Tocilizumab 8mg/kg once off or 2 doses (n=17) (delivered intravenously)	Standard care (n=9)	Serious adverse events	90 days	Public/ non profit	Low RoB
Derde et al. 2021[85] (status: preprint) REMAP-CAP (NCT02735707)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 133 centres in 9 countries (UK, Netherlands, Ireland, Australia,	Severe to critical Mean age: NR but includes adults	2253 (multi-arm trial)	Tocilizumab, 8 mg/kg once-off (n=972) (delivered intravenously)	Standard care (n=418)	Time to death	90 days	Mixed	Some concerns

		New Zealand, Canada, Finland, Italy, Saudi-Arabia)	aged >18 years							
Gordon et al. 2021[86] (status : published) REMAP-CAP (NCT02735707)	RCT, unblinded	Patients with confirmed or suspected COVID-19 admitted to 113 centres in Australia, Ireland, the Netherlands, New Zealand, Saudi Arabia, UK	Severe to critical Mean age: NR (no further details provided)	826 (multi-arm trial)	Tocilizumab, 8 mg/kg once-off (n=366) (delivered intravenously)	Standard care (n=412)	Serious adverse events	90 days	Mixed	Some concerns
Hermine et al. 2020[87] (status: published) CORIMUNO-19 (NCT04331808)	RCT, unblinded	Patients with COVID-19 admitted to 9 centres in France	Moderate to severe Mean age: NR (no further details provided)	131	Tocilizumab 8 mg/kg (n=64) (delivered intravenously)	Standard care (n=67)	Time to death, Clinical improvement, (28 day); serious adverse events	60 days	Public/ non profit	Some concerns
Hermine et al. 2022[88] (status: published)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 12 centres in France.	Severe to critical Mean age:	97	Tocilizumab 8 mg/kg once-off (n=51)	Standard care (n=46)	Time to death, clinical improvement, (28 day); serious	90 days	Public/ non profit	Some concerns

CORIMUNO-TOCI-2, ICU (NCT04331808 and NCT04324073)			NR (no further details provided)		(delivery method NR)		adverse events			
HMO-0224-20, 2021 (status: unpublished)	RCT, unblinded	Patients with confirmed COVID-19 admitted to multiple centres in Israel.	Severe-critical Mean age: NR but includes adults aged ≥18 years	54	Tocilizumab 8 mg/kg once-off (n=37) (delivered intravenously)	Placebo (n=17)	Clinical improvement, (28 day)	90 days	Public/ non profit	High RoB
Horby et al. 2021[89] (status: published) RECOVERY (TCZ) (NCT04381936)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 131 centres in the UK	Moderate to critical Mean age: NR (no further details provided)	4116	Tocilizumab 400 to 800 mg, depending on weight (n=2022) (delivered intravenously)	Standard care (n=2094)	Clinical improvement, (28 day)	28 days	Public/ non profit	Some concerns
IMMCOVA, 2021 (status: unpublished) (NCT04412291)	RCT, unblinded	Patients with confirmed COVID-19 admitted to multiple centres in Sweden	Moderate to severe Mean age:	49	Tocilizumab, 8 mg/kg once-off (n=22)	Standard care (n=27)	Clinical improvement, (28 day); serious	28 days	Public/ non profit	Low RoB

			NR but includes adults aged ≥18 years		(delivered intravenously)		adverse events			
Rosas et al. 2021[90] (status: published) COVACTA (NCT04320615)	RCT, blinding NR	Patients with confirmed COVID-19 admitted to multiple centres across 9 countries (Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA)	Mild to critical Mean age: NR but includes adults aged ≥18 years	452	Tocilizumab, 8 mg/kg (n=301) (delivered intravenously)	Placebo (n=151)	Clinical improvement, (28 day); serious adverse events	60 days	Mixed	Low RoB
Rosas et al. 2021[91] (status: published) REMDACTA (NCT04409262)	RCT, double blind	Patients with confirmed COVID-19 admitted to multiple centres in Spain, USA, Brazil and Russia	Severe to critical Mean age: NR (no further details provided)	649	Tocilizumab 8 mg/kg once-off or twice (n=434) (delivery method NR)	Placebo (n=215)	Time to death; clinical improvement, (28 day); time to hospital discharge; serious adverse events	60 days	Private	Some concerns
Rutgers et al. 2021[92] (status: preprint)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 11	Moderate to critical	354	Tocilizumab, 8 mg/kg once-off (n=174)	Standard care (n=180)	Time to death	90 days	Mixed	Some concerns

(Trial NL8504)		centres in the Netherlands.	Mean age: NR but includes adults aged ≥18 years		(delivered intravenously)					
Salama et al. 2020[93] (status : published) EMPACTA (NCT04372186)	RCT, double blind	Patients with confirmed COVID-19 admitted to 65 centres in Brazil, Kenya, Mexico, Peru, South Africa, and USA	Mild to severe Mean age: NR but includes adults aged ≥18 years	388	Tocilizumab, 8 mg/kg (n=259) (delivered intravenously)	Placebo (n=129)	Clinical improvement, (28 day); time to hospital discharge; serious adverse events	60 days	Private	Some concerns
Salvarani et al. 2020[94] (status: published) (NCT04346355)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 24 centres in Italy	Severe Mean age: NR but includes adults aged ≥18 years	126	Tocilizumab, 8 mg/kg (n=60) (delivered intravenously)	Standard care (n=66)	Clinical improvement, (28 day); serious adverse events	30 days	Mixed	Some concerns
Soin et al. 2021[95] (status: published) COVINTOC	RCT, unblinded	Patients with confirmed COVID-19 admitted to 12 centres in India	Moderate to critical Mean age: NR but includes	180	Tocilizumab, 6 mg/kg (n=90) (delivered intravenously)	Standard care (n=90)	Serious adverse events	30 days	Mixed	Some concerns

(CTRI/2020/05/025369)			adults aged ≥18 years							
Stone et al. 2020[96] (status: published) (NCT04356937)	RCT, double blind	Patients with COVID-19 admitted to 7 centres in the USA	Mild to severe Mean age: NR but includes adults aged 19 to 85 years	243	Tocilizumab, 8 mg/kg once-off (n=161) (delivered intravenously)	Placebo (n=82)	Time to death; clinical improvement, (28 day); serious adverse events	28 days	Private	Low RoB
Talaschian et al. 2021[97] (status: preprint) IRCT20081027001411N4	RCT, double blind	Patients with confirmed COVID-19 admitted to a single centre in Iran	Moderate to severe Mean age: NR (no further details provided)	40	Tocilizumab, 8 mg/kg (n=20) (delivered intravenously)	Standard care (n=20)	Time to death; clinical improvement, (28 day); serious adverse events	28 days	Public/ non profit	High RoB
TOCOVID, 2021 (status: unpublished) (NCT04332094)	RCT, unblinded	Patients with confirmed COVID-19 admitted to multiple centres in Spain.	Mild to moderate Mean age: NR but includes	270	Tocilizumab, 648 mg/day in 4 doses (n=136) (delivered subcutaneously)	Standard care (n=134)	Clinical improvement, (28 day); serious adverse events	90 days	Public/ non profit	Low RoB

			adults aged ≥18 years							
Veiga et al. 2021[98] (status: published) TOCIBRAS (NCT04403685)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 9 centres in Brazil	Moderate to critical Mean age: NR but includes adults aged ≥18 years	129	Tocilizumab, 8 mg/kg once off (n=65) (delivered intravenously)	Standard care (n=64)	Clinical improvement, (28 day); serious adverse events	29 days	Mixed	Some concerns
Wang et al. 2021[99] (status: published) (ChiCTR2000029765)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 6 centres in China	Moderate to severe Mean age: NR but includes adults aged 18 to 85 years	65	Tocilizumab 400 mg (n=33) (delivered intravenously)	Standard care (n=32)	Serious adverse events	14 days	Public/ non profit	Some concerns

NR, not reported; RCT, randomised controlled trial; RoB, risk of bias

[a] Different remdesivir loading dose

[b] Data from http://www.metaevidence.org/covid19.aspx[10]

[c] For this outcome (hospital discharge), data reported for seronegative patients only: REGN-COV2, n=1633; standard care, n=1520

[d] For this outcome (hospital discharge), data reported for combined doses only: 2.4 g REGEN-COV (1.2 g casirivimab and1.2 g imdevimab), 8.0g REGEN-COV (4.0 g casirivimab/4.0 g imdevimab), n=804

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. Deadline for comments **5pm** on **Friday 29 July**. **Please submit via NICE Docs**.

[redacted]	
AstraZeneca	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

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Please comment on the assessment report

We thank ScHARR for the detailed Assessment Report and we understand the compromises that had to be made due to stringent timelines. We have separated the comments by topic and detailed additional considerations, analyses and potential inputs sources that we believe would strengthen the report and provide a more comprehensive evaluation of therapeutics for people with COVID-19. Our comments mostly focus on the outpatient treatment analysis (i.e. *people with mild COVID-19 at high-risk of progressing to severe COVID-19 – page 16*), if not otherwise stated.

Comment 1. Population of interest for the analysis

The current definition of patients at high-risk is aligned with the PANORAMIC trial[1], which is a relatively wide definition that includes diseases such as chronic obstructive pulmonary disease, coronary heart disease, atrial fibrillation and congestive cardiac failure, and in whom hazard ratios for COVID-19 hospital admission are marginally higher than 1 (falling in the range 1.13-1.37, based on findings by Hippisley-Cox and colleagues[2]).

While the PANORAMIC trial definition is broadly aligned with outpatient randomised controlled trial inclusion/exclusion criteria[3-6], it is not aligned with the definition of the "*highest-risk clinical subgroups*" cohort from the independent advisory group[7] commissioned by the Department of Health and Social Care (DHSC), and the advisory group[8] commissioned by the Deputy Chief Medical Officer and supported by the NHS England RAPID-C19 team. The purpose of the set of conditions outlined by these advisory groups was to prioritise treatment with monoclonal antibodies and antivirals, and in whom one can reasonably expect the risk of COVID-19 hospitalisation on SoC to be significantly higher than the 1.8% used in the Assessment Report. These conditions are summarised below:

1. Down's syndrome
2. Solid cancer
3. Haematological disease and stem cell transplant
4. Renal disease
5. Liver disease
6. Immune-mediated inflammatory disorders
7. Immune deficiencies
8. HIV/AIDS
9. Solid organ transplants
10. Rare neurological conditions

For instance, focusing on COVID-19 hospitalisation, Hippisley-Cox *et al*[2] reports a HR = 1.73 – 7.37 for chronic kidney disease stage 4/5, HR = 6.81 – 12.82 for bone marrow or solid organ transplant, HR=2.55 for Down's syndrome and HR=2.3 for rare neurological conditions. A similar pattern is observed for COVID-19 death, with marked risk increase associated with chemotherapy recipients, CKD stage 4/5, Down's syndrome, solid organ transplants and rare neurological conditions. This is further supported by disease specific evidence, with Pinato *et al*.[9] reporting 87.39% risk of hospitalisation in the UK cohort of the study (adult patients with cancer and consequent COVID-19 diagnosis) and Crolley 2020[10] reporting 88% risk of hospitalisation in adults with COVID-19 with cancer treated with SACT. Furthermore, Bierle, *et al.*[11] (US study in fully vaccinated individuals eligible for outpatient treatment with monoclonal antibodies) showed that the risk of hospitalisation markedly increases from 2.1% for patients with a MASS score of 0 (BMI = 25-35, hypertension and

age <55, chronic lung disease and age <55) up to 29.9% for patients with MASS score of 4+ (3 MASS points given for patient with chronic kidney disease or immunocompromised).

In conclusion, we believe that NICE decision making would benefit from the inclusion of sub-group analyses for (1) the *Highest-risk clinical subgroups* cohort; and (2) Disease-specific clinical sub-groups (e.g. immunocompromised, chronic kidney disease, solid organ transplants). This is because outpatient treatments (monoclonal and antiviral therapeutics) are likely to provide substantial benefit for these sub-groups, given the markedly higher hospitalisation risk associated with these conditions (vs. the 1.8% used in the Assessment Report) and that the risk of hospitalisation on SoC is one of the key drivers of cost-effectiveness (*page 12*). Failure to adopt such an approach may run the risk of denying access to patients who serve to benefit most from treatment.

Comment 2. Populations contra-indicated to nirmatrelvir/ritonavir

(1) Antiviral treatments are associated with a number of contra-indications as described in the UK Interim Clinical Commissioning Policy. Notably, nirmatrelvir/ritonavir is contra-indicated in severe liver and kidney disease and solid organ and islet transplants, and there are multiple significant drug-drug interactions to consider (as detailed on the COVID-19 drug interactions tool developed by the University of Liverpool[12]), some of which pertaining to commonly prescribed drugs[13] such as atorvastatin (tool outcome: potential interaction) and apixaban (tool outcome: do not co-administer). This highlights the need to consider separately patient groups who may only be eligible for treatment with monoclonal antibodies, or monoclonal antibodies and molnupiravir/remdesivir.

    Therefore, we recommend including a sub-group analysis focusing on the specific high/highest-risk population not eligible to receive nirmatrelvir/ritonavir. Note this suggestion overlaps with Comment 1, since part of the highest-risk cohort (e.g. solid organ transplant, chronic liver and kidney disease, broader immunocompromised population) is likely to be the key sub-groups in whom nirmatrelvir/ritonavir is contra-indicated.

(2) It is also worth noting there is a growing understanding that some patients do not respond to a normal 5-day course of nirmatrelvir/ritonavir.[14,15] Such patients may be treated with an extended course of nirmatrelvir/ritonavir monotherapy, however this does not always suppress viral replication and therefore alternative strategies are needed i.e. combination therapies with / without monoclonal antibodies, or monoclonal antibodies alone. We appreciate there may not be available data to inform treatment sequencing in the model, however this does highlight the need for other therapeutic strategies beyond antivirals.

Comment 3. Risk of hospitalisation on SoC

We note the UK Coronavirus dashboard estimate of 5% risk of hospitalisation was discarded from the base case (*page 39*) in favour of a more conservative estimate of 0.9% from Nyberg, *et al*.[16]. Given the smaller sample size of Nyberg *et al* vs. the UK coronavirus dashboard, we suggest that an intermediate value between the two estimates (e.g. ~3%) would be more appropriate. Based on the latest available data from the UK Coronavirus Dashboard for England[17,18] from 26 January to 8 July, the risk of hospitalisation can be estimated at 4.24% ([798,595-591,828]/[19,507,435-14,630,705]), while Menni 2022[19] reported a hospitalisation rate of 1.9% (94/4,990). While these sources have their own

limitations (likely underestimation of the denominator in the UK Coronavirus Dashboard; limited sample size in Menni 2022), it would appear that 0.9% represents a lower bound estimate rather than an average value representative of the risk of COVID-19 hospitalisations in the UK general population.

Furthermore, applying a HR of 2 (*page 39*) leads to a risk of hospitalisation on SoC for the high-risk cohort of 1.8%, which is lower than the general population estimates from the UK Coronavirus dashboard and Menni 2022, and therefore would appear to lack face validity. In addition, recent UK clinical expert advice (July 2022) highlighted that a ~2-3% risk of hospitalisation on SoC for the high-risk population seems to be an underestimation, with a more reasonable estimate being in the 5%-10% range. Furthermore, the expert advice suggested that for the highest risk population, a risk of hospitalisation >10% would be expected. Finally, the advice highlighted that the risk of hospitalisation is bound to increase given that continuing to vaccinate the high-risk cohort 3-4 times per year, as done so far, is not feasible.

In conclusion, we propose that the risk of hospitalisation on SoC for the high-risk cohort should be revised upwards to a more plausible evidence-based estimate. In addition, as highlighted in Comment 1, separate sub-group analyses should be undertaken for the highest risk cohort and for specific diseases with markedly higher risk of hospitalisation.

Comment 4. Impact of monoclonal antibody treatment on the reduction of oxygen needs (low-flow oxygen, high-flow oxygen or non-invasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation).

In the current Assessment Report, the outpatient treatment effect is captured with respect to hospitalisation or death and all-cause mortality (*Table 5 – page 27*). However, the monoclonal antibody trials of the treatments considered in the analysis, sotrovimab and casirivimab/imdevimab and, in the future, tixagevimab-cilgavimab have demonstrated a reduction of oxygen needs among hospitalised patients versus placebo (e.g. sotrovimab progression to severe COVID-19: 0.26 [0.12-0.59][3]; tixagevimab-cilgavimab prevention of respiratory failure 71.9% [0.3% - 92.1%][20]).

Data on the impact of antivirals in reducing oxygen needs are not available in the main trial publications for nirmatrelvir/ritonavir[21], molnupiravir[6] and remdesivir[5]. Nevertheless, UK clinical expert advice highlighted that antivirals are not expected to have an impact on reducing oxygen needs due to the different mechanism of action vs. monoclonal antibodies.

In conclusion, we believe there are significant uncaptured QALYs and would therefore urge the EAG to include the reduction in oxygen needs associated with monoclonal antibodies in the model and analysis, given the large utility decrements and costs associated with low-flow oxygen, high-flow oxygen and invasive mechanical ventilation vs. no supplemental oxygen.

Comment 5. Mean age of the cohort

It is unclear why an arbitrary base case value of 65 years of age was assumed for people with COVID-19 at high risk of hospitalisation (*page 41*). Given the lack of UK specific data, the outpatient clinical trial estimates may be a relevant source to consider, as summarised below.

- Sotrovimab - median age 53 years[3]
- Nirmatrelvir/ritonavir - median age 45-46.5 years[4]
- Molnupiravir – median age of 42-44 years[6]
- Casirivimab/imdevimab - median age of 48-50 years[22]

- Remdesivir – age of 50-51 years[5]

Comparing the trial-based estimates above, it is clear that the value of 65 years used in the Assessment Report overestimates the outpatient cohort age. As highlighted in the report (*page 67*), the outpatient cohort starting age is an important driver and strongly impacts the ICER with drugs becoming more cost-effective with decreasing age.

We therefore suggest amending the outpatient cohort age using the outpatient trial patient characteristics (as summarised above), until UK specific data to accurately estimate the outpatient cohort age becomes available.

Comment 6. Re-infections are not included in the model

Growing evidence suggests that COVID-19 natural immunity wanes over time and that COVID-19 vaccine-induced immunity is more protective than infection-induced immunity.[23,24] Reynolds *et al.*[25] observed that the likelihood of reinfection following Omicron is higher compared to other variants and therefore natural infection with Omicron is a poor booster of COVID-19 immunity.

In contrast to antivirals, monoclonal antibodies have the potential to confer longer lasting protection against re-infection than natural immunity from the virus itself. Data to differentiate protection derived from the virus as opposed to monoclonal antibodies is currently emerging; we therefore suggest that (1) this aspect should be discussed by the NICE Technology Appraisal Committee, where patient and public involvement will be leveraged; and (2) the model structure should be amended so that this value may be appropriately captured and explored.

Comment 7. Logistics of treatment

As highlighted in the report (*page 40*), the logistics of treatment in the community have not been assessed. However, the report does recognise that this could be an important factor in deciding which treatments may be preferred.

Whereas IV treatments such as sotrovimab, remdesivir, casirivimab/imdevimab can only be administered in a specialist, controlled environment (i.e. hospital setting) and have a requirement for observation over time, UK clinical expert advice suggests that oral and intramuscular treatments may be administered in a primary care setting without the need to access the COVID Medicines Delivery Unit, community hospital or out-patient facilities. This would bring benefits for patients in terms of easier access and, additionally, benefits to the NHS in terms of resource use.

This is an important aspect that should be discussed by the NICE Technology Appraisal Committee, where patient and public involvement will be leveraged. It may also be appropriate to undertake a full incremental analysis for the IV and oral/subcutaneous/ intramuscular treatments separately.

Checklist for submitting comments

- Consultation responses must not be longer than **10 pages**, excluding the references.
- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Process and methods manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the pro-forma response document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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National Institute for Health and Care Excellence
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Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. Deadline for comments **5pm** on **Friday 29 July**. **Please submit via NICE Docs**.

Your name	[redacted]
Organisation name	Gilead Sciences Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Summary

Gilead acknowledges the unique and inherent challenges of carrying out an assessment of the cost-effectiveness of treatments for COVID-19. We support the EAG's conclusion that remdesivir has been found to be plausibly cost-effective alongside other treatments for COVID-19, when compared to standard of care (SoC). Considering the challenges relating to the emergence of new variants, evidence shows that anti-virals, such as remdesivir, show reliability of effectiveness in COVID-19 regardless of the variant (Takashita et al., 2022)[1].

Whilst we acknowledge the unique challenges of rapidly appraising medicines in a pandemic or post-pandemic setting, Gilead has significant concerns about the conduct of this technology appraisal, primarily with regard to robustness, fairness, and a lack of methodological transparency.

NICE has substantially deviated from usual MTA process in terms of the process and the methods of technology appraisal. The Evidence Assessment Group (EAG) were commissioned and the Evidence Assessment Report (EAR) was published without formally starting the technology appraisal process. No other stakeholder submission has been considered as this stage in the technology appraisal process. Gilead is of the opinion that NICE have potentially failed to act fairly by breaching its own published process and methods for the development of guidance. We believe that NICE has potentially acted outside of its remit by formally starting the technology appraisal despite claims that process has not formally begun and has potentially exceeded its powers by 'resequencing the steps of the MTA'. Companies have potentially been treated unfairly during the first phase of this assessment. It is unclear if there will be any mechanism to appeal, rectify or otherwise meaningfully contribute to the development of robust guidance on the use of COVID-19 therapeutics.

In this new and undefined HTA process, it is not clear the extent to which companies will be permitted to submit evidence, in particular clinical study reports (CSRs). HTAs which adhere to the published NICE process and methods guidelines permit the submission and consideration of CSRs. CSRs represent an important source of clinical and safety data on interventions and comparators. Companies have not been invited to submit an evidence submission before the development of the EAR; it is unclear if and how this evidence will be considered by the EAG and the committee. It is also unclear if, how and when commercial in confidence patient access schemes (PAS) net price discounts will be considered in the technology appraisal process, which in turn unfairly constrains companies' participation in the technology appraisal process and may limit patient access to effective treatments.

These issues, and others, are fundamental to the way the technology appraisal is being conducted. While challenges such as changing vaccination status and changing COVID-19 variants are unavoidable, we would respectfully request amendments regarding the following specific elements of the EAG's analysis.

1. **The incremental cost-effectiveness analysis included in Section 4.1. is unhelpful and potentially obfuscating for decision-making**

The incremental analysis undertaken by the EAG, which includes all comparators within each of the populations, is inappropriate and methodologically flawed. Gilead is of the opinion that any recommendation based upon the incremental analysis may be unreasonable given the methodological flaws in the analysis and due to the substantial deviation from normal NICE process and methods. The EAG notes that "the EAG did not feel confident that it could robustly identify a treatment that was more efficacious than others" (pp.69) therefore it is important to carefully consider how the incremental analysis is positioned within the report and any subsequent NICE guidance.

Typically, incremental analyses are used to assess comparators that are mutually exclusive and could in practice displace each other; however, this is not the case for the treatments compared within this appraisal. For example, in clinical practice remdesivir, baricitinib, tocilizumab or lenzilumab can be used in the same patient at different stages of their disease progression. This is due to their very different but complementary mode of actions making these therapies role in the treatment of COVID-19 not mutually exclusive: remdesivir targets viral replication while tocilizumab, baricitinib and lenzilumab act against the inflammatory phase induced by the patient's own immune system. This is clearly evidenced by the fact that remdesivir is used as a backbone or component of SoC in a number of trials for other medicines included in the MTA. These include baricitinib and lenlizumab, and in fact data on remdesivir's combination with the former is referred to by the EAG in the overview of evidence for this intervention (ACTT-2). There is a growing body of literature supporting the positioning of remdesivir as a backbone for therapy, for example, Ngo. D. et al (2022), which explored the combination of dexamethasone, remdesivir and baricitinib in severe COVID-19. As we outlined in our response to the scoping exercise, there is further evidence of remdesivir being considered standard of care in the clinical trials of other treatments being studied for use in hospitals, for example:

- The US National Institute of Allergy & Infectious Diseases ACTT and ACTIV platform trials:
    - ACTT-2: evaluated the combination of baricitinib and remdesivir compared to remdesivir alone
    - ACTT-3: evaluated the combination of interferon beta-1a and remdesivir compared to remdesivir alone
    - ACTT-4: evaluated the combination of baricitinib and remdesivir compared to dexamethasone and remdesivir
    - ACTIV-3: evaluating the combination of ACTIV-3 investigational treatments and remdesivir compared to remdesivir plus placebo
    - ACTIV-5 (BET-A): evaluated the combination of remdesivir and Risankizumab compared to remdesivir plus placebo

[1] Takashita E, Yamayoshi S, Simon V, van Bakel H, Sordillo EM, Pekosz A, Fukushi S, Suzuki T, Maeda K, Halfmann P, Sakai-Tagawa Y, Ito M, Watanabe S, Imai M, Hasegawa H, Kawaoka Y. Efficacy of Antibodies and Antiviral Drugs against Omicron BA.2.12.1, BA.4, and BA.5 Subvariants. N Engl J Med. 2022 Jul 20. doi: 10.1056/NEJMc2207519. Epub ahead of print. PMID: 35857646.

- ACTIV-5 (BET-B): recruiting to evaluate the combination of lenzilumab and remdesivir compared to remdesivir plus placebo

- ACTIV-5 (BET-C): recruiting to evaluate the combination of danicopan and remdesivir compared to remdesivir plus placebo in patients younger than or older and equal to 70 years old

- ITAC trial (NIAID, NIH and INSIGHT): evaluating the combination of hyperimmune immunoglobin to SARS-CoV-2 (hIVIG) and remdesivir compared to remdesivir plus placebo

- Casirivimab and Imdevimab for Treatment of Hospitalized Patients With COVID-19 Receiving Low Flow or No Supplemental Oxygen

In this example, the pairwise analysis showed that all of these treatments were cost-effective against SoC, but the incremental analysis suggested that all were dominated or extendedly dominated. The real-world comparators of remdesivir in combination with tocilizumab, baricitinib or lenzilumab are not considered due to lack of evidence, although their inclusion may have theoretically altered the results of the incremental analysis.

While current NICE guidelines recommend that ideally a full incremental analysis is carried out, in this instance, inclusion of the incremental analysis in the main body of the report encourages decision-making based on flawed evidence. We therefore suggest the incremental analysis is removed or reported within the appendices for information purposes only, and further cautionary notes are included regarding the interpretation of the EAG's incremental analysis.

2. The analysis does not appropriately segment patient in the 'in hospital' setting by oxygen use, and should do so

Related to the clinically irrelevant comparisons between some interventions, is the inappropriate patient segmentation within the hospital setting. The EAG fails to segment the patient population according to oxygen use, which is important to do, not only to reflect clinical practice and treatment decisions and sequencing, but also to reflect the correct wording of the regulatory labels of the various interventions. For example, the labels for nirmatrelvir/ritonavir, molnupiravir and sotrovimab specifically state there should be no requirement for supplemental oxygen. The label for tocilizumab refers to supplemental oxygen and mechanical ventilation, while the data included in the EAG report for lenlizumab (LIVE AIR) only considered survival without ventilation as an endpoint. Although baricitinib is yet to receive a label, the NHSE commissioning highlights in order to treat patients with baricitinib they need to be receiving supplemental oxygen or respiratory support. Meanwhile, the label for remdesivir, which has recently received positive CHMP opinion for a full marketing authorisation from a conditional approval, includes its use in patients not requiring supplemental oxygen up until patients requiring, low flow, high flow and non-invasive mechanical ventilation.

Furthermore, the use of these therapies at different stages of their disease progression is important to understand. For example, the use of therapies with an immunomodulatory mode of action too early (such as in a patient not yet requiring supplementary oxygen support) can be detrimental to a patient's outcomes as outlined in the RECOVERY trial for dexamethasone. The EAG seem to discount this clinically important note when assessing clinical and cost effectiveness of the therapies in the different disease settings.

Therefore, we request that the EAG structures the model to appropriately reflect the various patient groups within the hospitalised setting which are people with COVID-19 who are in hospital and require low flow supplemental oxygen for the management of their COVID-19 disease, people with COVID-19 who are in hospital and require high flow oxygen, and people with COVID-19 who are in hospital and require mechanical ventilation / ECMO. This split would therefore enable the EAG to conduct clinically relevant comparisons, rather than seeking to assess medicines in a patient population without recognising key stages of disease progression. Due to this reasoning, this makes many of the figures (such as figure 5) included in the report uninterpretable and potentially misleading.

3. **The model structure excludes the impact of more severe disease on longer-term outcomes**

The existing EAG model structure assumes that a proportion of patients experience 'long COVID', with an associated reduction in quality of life (QoL) and higher mortality risk. This approach currently does not differentiate between hospitalised patients with lower-intensity oxygen requirements and those with more severe disease requiring admission to ICU and/or need for mechanical ventilation or ECMO. The Sheinson et al. (2021), economic evaluation of treatment for patients hospitalised with COVID-19 applies a disutility for patients requiring mechanical ventilation for a period of 5-years post-discharge based on evidence that even relatively young patients who survived acute respiratory distress syndrome (ARDS) had persistent exercise limitations and a reduced physical quality of life 5 years after their critical illness.

The same model applied a hazard ratio for post-discharge mortality for ventilated patients vs. general population for 5 years based on evidence that there is an increased risk of death (33%) and hospital readmission rate (22%) in patients surviving an episode of intensive care compared with hospital control subjects in the 5 years after discharge from hospital, after adjusting for important confounders.

These structural additions would be expected to increase QALY gain and therefore reduce the ICER for comparators demonstrated to reduce the need for mechanical ventilation or ECMO.

4. Rationale for selection of certain sources of evidence and studies are unclear and should be more fully justified by the EAG

It is not clear which sources of evidence the EAG has chosen to include and exclude. Equally, where some sources of evidence were excluded, these are not described in detail, and the EAG states "were deemed to lack full transparency in the extracted outcome data".

Regarding extraction of particular studies, the EAG states that all data extractions were undertaken by the end of May 2022 but certain key studies which one would reasonably expect to be included, for example the SOLIDARITY study, were not. The EAG provide no explanation of the reasons for excluding such studies. With regard to SOLIDARITY in particular, this is the full data set for which DISCOVERY is a sub study and was included (see table 23 of the EAG report), so it is not clear why the EAG has not used the full data set, which would enable a more comprehensive appraisal of the available evidence. In addition, NICE has recently updated the living guidelines for the management of COVID-19 using the SOLIDARITY data set which confirms the relevance of this source of evidence. The guideline also splits patient groups in hospital by oxygen usage, so we would hope the EAG would reflect this in its report and ensure alignment between various NICE guidelines associated with the treatment and management of COVID-19.

Furthermore, on the studies selected to estimate the efficacy of each treatment, the EAG notes how many studies were used but does not indicate which studies these were. The approach to identifying and selecting key sources of clinical evidence and lack of transparency regarding data selection is unsystematic and contrary to the normal NICE methods.

It appears that the selection of interventional studies, and therefore the appraisal of the benefit is inequitable and unbalanced. For example, the EAG's assessment of nirmatrelvir/ritonavir is based on only one study (EPIC-HR) despite the fact that there are multiple additional sources of evidence to consider. Equally, the evidence for baricitinib is drawn from COV BARRIER, when RECOVERY offers a meta-analysis of all trials for the intervention, including COV BARRIER. Therefore, we do not believe the most relevant or applicable data has been selected for many of the interventions, and this flaw in the analysis highlights the importance of a systematic literature review underpinning any HTA.

Additionally, in regard to the studies that were specifically selected for remdesivir, the EAG gave no clear rationale for why certain outcomes were chosen from these studies. An example is the inclusion of the pivotal study ACTT-1 (Biegel et al, 2020) – this study had a clear primary endpoint of time to recovery, however the EAG chose to select this study to look at the outcome of time to death. If the EAG had included SOLIDARITY in their assessment, this outcome would make more sense to be retrieved from this study given the primary endpoint of investigating mortality in a much larger population. The EAG discount the outcome of time to discharge for remdesivir, which is an outcome that could easily be retrieved from ACTT-1. Furthermore, the EAG have chosen to include Wang et al, a study that was halted early due to the lockdown in China and led to a study that could not be completed efficiently and gave an underpowered trial, which taken alone, gives inconclusive findings. Given that this study was selected to assess the outcomes time to death and clinical improvement, both ACTT-1 and SOLIDARITY amongst others are far more robust

data sets from which to retrieve these outcomes for assessment. Gilead is of the opinion that the EAG's arbitrary selection of studies and outcomes may lead to unreasonable recommendations in light of the evidence that is available.

Gilead strongly recommends that the EAG conduct a fully systematic review of all literature (clinical, humanistic and economic), and fully describes the rationale for inclusions and exclusion of sources of evidence and the studies themselves as well as rationale for selecting certain outcomes from each study selected. The information should be presented in a PRISMA diagram and the appraisal should adhere to the NICE Reference Case.

Checklist for submitting comments

- Consultation responses must not be longer than **10 pages**, excluding the references.
- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Process and methods manual (section 5.4) for more information.
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- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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National Institute for Health and Care Excellence
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Gilead Scienced Ltd – Pro-forma Response

Executable Model

Therapeutics for people with COVID-19 [ID4038]

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by **ScHARR**. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Agreement Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. If asked, you must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

July 2022

Issue 1 Model size

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Due to the number of comparator model engines required in the model, the use of weekly cycle lengths (amounting to approximately 2,500 cycles), appears to render the model computation process slow and cumbersome. This makes review (and one would presume the developers' use), of the model difficult. Are such short cycle lengths required?	For the effect of long covid the model appears to apply a single pay-off based on status at 10 weeks. There does not appear to be any facet of the model over the longer term that would prevent an analogous approach to be taken for patients in all states beyond a certain time point: i.e. could a pay-off conditional upon state occupancy at, say, 12 months, not be applied across all states? Alternatively, could not shorter cycle lengths be considered.	Not applicable.

Issue 2 Long covid discounting

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The pay-off assigned for long covid mentioned in (1) is assigned in cycle 1. There appears to be an error in the implementation of this in terms of discounting. Presumably, influenced by the assignment being made in cycle 1, the necessity to discount the relevant quantities appears to have been overlooked.	Due to the cumbersomeness of the model we have not attempted to re-program the implementation of the long covid related pay-offs. No doubt the issue has arisen as an oversight and the model developers will be aware of the adjustments required (discount costs and outcomes from point of long covid initiation and discount resulting quantities back to time zero).	Not attempted due to cumbersomeness of electronic model. The impact of long covid in all comparator arms is expected to be reduced; the relative impacts between comparators are difficult to predict.

Issue 3 Lack of attribution of impact of ICU admission on long-term outcomes

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The long covid pay-offs (undiscounted) appear to be calculated based on a specified period of long covid (approximately two years). This appears to be independent of health state distribution at 10 weeks. This may be reasonable, but as there does not appear to be any other adjustment of prognosis for longer term mortality, need for invasive ventilation or intensive care stay appears to carry no future risk. This appears contrary to evidence suggesting intensive care stay is associated with additional mortality risk and quality of life impact over periods of five years or more.	Rather than implement a single long covid penalty, joint risks due to long covid and past intensive care stay might be considered. We recognise that some historical SMRs for ICU stay might not be wholly transferable to a population of covid patients (e.g. elevated risk due to trauma may not be appropriate), but it does seem possible that insufficient importance is currently attached to the avoidance of ICU. However, the mechanism by which ICU avoidance could be modelled within the current model structure is unclear, due to the simple linear interpolation between day zero and day 15 (in the hospitalised setting). Explicit probabilities for ICU admission may be required.	We would expect that greater recognition of the benefits of active therapies in avoiding ICU stay should yield greater health outcomes (in terms of survival and quality of life), for active therapies relative to standard of care than is presently the case.

Issue 4 Utility decrements

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Utility decrements appear to be implemented as absolute decrements rather than multiplicatively.	Consider multiplicative approach.	As we understand the model, utility decrements are applied only while patients remain in hospital (other than to the extent a decrement due to long covid is incorporated). The manner of implementation might therefore be of little consequence in the current model. However, were longer term

		decrements to be incorporated this might be a more material issue.

Issue 5 Inadequate uncertainty analyses

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The EAG report is at pains to emphasise the uncertainty in the estimates of relative treatment effects. Given this it is puzzling that probabilistic analysis is not presented and other uncertainty analyses appear limited in scope.	Implementation of probabilistic analyses. Further scenario analyses.	In and of themselves these additional analyses would not impact the base case results currently reported but would provide further relevant information for decision-makers.

Issue 6 Arbitrary or spurious treatment effect differences

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Where relative treatment effects for certain comparators are not available the model adopts the arbitrary assumption that there is equivalence between active therapies and standard of care (SoC). This appears to be based on the conclusion that where treatment effects are available they are close to unity relative to SoC and have little impact within the analyses.	Review assumptions where data is unavailable, but also consider extent to which numerical differences in relative treatment effects should be applied in the model, particularly in deterministic analyses, and particularly given the limitation of the model structure being based on partitioned survival for mortality and discharge, meaning that both are modelled independently of each other and of clinical improvement.	In the example of remdesivir versus tocilizumab it is apparent that minor rounding of point estimates and an assumption of the discharge HR then being in line with other parameters (rather than being dismissed as inconsequential and arbitrarily assumed equal to SoC), would remove any QALY difference between these active therapies. The comparison between remdesivir and tocilizumab is merely illustrative of the

As an example, in the hospitalised context, the hazard ratios for mortality for remdesivir and tocilizumab are 0.7791 and 0.7718 respectively, with those for clinical improvement being 1.0404 and 1.0403 respectively. Not only might such differences in point estimates be considered spurious, but the assumption applied for remdesivir for discharge is that there is no effect versus SoC whereas the effect for tocilizumab is 1.05. This implies a benefit for tocilizumab versus remdesivir in the current model based entirely on the arbitrary assumption that remdesivir has no impact on discharge despite having a virtually identical effect to tocilizumab in terms of clinical improvement. In one instance the hazard ratio for remdesivir relative to placebo is applied as 1.00 with a confidence interval of 0 – 50 based purely on application of a continuity correction in both arms, due to zero events. Set against the other evidence both for remdesivir and other therapies this seems implausible.		general point that arbitrary assumptions and minor numerical differences may overstate any apparent differences between therapy options.

Issue 7 Implementation of clinical improvement within hospital

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
There appear to be errors in the implementation of clinical improvement treatment effects. Firstly, the treatment effect appears to be applied only where there is a minimum of a two-step improvement. Thus, for example, for patients initially in state four there is no effect in terms of possible movement to state three. Secondly, where the effect is implemented, this is as the probability for SoC multiplied by the reciprocal of the relative risk. This implies that the treatment effects are intended to reflect worse outcomes with treatment than with SoC, which presumably they are not.	Extend definition of clinical improvement to include improvements of one ordinal state. Review and correct application of treatment effects.	If our reading of the model in this respect is correct than we would expect some improvement in within hospital outcomes for all active therapies relative to SoC.

Issue 8 Use of remdesivir in patients at ordinal state seven

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Notwithstanding the issue above re application of treatment effects for clinical improvement, there is a possible issue that the treatment effects for remdesivir are treated as homogenous across ordinal classifications. Remdesivir should not be used for patients in ordinal state seven	It may be difficult to calibrate relative treatment effects to reflect this issue, and depending on the prevalence of subjects at state seven at baseline in the relevant trials the impact may not be very great. Therefore, we would suggest this be noted in the reporting, and borne in mind when considering assumptions as to treatment effects (whether in the absence of estimates for certain parameters, or where	We would expect improvements in remdesivir outcomes were it possible to reflect the difference in expected outcomes between patients at ordinal state seven and those in less severe states at baseline.

(hospitalized, receiving invasive mechanical ventilation or ECMO). Treatment effects may therefore not fully reflect the potential benefits of remdesivir if the clinical estimates applied in the model reflect outcomes in these patients.	minor differences between therapies are applied, as discussed above). This also implies that the decision problem where remdesivir is considered should exclude patients at ordinal state seven.	

National Institute for Health and Care Excellence
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Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not fille d in correctly. Deadline for comments **5pm** on **Friday 29 July**. **Please submit via NICE Docs**.

Your name	[redacted]
Organisation name	GlaxoSmithKline
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Please comment on the assessment report

In the last few months, millions of UK COVID-19 infections have been recorded, resulting in a corresponding upturn in both hospitalisations and mortality (Alastair McLellan 2022). Considering the potential virulence of some reported variants of concern/interest, it is vital that all efforts are exhausted to ensure the most accurate assessment of available therapeutics, so as not to exclude interventions that provide significant therapeutic benefit and value in the continuing management of the COVID-19 pandemic.

After reviewing the External Assessment Group (EAG) report, a number of significant issues were identified relating to the process, methodology, and inputs used by the EAG in this analysis. The issues identified include:

- Baseline hospitalisation rate
- Exclusion of age from high-risk population definition
- Effect Modifiers
- Comparative Efficacy
- ICER threshold and outbreak status
- Administration cost
- Absence of Safety Profile
- Clinical inputs

Issues specifically related to the implementation of the economic analysis are provided in the separate pro-forma, as requested.

1. **Baseline hospitalisation rate** (*section 3.1.2, pg.38)*

Description of problem
"Hospitalisation rates for patients on SoC (Standard of Care) were taken from Nyberg et al. where recent risks of hospitalisations associated with the Omicron variant were reported. Hospital admission up to 14 days after positive test was approximately 0.9% (over 9,000 patients admitted from a reported million cases)."

"Based on these data and clinical advice, the EAG applied a multiplier of 2 to the average hospitalisation rate for all patients to estimate the rate in people at high-risk of hospitalisation in the base case and increased it in sensitivity analyses"

Proposed amendment
Given that this parameter is a key driver of the cost-effectiveness analysis, we believe that the non-systematic approach to identifying a source for this value is a significant limitation of the analysis.

The authors highlight limitations in the study that could have impacted the estimated hospitalisation rate. (Nyberg et al. 2022) The authors noted the study excluded hospitalisations in the following cases:

"Cases were excluded if the NHS number recorded was missing or invalid (since such cases could not be linked to hospitalisation or vaccination records); information was missing for any adjustment variables; there were more than 14 days between the date of the first positive test and the date of the test which led to the variant being identified (via sequencing, genotyping, or S-gene positivity); or the specimen date was after an individual had died. We also excluded a small number of cases in individuals who had received (1) a vaccine other than Oxford–AstraZeneca, Pfizer–BioNTech, or Moderna or more than three doses of vaccine; (2) a third dose of vaccine that was not Pfizer or Moderna; or (3) a third dose of vaccine less than 80 days after the second dose."

In addition, viral evolution, as reported by UK Health Security Agency(UKHSA 2022), impacts the severity of COVID-19, with the risk of hospitalisation varying with variants of the SARS-CoV-2 virus. Since hospitalisation rate is the major driver of cost effectiveness for non-hospitalised interventions, we believe more work is required to identify and validate a more realistic hospitalisation rate.

The EAG attempt to adjust the Nyberg et al(Nyberg et al. 2022) hospitalisation rate by applying a multiplier of 2 to account for people in high-risk populations, a value derived from *"…these data and clinical advice."* Few details are given about how this value was derived, including the uncertainty around such a critical model parameter. Given the significant uncertainty and lack of clarity about how these values were identified and validated, we request that the EAG conduct a more formal targeted review of the literature to inform this parameter.

GSK notes the EAG does not believe that the estimated 5% hospitalisation rate derived from the UK Coronavirus dashboard is valid, given *"…it may be the case that half of patients with COVID-19 in hospital, were not hospitalised due to COVID-19."* (Page 39), However, the EAG report states *"The population considered within the EAG report has been divided into two broad groups. The first group consists of people who have been hospitalised due to COVID-19 and the second group consists of people who are at high-risk of requiring hospital care due to COVID-19. Patients who were hospitalised for reasons other than COVID-19 and contracted COVID-19 in hospital and were at high-risk of requiring hospital care for COVID-19 in itself were categorised within the second group"*, so patients who are treated for COVID-19 infection acquired within the hospital are still eligible for these treatments and are therefore considered as part of the population for community treatment.

Finally, the baseline hospitalisation rate assumes that this value will hold for the future for which any NICE guidance may apply. However, the hospitalisation rate could plausibly increase if future variants are more virulent, or if protection offered by vaccines wanes. If treatments are reserved for specific 'ultra-high risk' populations, then the baseline hospitalisation rate should be adjusted to account for the increased baseline risk of hospitalisation in any appropriate subgroup analyses.

Expected Impact on result
A higher baseline hospitalisation rate will lower the estimated ICER versus standard of care for effective interventions given in the community to patients at high-risk of hospitalisation for COVID-19.

[redacted]

2. **Exclusion of Age from High-Risk Population Definition** *(section 1.4.1 Paragraph 2, pg.17)*

Description of problem
"Following discussions with NICE, the definition for patients at high-risk was aligned to that considered within the Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community (PANORAMIC) clinical study(PANORAMIC 2022), with the exception that being aged 50 years or over was not considered to be a high-risk factor."

Evidence from the UK suggests that the risk of poorer outcomes from COVID-19 infection increases substantially with age among healthy adults and adults with underlying health conditions. People older than 65 are by far the most at risk, and the risk increases with age (Hippisley-Cox et al. 2021).

Proposed amendment
GSK disagrees with the exclusion of age as a risk factor and asks for this assumption to be reconsidered for the following reason(s):

Office of National Statistics (ONS 2022) data shows there is a clear correlation between age and hospitalisation rate. Data for the week ending 3rd July 2022, showed overall hospital admissions were highest for those aged 85 years and over and lowest for those aged between 5 and 14 years. Real world evidence has shown that

"Although overall hospital admission rates have consistently been highest in the oldest age group, the highest ICU (Intensive Care Unit) and HDU admission rates have varied across groups aged 55 years and over." (ONS 2022) The ONS data and above statement confirmed a consistent trend throughout the pandemic.

Based on consultation with UK clinical experts, we request the inclusion of people aged over 50 years and also, the inclusion of clinical frailty score as risk factors for the high-risk group.

Expected Impact on result
The inclusion of age as a risk factor could / is likely to increase the hospitalization rate of the high-risk group. This key clinically relevant parameter will lower the estimated ICER for effective interventions given in the community to patients at high-risk of hospitalisation for COVID-19.

In addition, including age 50 years and over could have an increasing impact on the proportional shortfall calculation, which could influence the application of a severity modifier and a higher cost effectiveness threshold.

3. **Analytical perspective: Effect Modifiers** *(section 2.1.5 pg.24)*

Description of problem
The EAG stated "The conditions under which each study was evaluated were heterogeneous. Across time SoC has changed markedly, most particularly with reference to the widespread use of corticosteroids such as dexamethasone and change in SARS-CoV-2 variants. The vaccine roll-out in England has provided [25] protection that was not available to patients recruited to early studies, similarly, there is likely to be an increased level of protection associated with prior infection. Ideally there would be attempts to establish the impact of different circumstances on the observed clinical effectiveness of interventions in studies, although this was not possible within the timescales of the project. As such, the EAG had to make a simplistic assumption that none of the changes were treatment effect modifiers, and that given this, the relative benefits observed in the studies were transportable and could be applied to the estimated outcomes for patients with COVID-19 in England in Summer 2022."

Each study assessed by the EAG in this analysis was conducted at different periods of the pandemic. Taking into consideration the continuous evolution of effect modifiers (SoC, SARS-CoV-2 variant, vaccination status, case mix, and prior infection) throughout the pandemic, we believe the analysis should have considered adjustment for these effect modifying factors.

Because these effect modifiers have not been accounted for, we believe that naïve comparisons being performed to assess the potential relative efficacy and subsequent incremental cost-effectiveness between interventions are misleading.

Contributing to the challenge of comparing treatments against each other for the purpose of conducting a fully incremental analysis, is the fact that placeholder values have been used to inform the treatment cost of key comparators. This invalidates any comparative ICERs and adds to our view that these ICERs should be removed.

Proposed amendment
Consider the adjustment of treatment efficacy by accounting for the impact of effect modifying factors present at the time of the relevant trials, before attempting any form of comparative efficacy or fully incremental cost-effectiveness analysis.

Expected Impact on result
It is not possible to approximate the impact of this amendment on the results. If it is not possible to formally account for these treatment effect modifiers, then we suggest that conclusions regarding comparative efficacy and fully incremental cost-effectiveness analyses should be removed from the EAG report, and instead each treatment should be evaluated independently versus standard of care in the authorised patient population.

4. **Analytical perspective: Comparative Efficacy** *(section 2.1.1 pg.23)*

Description of problem
"The need for rapid information on COVID-19 has resulted in a paradigm shift, especially in the communication of scientific results. Traditional systematic reviews can date quickly but 'living' systematic reviews search for evidence much more regularly than standard reviews and incorporate relevant new evidence as it becomes available. This is important in the context of COVID-19, in which the evidence-base is rapidly changing as new data emerge. The ability of a 'living' systematic review and network meta-analysis (NMA) to regularly update and incorporate relevant new evidence as it becomes available makes it the best type of evidence synthesis, in the opinion of the EAG, to inform this pragmatic rapid evaluation."

Proposed amendment
We do not consider the study populations in the trials for the assessed treatments to be similar. A large category of patients identified as high-risk, as highlighted by the PANORAMIC study (PANORAMIC 2022) are not captured in the study population of oral antiviral trials.

A considerable number of high-risk factors were excluded from EPIC-HR(Medicine 2022), due to the adverse prognosis of patient outcomes. With this considered, we think that owing to the level of differences in the study populations and the heterogeneity of study methodology, it is inaccurate to imply which treatment is the most/least cost-effective, especially without an Indirect Treatment Comparison (ITC)/Network Meta Analysis (NMA) to inform comparative efficacy.

In the EAG analysis as it is, sotrovimab and other monoclonal antibody therapies are put at an unfair disadvantage due to the fact they had broader inclusion criteria, meaning the trial results are a truer reflection of their effectiveness in a high-risk group.

Expected Impact on result
An ITC/NMA could provide a more robust estimate of comparative efficacy, and therefore we believe a feasibility assessment should have been considered.

5. **ICER threshold and 'post-pandemic/endemic'** *(section 1.1 pg.16)*

Description of problem
"Should the risk of death following COVID-19 remain at low levels and SARS-CoV-2 becomes endemic in society, then treatments for patients with COVID-19 may no longer be treated differently to interventions for other conditions such as breast cancer or heart disease."

Proposed amendment
Given cases, hospitalisations, and deaths are currently rising in the UK during the time of this consultation (15 July 2022), we would challenge the assumption that we are in a post-pandemic or endemic situation. There are currently minimal public health interventions aiming to control the spread of the virus, relative to earlier in the pandemic, and approximately three million people in England remain unvaccinated, and are at greater risk of becoming hospitalised or dying because of COVID-19 than if they were vaccinated (Commons and Accounts 4 July 2022). Therefore, treatments that prevent progression of COVID-19 have an important role to play in avoiding significant morbidity and mortality at a population level. We challenge the view that these treatments can be evaluated using the standard NICE decision-making framework and the assumptions relating to low rates of hospitalisation.

By using the lower end of the £20,000 to £30,000 per QALY (Quality Adjusted Life Year) threshold range to judge potential cost-effectiveness, the value of treatments in reducing transmission of the virus has not been accounted for within the EAG's analysis. This is contrary to treatments for other infectious diseases that have been appraised by NICE, such as HCV ((NICE) 2015). As well as the potential benefit of reducing onward transmission, the availability of treatments with the capacity to avoid hospitalisations have additional value if the numbers of cases are high and bed/ICU capacity is being exceeded. In this situation, there are significant uncaptured benefits and non-health factors which are valid considerations to enable the Committee to apply a higher ICER threshold as part of their decision-making process.

Expected Impact on result

While we do not expect the ICERs to change unless the model structure is revised to formally account for the potential benefit of reduced onward transmission, we believe that the Committee should consider applying a higher ICER threshold for determining if the treatments are cost-effective given the fact that this is an infectious disease (that can lead to significant morbidity and increased mortality, particularly in the immunocompromised populations where effective vaccination is not always possible), and that there are significant uncaptured benefits and non-health factors due to the nature of the COVID-19 pandemic.

6. **Administration Cost** *(section 3.3.2 pg.50-51)*

Description of problem
"It was assumed that the costs associated with treatment administration whilst in hospital would be incorporated in the unit costs associated with hospitalisation (see Section 3.3.3). Additional administration costs were assumed for intravenous treatment in the community, but for simplicity, not for oral or subcutaneous treatments. For each intravenous administration, a cost of £221 was incurred which was that of NHS reference code SB12Z. Within the analyses it has been assumed that there is likely to be a delay in patients receiving intravenous casirivimab/imdevimab and that subcutaneous version would be used instead."

The EAG use the NHS reference code SB12Z for the cost of administration of intravenous treatments. This code is specifically for parenteral infusion of chemotherapy. As per the recommending dosing schedule as indicated in Table 2 on page 20 of the EAG report, and consistent with the sotrovimab SmPC ((MHRA) 2022), treatment with sotrovimab is administered intravenously over 30 minutes. We believe using the chemotherapy unit cost is likely to be an overestimate, given chemotherapy can often be associated with a longer infusion duration. Also, given that in-hospital treatment with sotrovimab is a possibility for a proportion of patients who acquire COVID-19 within hospital (approximately 10% of sotrovimab administration is in-hospital, based on the weekly COVID-19 therapeutics summary), these individuals may receive the infusion with sotrovimab as part of their bed stay cost (as is assumed for the in-hospital treatment population), and therefore the sotrovimab administration cost is likely an overestimate for this population.

Similarly, assuming all patients eligible for intravenous casirivimab/imdevimab would instead be completely switched to a subcutaneous version is unlikely to be reasonable, and subcutaneous administration is likely to be associated with some level of resource. The subcutaneous route for casirivimab/imdevimab involves higher needle burden and a monitoring period of at least one hour post administration impacting the resource use which should be captured in the administration cost.

Finally, the model does not include any administration or logistical resource use for shipping oral-antiviral therapies direct to patients. This therefore likely underestimates the true cost to the NHS for provision of these treatments.

Proposed amendment
We request that the EAG re-consider the assumptions and inputs related to administration costs for all therapies included within the analysis. In particular, considering the following amends:

- Using a more appropriate infusion administration NHS unit cost. For example, £173.01 (2019 prices) from TA676 ((NICE) 2021).
- Including an adjustment for infusion administration costs where treatment is provided to patients already hospitalised. For example, approximately 10% of sotrovimab is administered in-hospital (NHS-England checked 22/07/2022).
- Including a proportion of patients treated with casirivimab/imdevimab via intravenous administration
- Include an estimate of the cost to the NHS of shipping/ dispatching oral antivirals direct to patients' homes.

Expected Impact on result
We anticipate relatively small improvements in the ICERs for sotrovimab versus SoC.

7. **Absence of safety profile** *(section 2.1.4 pg.24)*

Description of problem
"As such, many interventions were associated with less SAEs (Serious Adverse Events) than SoC, which is generally atypical for efficacious pharmacological treatments. As the model was explicitly tracking the severity of patients through the use of the 8-point ordinal scale the EAG decided to omit SAEs from the model."

Proposed amendment
According to their Summary of Product Characteristics, some of the interventions in this analysis, especially the oral antivirals like nirmatrelvir/ ritonavir (Care 09/02/2022 update), have the potential to cause clinically serious adverse events(Hammond et al. 2022), the incidence of these adverse events could be higher when taken by some comorbid patients in the high-risk group.

For example, the COVID-19 rapid guideline ([NG191] 14 July 2022 Update), states the following: "Ritonavir is a potent CYP3A inhibitor and has interactions with many other medicines, some of which may lead to severe, life-threatening or fatal events". A full medication review (including over-the-counter and herbal medicines) is needed before prescribing nirmatrelvir and ritonavir (Care 09/02/2022 update).

Excluding the consideration of adverse events and the risk of drug-drug interactions in the clinical and cost effectiveness analysis will result in an inaccurate estimation of the clinical safety and potential cost-effectiveness of these treatments. We request that this assumption is revisited, and the safety implications of these therapies are included either formally or in a qualitative way, to ensure that any resulting guidance is appropriate for the high-risk and comorbid patient population.

Expected Impact on result
We expect that the inclusion of adverse events would be a more accurate reflection of the overall impact of the therapeutics.

8. **Incorrect relative risks for sotrovimab**

Description of problem
We would like to call the EAG's attention to the disparity in the COMET-ICE trial results and those presented by the EAG in Figures 6-7 and Table 5 and subsequently used in the analysis and the impact of this error on the analysis. The EAG's report stated:

"All treatments used in the community had favourable median RRs for hospitalisation and death at 28 days, although due to wide CIs no firm conclusions could be made regarding the relative efficacy of these treatments. The median RR associated with death at 28 days were favourable for all interventions, except for remdesivir where the median estimate was unity. The CIs were wide and spanned 1 for all treatments except for molnupiravir and nirmatrelvir/ ritonavir. As such, no clear conclusions relating to the relative efficacy of the interventions could be made regarding avoiding death at 28 days."

In COMET-ICE and as reported in (Gupta et al. 2021), the adjusted relative risk for all-cause hospitalisation lasting >24 hours for acute illness management or death due to any cause through 29 days was 0.21. A corresponding relative risk of 0.20 for all-cause mortality can be derived (0/528 from sotrovimab group, 2/529 from placebo group). The EAG model wrongly uses a median relative risk of 0.65 derived from the confidence intervals, instead of the mean relative risk in its baseline analysis, contrary to best practice. The resulting impact is an inflated estimate of mortality in the sotrovimab treated population, with 75% of patients dying if hospitalised on sotrovimab, compared with 25% of patients dying if standard of care was received. This lacks clinical and face validity and is inconsistent with the outcomes of the clinical study.

Proposed amendment
We recommend that the base case analysis be re-run using the correct clinical data.

Expected Impact on result
An improvement in the ICER for sotrovimab with event outcomes including mortality that are consistent with the clinical study.

Checklist for submitting comments

- Consultation responses must not be longer than **10 pages**, excluding the references.
- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Process and methods manual (Section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the pro-forma response document, please submit these separately.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Therapeutics for people with COVID-19 [ID4038]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

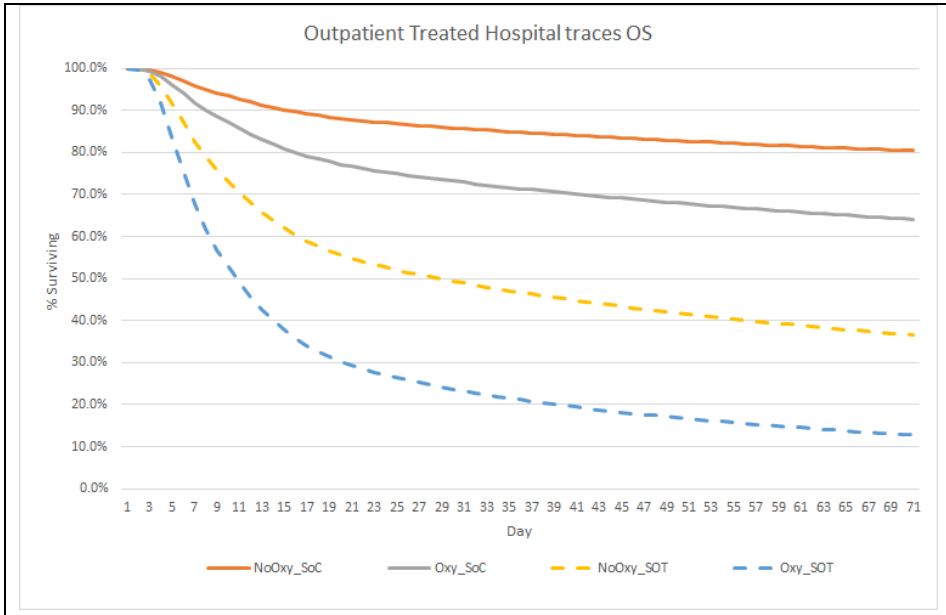
Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

Issue 1 Incorrect RR for mortality for sotrovimab

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The technical report states that "*A separate RR was calculated for each intervention for deaths within hospital such that the overall RR for death at 28 days was consistent with the published estimate reported in Table 4 and Table 5*". In Table 5, the published RR for sotrovimab is 0.2 (0.01 - 4.16) which is also the reported outcome from the COMET-ICE trial, whereas the model estimated the RR for sotrovimab based on the calculations on "Decision Trees Outpatients" tab as 0.65. The same value of 0.65 is also shown in "Parameters" tab, Column F (Active). Within the technical report, there was not a sufficient explanation as to how 0.65 was estimated or why 0.2 was used as the median HR, rather than the mean HR as the target hospital mortality RR with sotrovimab. Hence, we cannot comment on the appropriateness or methodological rigor of the estimation process. However, the final value used in the model (i.e., 0.65 HR) does not align with the trial results or the summary of clinical effectiveness inputs displayed in Table 5, as the report suggests. Furthermore, in order to achieve 0.65 as the RR, the model assumes a higher in-hospital mortality rate with sotrovimab compared to SoC, as fewer patients are required to be hospitalised when treated with sotrovimab in the outpatient setting. As the below graph of model overall survival (OS) traces during the first 70 days of the model analysis clearly shows, model estimated mortality estimates do not align with what is observed in the COMET-ICE clinical trial nor what has been observed in the real-world setting. Therefore, we believe model predictions in its current form are implausible and lack clinical and face validity.	We propose to set the mean RR used in the model to 0.2, as Table 5 indicates and aligned with the COMET-ICE trial results. This amendment also addresses the implausible survival estimates from the model, and mostly results in similar SoC and sotrovimab mortality within hospital. Thus, the RR for Day 28 (D28) mortality is effectively the RR for hospitalisation in the decision tree, which will be 0.2 if the model is calibrated to an overall D28 mortality RR of 0.2. This is again aligned with the COMET-ICE study where no deaths in the sotrovimab arm and only 2 deaths in the placebo arm were observed.	Calibrating to produce an overall 28-day mortality RR of 0.2 results in an ICER for sotrovimab vs SoC = £41,871, considerably lower than the current base case


Outpatient Treated Hospital traces OS
100.0%
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1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67 69 71
Day
NoOxy_SoC
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Oxy_SOT

Issue 2 Error in Formula used to capture the impact of Long Covid on QALY

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In the model, for patients treated in Outpatients, a one-time adjustment to the QALY estimates is made to account for impact of long-Covid for patients who are discharged from the hospital. The adjustment is applied in "Trace…" tabs in columns AN (undiscounted) of the model worksheet for all interventions that are used in outpatient setting. However, we believe the formula that is used for the adjustment has an error in it: instead of applying disutility associated with long-Covid for the duration of long covid and thus reducing overall QALYs, it adds a positive QALY amount for this duration actually increasing overall QALYs. As a demonstration of the issue, the formula that is used in the model (below) in column AN, is missing a multiplication symbol before the -long_disutility parameter (there is currently only a space), which is needed to adjust the aggregation of QALYs for the patients who are discharged from the hospital during the long-Covid period =VLOOKUP(start_weeklyCL,F9:N80,9,FALSE)*(long_duration*(day_inWeek/day_inYear)) -long_disutility The modelling of long-Covid by estimating a lump sum QALY loss and cost does not account for discounting over the two-year duration of long-Covid, as in effect all of the long-Covid impact is assumed to happen in the first cycle of the model.	GSK recommend correcting the formula by replacing the space with the multiplication symbol (see below) to appropriately adjust for long-Covid, in line with the non-hospitlalised equation In all the hospitalised traces replace: =VLOOKUP(start_weeklyCL,F9:N80,9,FALSE)*(long_duration*(day_inWeek/day_inYear)) -long_disutility With: =VLOOKUP(start_weeklyCL,F9:N80,9,FALSE)*(long_duration*(day_inWeek/day_inYear))*(-long_disutility)	Changing the calculation in the Outpatients hospitalised traces reduces total QALYs for all treatments and results in an ICER for sotrovimab vs SoC of £38,086. If, additionally, sotrovimab overall 28-day mortality RR is calibrated to 0.2, this results in an ICER of £30,633 Correcting the long-Covid calculation to account for discounting is expected to have a negligible impact on the results.

Issue 3 Lack of Model Validation

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
We acknowledge that the authors in the EAG report highlight that they were under significant time pressure to implement the model and analysis, however we are concerned that there is no reporting of any validation or verification activities completed to minimise the risk of model errors, or to demonstrate the face validity of the model results. Given the significant errors identified when reviewing the model, we are concerned about the use of this model before a thorough technical validation and verification of the model has been conducted. In many places the model is not clearly presented and annotated, making debugging extremely challenging for anyone who was not the original model developer. This is combined with the limited technical details provided within the EAG report describing aspects of the model including the calibration of efficacy parameters, and the accounting for in-hospital mortality. Finally, the model assumptions, inputs, and results, are not presented in a l way that would be usually seen in a company submission for an STA. This means that it is not possible to quickly gain confidence in the model's accuracy. Therefore, we would urge caution at this stage with using this model for informing the NICE Committee, and request that a thorough validation and verification is conducted and reported.	Conduct a validation and verification of the economic model. Update the EAG report to include greater detail regarding assumptions and inputs and disaggregate the model results by QALY component/event, and cost type, so that the results can be more easily interpreted and understood.	N/A

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. Deadline for comments **5pm** on **Friday 29 July**. **Please submit via NICE Docs**.

Your name	[redacted]
Organisation name	Merck Sharp & Dohme (UK) Limited
Disclosure Please disclose any past or current, direct, or indirect links to, or funding from, the tobacco industry.	None

Please comment on the assessment report
The Company would like to thank NICE and the EAG for the opportunity to review and respond to the assessment report. Given the challenges in the data, we considered the report a fair representation of what is currently known about COVID-19 therapeutics. However, we consider it important to highlight that treatment of COVID-19 is an area of intense scientific development, as evidenced by the rapidly evolving clinical evidence base, which could impact on the relevance of the conclusions drawn from the multiple technology appraisal (MTA). Having reviewed the Evidence Assessment Group (EAG) report, we consider it important to expand on points raised by the EAG in the following areas: • Inappropriateness of the ranking of treatments by cost effectiveness; • Lack of exploration of potential impact of drug–drug interactions on cost effectiveness; • Lack of evaluation of the logistics of use of community-based treatments on cost effectiveness; • Additional considerations for health-related quality-of-life; • Lack of consideration of the direct cost to the NHS of absences in the NHS and social care workforce due to COVID-19; • Additional considerations for a societal perspective; • Relevance of the findings to the current landscape of treatment for COVID-19.
The proposed ranking of COVID-19 interventions based on the estimated cost-effectiveness is flawed given the high level of uncertainty in the relative efficacy of treatments. On page 9, the EAG report states: *"Given the timescale of the project, where there was less than three months between the publication of the final scope and the report deadline, a literature review following best practice was not possible. Instead, a pragmatic, alternative approach was undertaken where evidence was taken from two living systematic reviews (supported by the COVID-NMA initiative and the metaEvidence initiative)."* The indirect treatment comparison assumes transportability of relative treatment effects. The EAG note that this means that *"the same treatment effects, either hazard ratios (HRs) or relative risks (RRs), were assumed applicable regardless of study characteristics which include: the age, perceived severity, vaccination status, and history of SARS-CoV-2 infection of patients; the SoC at that time; the geographical location; and the dosage of the intervention used.*" This assumption cannot be justified due to the differences in study design and settings, which limits the generalisability of outcomes. A specific example is in comparison of the outcomes observed in studies of nirmatrelvir/ritonavir and molnupiravir where the trial populations were quite different. Specifically, regarding co-morbidities and their concomitant medication, patients taking certain concomitant medications were not allowed in the nirmatrelvir/ritonavir

study; therefore, the patient population treated were on average less medically complicated than the MOVe-OUT study. Indeed, the EAG acknowledge the weakness of the assumption of transportability by stating *"it is acknowledged that this assumption may be incorrect"*.

Given the differences across studies, it would be expected that adjustments would be made for time-related factors, such as vaccination rates and variant type. Additionally, adjustments would be expected to account for variation across studies in baseline antibody levels (reflecting prior exposure to SARS-CoV-2 and thus likely some degree of innate protection against COVID-19) and other aspects of population heterogeneity. These factors would have contributed to the observed differences in the event rates of study outcomes in placebo arms. For example, a UK study reported that race, social background, gender, age, and presence of severe asthma are all key risk factors associated with death from COVID-19.[1] Since these differences between studies were not adjusted for in the network meta-analysis (NMA), the company considers it inappropriate to assume transportability of the results on comparative clinical effectiveness derived from the NMA. This is demonstrated in Figure 9 of the EAG report as there is considerable uncertainty in the ranking of efficacy amongst interventions.

Having reviewed the studies informing the NMA, we have concluded that it is not possible to mitigate the study differences to derive robust estimates of relative treatment effects between interventions. For example, whilst a matched adjusted indirect comparison would likely capture unobserved prognostic factors and effect modifiers distributed differently between trials, it would remain impossible to adjust for time-related factors such as variant type. Therefore, we posit that it is inappropriate to formally rank interventions for the purposes of the MTA, and instead the focus should be on head-to-head comparisons versus standard of care (SoC). We are also aware that data from use of antivirals in the community setting are currently being collected. We consider that even these may not resolve some of the clinical uncertainties due to the evolution of the virus over time.

Therefore, the company consider that robust conclusions cannot be drawn on relative clinical effectiveness between treatments (recognised by the EAG in page 3) and ask that only head-to-head comparisons versus SoC are considered for decision making purposes.

Indeed, despite the EAG concluding that *"nirmatrelvir with ritonavir (at an estimated price) may be the most cost-effective treatment in the community setting"* (on page 3 of the report), this statement was followed by another statement highlighting the considerable levels of uncertainty in the incremental analysis. Uncertainty relating to relative treatment effects that inform pairwise comparisons of cost-effectiveness was mentioned on pages 12, 13, 24, 27, 30, 32, and 70 of the report. As such, it is not appropriate to conclude one therapy as "the most cost-effective treatment" based on the network meta-analysis. The limitations associated with such analyses should be elaborated under each table presenting such results to provide context.

Molnupiravir has fewer drug-drug interactions than its comparators and the full implications of this are not explored in the EAG assessment.

Molnupiravir has reduced complications compared to treatments with proven drug-drug interactions

COVID-19 treatment is targeted at a high-risk population, which the PANORAMIC study defines as adults with at least one of the following medical conditions: chronic respiratory disease; chronic heart or vascular disease; chronic kidney disease; chronic liver disease; chronic neurological disease; severe and profound learning disability; Down's syndrome; diabetes; immunosuppression (either caused by inherited immune disorders, or caused by disease or treatment); solid organ, bone marrow and stem cell transplant recipient; morbid obesity; severe mental illness; care home resident; or, judged to be clinically vulnerable.[2] Many of the medical conditions denoting high-risk status require pharmacological management. Therefore, patients eligible for treatment in the community considered in this appraisal are highly likely to be already receiving pharmacological treatments.

As there are no known clinically meaningful drug-drug interactions associated with the use of molnupiravir, it is unlikely to cause an adverse reaction when administered concomitantly with other medications.[3] An additional benefit of molnupiravir is that dose adjustment is not required for treatment administration or when used concomitantly with medications for comorbidities.

Conversely, other treatments are associated with several drug-drug interactions, including interactions with anticoagulants, anticonvulsants and antiarrhythmics,[4,5] which are common treatments for the comorbid conditions defining high-risk patients. These drug-drug interactions may prevent or complicate the use of treatments other than molnupiravir in a substantial proportion of patients at high-risk of COVID-19 and such implications have not been captured within the model.[6] Drug-drug interactions complicate the ability for pharmacists to easily prescribe additional medication; they must perform a full medication review, which is time consuming. Following medication review, a dose adjustment may be required, which complicates treatment for the patient, increasing the likelihood of dosing errors. These complications of drug-drug interactions come with unquantifiable costs for both the NHS and the patient. The extensive diagnosis and treatment pathway is demonstrated through the NHS England published assessment pathways and guides.[5,7] These elements are of particular importance in the UK, where the aging population is likely to have been diagnosed with comorbidities requiring polypharmacy.[8] If patients in the UK can be treated within the community with molnupiravir, an easy to administer drug with no known drug-drug interactions, then considerable time and resource use is saved compared with the treatment of other community drugs for high-risk patients with COVID-19.

Moreover, some patients may be ineligible for some COVID-19 treatments, such as nirmatrelvir/ritonavir, due to concomitant medication for comorbidities. Patients ineligible for a COVID-19 treatment because of an ongoing treatment regimen are more likely to have a worse prognosis than those treated with molnupiravir because they would need to pause their concomitant treatment to treat their COVID-19 with the prescribed intervention. As

molnupiravir has no clinically meaningful drug-drug interactions, these patients can be treated for COVID-19 without interruption to treatment for comorbidities.

Since treatment with molnupiravir does not require dose adjustment or a pause of any concomitant medications, the likelihood of exacerbating comorbidities is reduced compared to treatments where there are drug-drug interactions. Moreover, there is not the chance of side effects caused by mismanaged drug-drug interactions. Exacerbation of underlying comorbid conditions as a result of suspending treatment and adverse effects arising from drug-drug interactions can be costly to manage and can negatively impact quality of life. Therefore, the costs avoided and the QALYs gained are larger with molnupiravir than products with drug-drug interactions.

Reduced pharmacy costs compared to treatments with proven drug-drug interactions
Pharmacy prescription costs are not accurately captured within the model. Choosing an appropriate treatment for patients with comorbidities is complicated and requires careful consideration of their other medication. In particular, ritonavir (in the nirmatrelvir and ritonavir combination) is a potent CYP38 inhibitor and interactions with other medicines may lead to severe, life-threatening or fatal events.[9] This is especially true for patients age 65 and above, which accounts for a larger proportion of the UK population compared to other markets.[8,10,11] As such, a full medication review is required before prescribing nirmatrelvir and ritonavir, which will delay the administration of treatment.[9] As molnupiravir is simple to administer and there are no known drug-drug interactions with the use of the drug, pharmacy costs will be lower for patients receiving molnupiravir compared to other treatments. Additionally, patients will be able to initiate treatment faster, leading to a much simpler process for the patient.[12] Additional evidence is required detailing the most common comorbidities in patients with COVID-19 and a high-risk of hospitalisation.

The impact of drug-drug interactions should be captured within the model
Finally, the Company believes that both costs and utilities associated with unmanaged drug-drug interactions should be included in the economic model. Unmanaged drug-drug interactions may result in adverse events, hospitalisation, prolonged time to recovery, and death. The NHS operates within fixed budgets for both labour and capital resources and managing the drug-drug interactions is a direct cost to the healthcare system.[13] Additionally, adverse events and increased patient management are likely to have a negative impact on patients' utility. If a utility decrement was applied in the model to capture the impact of drug-drug interactions, molnupiravir will show a relatively greater benefit to the patients and the clinical and cost-effectiveness will be more balanced.

Therefore, additional prescribing requirement, such as pharmacist assessment time for community antivirals, should be captured for the purposes of decision making.

Omitting assessment of the logistics and resource use for community-based treatments from the economic evaluation disregards key benefits of molnupiravir.

On pages 10 and 40 the EAG report states:

> *"The modelling did not assess the logistics of treatment in the community, but the EAG notes that this could be a large factor in deciding which treatments could be preferred,*

as oral treatments could be more acceptable to patients and healthcare systems than treatments that are given intravenously or subcutaneously."

Molnupiravir is easy to prescribe in the outpatient setting. It is not necessary for patients or clinicians to check a long list of concomitant medications before prescribing molnupiravir, and dose adjustments of concomitant medications are not required, both of which minimise the risk of pill confusion among patients taking molnupiravir.[14] Additionally, molnupiravir is given as a single oral tablet, which further reduces the risk of pill confusion.

Reduced GP and pharmacist time

Molnupiravir is an orally administered, outpatient treatment without any known drug-drug interactions.[15] Additionally, molnupiravir's simple administration means that infectious patients are kept out of the hospital, thereby reducing the likelihood of community transmission of COVID-19.

Compared with molnupiravir, many of the other treatments for COVID-19 included within the economic model do not have a simple administration and do have clinically meaningful drug-drug interactions.[16] Dosing errors occurring from incorrect patient self-administration, incorrect electronic prescribing, incorrect handling within pharmacy and failure to take multiple tablets together when self-administering (for COVID-19 and comborbidities)[14,17] are all issues not currently captured within the economic model that would not be associated with use of molnupiravir.

Furthermore, the economic model does not capture the pharmacological assessment costs associated with community drugs, for example, renal and hepatic laboratory tests associated with the administration of nirmatrelvir/ritonavir are not considered. Moreover, IV administration in the community was assumed to be the same for all community IV treatments, which the company considers does not reflect clinical practice in the UK; remdesivir in particular requires an observation period following administration, which has been omitted from the model.[18] Further consideration is needed for the full costs associated with the administration of IV treatments for COVID-19 in the community. This results in an unbalanced assessment of the costs associated with treatments in the community and introduces uncertainty within the cost-effectiveness analysis.

Benefits of treatment in the community

Patients receiving molnupiravir may be suffering burdensome symptoms from their COVID-19 infection, including fever, body aches, diarrhoea, nausea, fatigue and exhaustion.[19] As such, community treatment is likely to be favoured by patients to reduce disruption to their lives.[20] Similarly, patients with mild symptoms of COVID-19 will also prefer community treatment as they can remain at home with limited disruption to their lives. As an orally administered community treatment, molnupiravir enables patients to rest and recover in the comfort of their own homes, rather than travelling to the hospital for IV treatment. The ability to rest and recover at home would bring additional quality of life benefits to patients with COVID-19.

Reduced requirement for hospital administration

The proven effectiveness of molnupiravir in a community setting allows for a variety of patients to be treated at home, including those with complex additional needs, such as the elderly and those with disabilities who may otherwise struggle to receive treatment due to difficulties getting to the hospital.[9] In addition, these patient groups are more likely to have

comorbidities and experience drug-drug interactions. Molnupiravir has no known drug-drug interactions and a demonstrated manageable safety profile as an outpatient treatment option.[3]

Removal of geographic barriers to treatment

For those with geographic barriers, if an oral treatment option that requires limited pharmacist assessment for potential drug-drug interactions is not available, transport will be required for these patients, which results in additional costs to the NHS and/or families and increases risk of COVID-19 onward transmission to NHS Ambulatory staff.[9] While the company considers that it is not possible to fully capture the risk of transmission of COVID-19 to ambulance staff within the economic model, its omission means that the cost-effectiveness is overestimated for the drugs the use of which would be potentially associated with this risk.

Overall, omitting the logistics of treatment in the community from the economic evaluation, such as consequences of drug-drug interaction in patients with comorbidities, and the increased risk of COVID-19 transmission in the transporting of patients receiving community drug that require further pharmacological assessment, disregards a key benefit of molnupiravir compared to other available COVID-19 treatments. Therefore, the cost-effectiveness of molnupiravir relative to SoC is underestimated.

Alternative methods to parametrise QALYs are available and are more robust than using values derived from proxy conditions.

Page 53 of the EAG report states that:

> *"Due to the nature of this rapid assessment, no formal systematic review of the literature was conducted to identify the most appropriate utility values."*

The utility decrements used in the model were sourced from a paper by Rafia *et al.* which estimated the cost-effectiveness of remdesivir.[21] The authors sourced these values for the study from proxy conditions (recurrent *Clostridium difficile* infection and influenza) instead of the values being derived from patients with COVID-19. As such, uncertainty exists as to the generalisability of utilities for proxy conditions to patients with COVID-19.

A formal systematic review of the literature would have ensured that all clinically relevant data had been reviewed and assessed, and that the utility values used in the model were obtained from the most relevant data sources. An alternative method to quantify HRQoL in the model would be to conduct a utility study by developing a series of vignettes to describe the range of health states that characterise different levels of severity of COVID-19. The general public would then complete the EQ-5D-3L, a generic, preference-based HRQoL tool, for these health states, acting as proxies on behalf of patients. In the absence of utility values identified from a systematic literature review, the vignette approach would be more robust than assuming alternative diseases are a suitable proxy for COVID-19, aligning with the hierarchy of preferred HRQoL evidence outlined in the NICE health technology evaluations manual (2022).[22]

HRQoL benefits of patients in the community are underestimated

The economic model does not currently distinguish patients who are not hospitalised and experience no limitations of activities (health state 1) from patients who are not hospitalised and who do still experience limitations of activities, home oxygen requirements or both (health

state 2). Therefore, a quality-adjusted life-year (QALY) decrement is not applied to patients who receive treatment in the community setting and go on to experience limitations of activities or require oxygen at home. Additionally, in patients who are hospitalised, a QALY decrement is not applied to patients who have been discharged from hospital but are still experiencing limitations of activities or require oxygen at home.

This does not capture the full health benefit of molnupiravir treatment. For most COVID-19 signs and symptoms, sustained improvement or resolution was more likely, and worsening progression of signs or symptoms was less likely, in the molnupiravir group than in the placebo group.[15] Therefore, lack of distinction between health state 1 and health state 2 eliminates the ability to characterise the full benefit of molnupiravir relative to SoC.

The therapeutics considered in the assessment were centrally procured as part of the Government's response to the COVID-19 pandemic. Therefore, the list price of some COVID-19 therapeutic agents included in the EAG report are currently unknown and robust cost-effectiveness conclusions cannot be drawn.

Page 50 of the EAG report states that:

> *"…list price for remdesivir, tocilizumab, baricitinib, lenzilumab, and sotrovimab. However, list prices were not available for molnupiravir, casirivimab/imdevimab, and nirmatrelvir/ritonavir. NICE requested that placeholder prices be used which were estimated from an Institute for Clinical & Economic Review report (dated March 2022) for molnupiravir and nirmatrelvir/ritonavir, and that the price for sotrovimab was used for casirivimab/imdevimab."*

Currently, the economic model uses indicative prices for some interventions including molnupiravir and nirmatrelvir/ritonavir. As noted within the assessment report, these were extracted from previous work conducted by the Institute for Clinical & Economic Review (ICER) report, which sourced inputs from US sources to inform the cost-effectiveness of alternative interventions in the US setting.

The UK list prices are not currently available for molnupiravir and nirmatrelvir/ritonavir.[23,24] In the absence of UK list prices, the Company is concerned that proxies from the ICER report may not be applicable. Additional generalisability issues arise as current treatment acquisition costs (list prices), used within the EAG report may include USA Government volume discounts that may be unavailable in other countries.[25]

The Company is aware that alternative list price proxies from other markets are available.[26,27] The Company also notes that stock of some antivirals were bought by the DHSC as part of the Government's response to the COVID-19 pandemic. To ensure efficient use of stock already acquired and to reflect value already in the system, this 'sunk cost' stock should be factored into the economic model at £0 until this stock is exhausted.

The direct cost to the NHS of sickness amongst the NHS workforce due to COVID-19 exposure should be considered

Front-line healthcare workers are at a higher risk of contracting COVID-19 than the general public due to the patient-facing nature of the role. Staff sickness among health care providers will result in significant direct costs to the health service due to staff absenteeism and

significant indirect costs from delayed or cancelled treatments. Preventing hospitalisation in high-risk patients with COVID-19 will reduce the transmission of COVID-19 to front-line healthcare workers, which would consequently result in the reduction of the costs associated with covering staff absences and delayed or cancelled treatments. These costs are borne by the NHS and so should inherently be included in the cost-effectiveness analysis as part of the NHS and PSS perspective.

Moreover, preventing hospitalisation in patients with COVID-19 reduces the risk of transmission to the front-line healthcare workers. As a treatment that is delivered entirely in the community, molnupiravir can reduce the exposure of the NHS workforce to COVID-19. Moreover, the phase II-III trial, MOVe-OUT,[15] found that molnupiravir reduced the risk of hospitalisation in at-risk unvaccinated adults compared to placebo.[15] Therefore, when patients are treated with molnupiravir in the community, front-line healthcare workers are at a reduced risk of contracting COVID-19. This key benefit of molnupiravir has been excluded from the economic model.

The EAG should adopt or present an analysis from a societal viewpoint to account for the impact COVID-19 treatments have on productivity, absenteeism, indirect costs, and utilities despite the deviation from NICE evaluation methods considering the wider implications COVID-19 infection.

The economic evaluation adopts a perspective which considers '*how the estimated efficacy for interventions used in hospital and for those at high-risk in the community impacted on patient health'*. Only direct costs to the health care system are included in the economic model: drug acquisition costs, administration costs and unit costs associated with hospitalisation. The model does not include indirect costs such as loss of productivity due to time off work.

COVID-19 increases the risk of sickness absence, both for physical and mental health, in the general workforce.[28–30] Furthermore, patients that contract COVID-19 may suffer from long-term sequalae, where the signs and symptoms of COVID-19 continue well beyond the first suspected COVID-19 infection, which can have profound effects for productivity.[31] Patients who contract COVID-19, whether they require hospitalisation or remain in the community, are required to take time off work to recover and prevent spreading the infection to co-workers. This results in absenteeism and considerable productivity losses at work which the current EAG model and report do not consider. The long-term costs and effects of COVID-19 are further heightened when considering long COVID as individuals experience extended periods off from work in recovery from poor health.

The phase II-III trial, MOVe-OUT,[15] found that progression of signs and symptoms of COVID-19 was less likely in the molnupiravir group than in the placebo group.[15] As such, patients treated with molnupiravir are less likely to suffer long-term sequalae of severe COVID-19, which will enable them to re-join the workforce more quickly and increase their overall productivity.

Adopting a societal perspective which considers all direct and indirect costs and effects attributed to the intervention, would optimise the decision-making process. This would result in a more robust analysis, demonstrating the broader cost-effectiveness of interventions.

Furthermore, the NICE manual 2022 states that under exceptional circumstances, the scope may adopt a broader perspective for costs.[22]

Even if the existing clinical data gaps are filled, the everchanging treatment landscape is a barrier to collecting and providing relevant data.

As highlighted in the EAG report, the evidence-base for COVID-19 is rapidly changing as new data emerge. This is paired with an everchanging environment in which the SoC, the percentage of people who have had a vaccination, and the dominant SARS-CoV-2 variant are variable. As such, this may limit the relevance of any conclusions made by the Appraisal Committee in the future. The Company want to ensure that the guidance issued by the Appraisal Committee remains appropriate and relevant to potential changes in the future.

The effects of molnupiravir on dominant SARS-CoV2 variants

Regarding variability in the dominant SARS-CoV-2 variant, molnupiravir has shown therapeutic value against the sublineages BA.2.12.1, BA.4, and BA.5 of SARS-CoV-2 omicron variant in an *in vitro* study.[32] Using molnupiravir, IC50 was higher by a factor of 1.1 in the BA.2.12.1 subvariant, 1.2 in the BA.4 subvariant and 1.5 in the BA.5 subvariant.[32]

The effects of molnupiravir on vaccinated patients

Molnupiravir has also shown meaningful benefits when administered to fully vaccinated patients with COVID-19. Page 25 of the EAG report states that:

> "*The vaccine roll-out in England has provided protection that was not available to patients recruited to early studies, similarly, there is likely to be an increased level of protection associated with prior infection. Ideally there would be attempts to establish the impact of different circumstances on the observed clinical effectiveness of interventions in studies, although this was not possible within the timescales of the project. As such, the EAG had to make a simplistic assumption that none of the changes were treatment effect modifiers, and that given this, the relative benefits observed in the studies were transportable and could be applied to the estimated outcomes for patients with COVID-19 in England in Summer 2022.*"

A recent study carried out in Italy has demonstrated meaningful benefits of molnupiravir within a fully vaccinated population. The early clinical experience demonstrated that out of 145 fully vaccinated patients enrolled with a mild to moderate breakthrough infection of COVID-19 treated with molnupiravir between January 2022 and February 2022, only 4 patients required hopsitalisation (2.7%) at day 30, no patient developed severe COVID-19, no patient was admitted to the ICU, and no patient died during the follow-up period.[33] Despite no comparator arm, the study shows that molnupiravir continues to provide a viable treatment option in a vaccinated population for high-risk patients when administered within the first 5 days of symptoms onset.[33] Similarly, a UK study found that, in a cohort of vaccinated and unvaccinated patients, patients with COVID-19 who were treated with molnupiravir returned a negative polymerase chain reaction (PCR) test three days faster than those treated with placebo; similar efficacy was observed in the vaccinated and unvaccinated cohort.[34]

The presented clinical data demonstrate that molnupiravir is expected to remain effective regardless of the vaccination status or variant of COVID-19, with the evidence base

suggesting that it remains more effective than SoC. This evidence base will continue to mature over time.

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- Consultation responses must not be longer than **10 pages**, excluding the references.
- Use this comment form and submit it as a Word document (not a PDF).
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- Do not paste other tables into this table – type directly into the table.
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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Therapeutics for people with COVID-19 [ID4038]

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by **ScHARR**. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Agreement Form that has already been signed and returned to the Institute by your organisation.

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The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

July 2022

Issue 1 The implications of drug-drug interactions for treatments administered in the community has not been considered

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
People who are at the greatest risk of developing severe COVID-19 are more likely to have comorbidities, of which many need managing medically. Some of the community treatments considered in this appraisal are associated with several drug-drug interactions including anticoagulants, anticonvulsants and antiarrhythmics.[1] These drug-drug interactions may prevent or complicate the use of treatment to reduce the risk of COVID-19 infection resulting in hospitalisation in a substantial proportion of patients in the indicated population and such implications have not been captured within the economic model.[2] Where community treatments to prevent the progression of COVID-19 have drug-drug interactions, the time spent by pharmacists choosing an appropriate treatment for patients with comorbidities has not been considered. For example, ritonavir (in the nirmatrelvir and ritonavir combination) is a potent CYP38 inhibitor and interactions with other medicines may lead to severe, life-threatening or fatal events.[3] As such, a full medication review is required before prescribing nirmatrelvir and ritonavir.[3] Since the NHS operates within fixed budgets for both labour and capital resources, managing the drug-drug interactions is a direct cost to the healthcare system.[4] Moreover, if side effects do occur due to drug-drug interactions, the implications of managing these events has not been considered. These considerations are not required for all COVID-19 treatments that are administered in the community. There are no known clinically meaningful drug-drug interactions associated with the use of molnupiravir, meaning that it is unlikely to cause an adverse reaction when administered concomitantly with other medications.[5] Furthermore, molnupiravir can be prescribed to patients such that their treatment for comorbidities is not interrupted. Therefore, omitting the costs associated with the prescription, administration and ongoing care associated with the treatment of individual drugs presents an imbalanced assessment of the total costs associated with the each of the treatments for COVID-19.	The company propose that costs associated with both full medication reviews and unmanaged drug-drug interactions are included. The disutilities of unmanaged drug-drug interactions should also be parametrised. Unmanaged drug-drug interactions may result in adverse events, hospitalisation, prolonged time to recovery, and death.	As molnupiravir has no known drug-drug interactions, pharmacy costs will be lower for patients receiving molnupiravir compared to other treatments and patients will be able to initiate treatment faster. This proposed amendment would more accurately characterise the incremental cost-effectiveness of molnupiravir compared to SoC.

Issue 2 The full cost of providing treatments in the community has not been appropriately characterised

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The costs of some aspects of the logistics of treatment in the community are omitted from the economic model. Currently, only the cost of IV administration is considered for remdesivir and sotrovimab. Moreover, IV administration in the community was assumed to be the same for all community IV treatments; remdesivir in particular requires an observational period following administration which has been omitted.[6] Not including all aspects disregards a key benefit of molnupiravir compared to other available COVID-19 treatments. In particular, laboratory tests, such as renal and hepatic tests, performed to monitor patients treated with nirmatrelvir/ritonavir are not considered.[7] Moreover, if these laboratory tests indicate toxicity, the cost of resolving side effects are not included. Additionally, if an oral treatment option is not available, then transport will need to be provided which bears additional costs to the NHS. These costs have not currently been included in the model.	The company propose that all costs associated with the logistics of treatment in the community, including monitoring tests and transport to the hospital, are included in the economic model for the necessary community drugs. Moreover, the differences in duration of time needed for IV administration of different treatments in the community should be reflected.	This proposed amendment will demonstrate the true cost of treatments in the community relative to SoC within the economic model. Therefore, the cost-effectiveness of treatments in the community relative to SoC can be assessed more accurately.

Issue 3 The utility decrements for health states have been proxied from recurrent Clostridium difficile infection and influenza rather than COVID-19

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The utility decrements used in the model were sourced from a publication by Rafia *et al* which estimated the cost-effectiveness of remdesivir.[8] The utility decrements from this study were sourced from proxy conditions (recurrent *Clostridium difficile* infection and influenza) instead of values derived from patients with COVID-19. As such, substantial uncertainty exists as to the generalisability these utilities when used as a proxy for patients with COVID-19.	The company propose that alternative utility values should be used within the economic model. A formal systematic review of the literature would have ensured that all clinically relevant data had been reviewed and assessed, and that the utility values used in the model were obtained from the most relevant data sources. An alternative method to quantify health-related quality-of-life (HRQoL) in the model would be to conduct a utility study by developing a series of vignettes to describe the range of health states that characterise different levels of severity of COVID-19. The general public would then complete the EQ-5D-3L, a generic, preference-based HRQoL tool, for these health states, acting as proxies on behalf of patients. In the absence of utility values identified from an SLR, the vignette approach would be more robust than assuming alternative diseases are a suitable proxy for COVID-19.	This proposed amendment would more accurately characterise the incremental cost-effectiveness of molnupiravir compared to SoC.

Issue 4 The direct cost to the NHS of sickness amongst the NHS workforce is not considered

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
COVID-19 is a highly transmissible disease. When patients with COVID-19 require hospital admission, healthcare workers who work directly with patients infected with COVID-19 are at risk of infection.[9,10] If healthcare workers contract COVID-19, they must take sick leave to protect other vulnerable patients in the hospital. These costs are borne by the NHS and so should inherently be included in the cost-effectiveness analysis as part of the NHS and PSS perspective. Patients who have been treated with molnupiravir in the community setting are less likely to see a progression of signs and symptoms of COVID-19 and as such, are less likely to be hospitalised or experience long-term sequalae of COVID-19. Moreover, their treatment can be delivered entirely in the community, and therefore healthcare workers are not at risk of infection in delivering their treatment. This reduces the risk of front-line healthcare workers contracting the infection and needing to take sick leave.	The company propose that the costs of healthcare workers contracting COVID-19 from both delivery of treatment within the community and from managing patients who are hospitalised due to COVID-19 are parametrised in the economic model.	This proposed amendment would more accurately characterise the incremental cost-effectiveness of molnupiravir compared to SoC.

Issue 5 The societal perspective should be considered

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The economic model only captures direct costs to the health care system associated with COVID-19; drug acquisition costs, administration costs, unit costs associated with hospitalisation, costs associated with COVID-19 infection following discharge and costs associated with long COVID. Costs associated with non-hospitalised patients or patients who have been discharged are assumed to be zero unless they have long COVID. The economic model does not capture indirect costs, such as social care costs or loss of productivity due to time off work. COVID-19 increases the risk of absence due to sickness in the general workforce. This results in absenteeism and considerable productivity losses at work which the current economic model does not consider. As patients who have been treated with molnupiravir in the community setting are less likely to see a progression of signs and symptoms of COVID-19, they are also less likely to be hospitalised or experience long-term sequalae of COVID-19. This reduces the loss of productivity due to COVID-19 for patients treated with molnupiravir compared to SoC.	The company propose that the indirect costs associated with COVID-19, such as social care costs or loss of productivity due to time off work, are included into the economic model so the wider implications of COVID-19 are captured.	Adopting the societal perspective, which considers all costs and effects attributed to the intervention, regardless of who experiences them, would enable optimal social decision making a more robust analysis and to demonstrate the broader cost-effectiveness of interventions. Therefore, this proposed amendment would more accurately characterise the incremental cost-effectiveness of molnupiravir compared to SoC.

Issue 6 Health state 1 is not considered in patients who are hospitalised, whereas health state 2 is not considered in patients who remain in the community

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The economic model does not currently distinguish patients who are not hospitalised and experience no limitations of activities (health state 1) from patients who are not hospitalised and who do still experience limitations of activities, home oxygen requirements or both (health state 2). Therefore, a quality-adjusted life-year (QALY) decrement is not applied to patients who receive treatment in the community setting and go on to experience limitations of activities or require oxygen at home. Additionally, in patients who are hospitalised, a QALY decrement is not applied to patients who have been discharged from hospital but are still experiencing limitations of activities or require oxygen at home. This does not capture the full benefit of molnupiravir treatment. For most COVID-19 signs and symptoms, sustained improvement or resolution was more likely and worsening progression of signs or symptoms was less likely in the molnupiravir group than in the placebo group.[11] Therefore, lack of distinction between health state 1 and health state 2 eliminates the ability to characterise the full benefit of molnupiravir relative to SoC.	The company propose that health state 1 is considered within the economic model such that patients in the community who are not hospitalised, or who have been discharged from hospital, have the opportunity to transition to a health state that represents perfect, or near perfect, health, with no lasting symptoms or long-term sequelae of COVID-19. Including health state 1 within the model then allows for a utility decrement to be applied to health state 2 to accurately capture the reduced quality of life within this health state in the outpatient setting.	This proposed amendment would more accurately characterise the incremental cost-effectiveness of molnupiravir compared to SoC within the community setting as molnupiravir is proven to reduce the progression of signs and symptoms of COVID-19.[11] As such, patients treated with molnupiravir are less likely to suffer long-term sequalae of severe COVID-19.

Issue 7 Rates of long COVID are assumed to be 100% and 10% amongst patients who are hospitalised and remain in the community, respectively, regardless of treatment received.

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The economic model assumes that rates of long COVID are independent of treatment, and that all patients who are hospitalised due to COVID-19 will suffer long COVID. The assumption on duration of long COVID was made due to the level of uncertainty in inputs derived from Evans *et al.*[12] The study estimated that at approximately 6 months, 51.7% of patients with non-missing data reported that they had not recovered from COVID; this value increased to 71.2% when patients stating "they were not sure if they had recovered" were also included. The study by Evans *et al.* evaluated patients who were hospitalised at the beginning of the pandemic, and it is stated that "*it is unclear how generalisable this result is to patients hospitalised in 2022*". Given the everchanging treatment landscape, the evolving clinical guidelines for SoC, and the percentage of people who have had a vaccination, the assumption that all patients who are hospitalised with COVID-19 experience long-COVID is an over-estimate. Additionally, as clinical trials for molnupiravir (phase II-III, MOVe-OUT)[11] found that the progression of signs and symptoms of COVID-19 was less likely in the molnupiravir group than in the placebo arm, the assumption that 100% of hospitalised patients experience long COVID does not capture the most likely scenario that the rate of long-COVID after hospitalisation is reduced in patients who were treated with molnupiravir compared to SoC. Moreover, it is anticipated that this benefit would extend to patients who remain in the community, and the impact of this assumption should be assessed.	The company propose that a more realistic assumptions for the proportion of hospitalised patients that develop long COVID is adopted in the base case. This will reflect the current treatment landscape and fully capture the benefits of molnupiravir. Moreover, the cost-effectiveness of molnupiravir should be considered where the rates of long COVID vary according to receipt of treatment in the community, both in patients who remain in the community and who are hospitalised.	This proposed amendment would more accurately characterise the incremental cost-effectiveness of molnupiravir compared to SoC. Additionally, the uncertainty of the impact of community treatment to rates of long COVID can be assessed,

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National Institute for Health and Care Excellence
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Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. Deadline for comments **5pm** on **Friday 29 July**. **Please submit via NICE Docs**.

Your name	[redacted]
Organisation name	Pfizer UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Please comment on the assessment report

Executive summary

The key issues we'd like to highlight from the assessment report are as follows:

- The definition for patients at high-risk was aligned to the PANORAMIC clinical study except for age which is currently excluded from this assessment. This proposed definition is overly restrictive and should not be based on a single source of evidence, the consequence of this is the exclusion of at-risk patients who would potentially benefit from treatment, including body mass index (BMI) > 25 kg/m2, smoking, hypertension, patients on cancer treatments, healthcare workers and unpaid carers. The omission of age as an independent risk factor also goes against the published evidence base and we suggest that this be included within the risk criteria
- Thorough assessment of any indirect comparison and clinical effectiveness evidence is not possible due to the lack of methodological detail presented. This omission presents a significant limitation when assessing the robustness and suitability of the data used to inform the modelling. Detailed methodology should be presented in line with standard requirements set out in NICE guidance.
- Whilst we acknowledge a pragmatic approach to this assessment was required due to time limitations, we believe it is critical that a probabilistic sensitivity analysis PSA be conducted to assess the full impact of uncertainties within the model and would request that the assessment group present this analysis for further interpretation.
- Transmission value should be captured in the model as has been done for other infection disease models appraised by NICE.

Comments on Assessment Report: Therapeutics for people with COVID-19 [ID4038]

The Assessment Group (AG) were commissioned to assess the clinical effectiveness of eight treatments, including nirmatrelvir/ritonavir (Paxlovid®), within their proposed marketing authorisations for treating people with coronavirus disease 2019 (COVID-19) in hospital and in the community. Given the current indication for Paxlovid®, this response focuses on the second population presented in the AG report: people who are at high risk of hospitalization due to COVID-19.

1. Comments on the decision problem

The definition of patients at high risk considered in the decision problem aligns with the population of the PANORAMIC study,[1] which enrols patients aged ≥ 50 years OR aged 18–49 years with any known underlying chronic health condition considered to make them clinically vulnerable. However, the definition applied in the appraisal excludes age ≥ 50 years as a high-risk factor. Furthermore, the PANORAMIC study criteria do not include other established risk factors for severe COVID-19, including

body mass index (BMI) > 25 kg/m^2, smoking, hypertension, patients on cancer treatments, healthcare workers and unpaid carers. The consequence of the current definition is the exclusion of at-risk patients who would potentially benefit from treatment. The use of a single definition of high risk does not seem reflective of the appropriate population and we request that the full evidence base quantifying risk factors be considered, above and beyond those derived from the PANORAMIC study.

Age as a risk factor

The Joint Committee on Vaccination and Immunisation (JCVI) has advised that all adults aged 50 years and over should be included in the autumn COVID-19 booster vaccination program.[2] Additionally, during initial vaccine roll out, prioritisation was based in part upon age, independent of other factors. In light of this continued prioritisation of the older population for vaccination, it seems contradictory to now exclude this population from the high-risk bracket when considering treatment for COVID-19. Further consideration should be given to the proposed marketing authorisations for treatments assessed in the community setting; not considering age as a high-risk factor would potentially exclude a portion of the licensed population from this NICE appraisal. We suggest that further consideration be given to the inclusion of age ≥ 50 years as an independent risk factor in this assessment.

There is a substantial UK and international evidence base that has demonstrated that age is an independent risk factor for developing severe COVID-19, requiring hospitalisation and death.[3-7] Notably, the living risk prediction algorithm for hospitalisation and death (QCOVID) includes age as an independent risk factor and has been validated in a large UK cohort.[8] Similarly, the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) risk score for predicting COVID-19 mortality includes age >50 as a risk factor and has been validated in a large cohort from 260 UK hospitals.[9] The CDC has linked age as a risk factor for severe COVID-19 in US populations of various vaccination status', including data to show hospitalisation is 3x more likely in patients aged 50-59 compared to a reference group (aged 18-29), which increases to 10x more likely in patients aged 85+.[10-12] Romero-Starke *et al*. 2021, an SLR and meta-analysis of 11 studies assessing COVID-19 hospitalisation rates, found age to be an independent risk factor of hospitalisation (risk ratio: 1.034; 95% CI 1.021 - 1.048) and that risk increased continuously with age.[13] Vahey *et al.* 2021 also found a significant association between age as an independent risk factor and hospitalisation, specifically patients aged 65+ (adjusted odds ratio: 3.22; CI 1.20 - 7.97).[14] In addition to increased risk of hospitalisation, an association between age and increased severity and mortality among patients already hospitalised has been shown.[15-20]

Hypertension and smoking

Whilst we believe the omission of age from the AG's risk criteria to be the primary issue, we also note that there is substantial evidence implicating hypertension[3,4,14,21] and smoking[4,22] as risk factors of hospitalisation due to COVID-19; particular consideration should be given to the links between smoking and other lung conditions (COPD, lung cancer etc.) which are already considered risk factors within the appraisal. We suggest that these factors also be considered for inclusion within the high-risk criteria.

Overweight, underweight and obesity

Adults with excess weight are shown to be at a consistently elevated risk of severe disease and hospitalisation from the Centres for Disease Control (CDC's) evidence review.[23] Additionally, data from the 'second wave' of the pandemic in England showed that patients with BMI reflective of being underweight (<18.5 kg/m2), overweight (> 25 kg/m2) and obese (> 30 kg/m2) have 10%, 24% and 93% higher odds of hospital admission compared to patients of a healthy weight.[24] We suggest that exclusion of these patients from the high-risk group be reconsidered.

Patients on cancer treatment and splenectomy patients

Patients currently receiving or having recently received cancer treatment can currently access treatment through the COVID medicines delivery unit (CMDU) for high-risk, non-hospitalised patients with COVID-19. However, it is unclear whether these patients would still be eligible under the PANORAMIC based definition of high risk. Considering this patient group is extremely vulnerable and at high risk, we request that the high-risk definition be updated to ensure alignment with CMDU criteria and avoid exclusion of at risk patients.[25]

People who have had a splenectomy, have been identified as being at high risk of severe COVID-19 and have hence been prioritised for vaccination.[26] However, they do not seem to be included in either the CMDU or the PANORAMIC eligibility list.

Healthcare workers (including care workers)

While this analysis is focusing on those at high risk of hospitalisation and severe COVID-19, we should not overlook the additional value community treatments can bring to the healthcare system. The COVID-19 pandemic has indeed exacerbated NHS capacity issues. The British Medical association estimated that the waiting list for consultant-led elective care has grown by 2.24 million from 4.24 million in March 2020 to 6.48 million in April 2022.[27] This has been driven in part by COVID-19 related hospitalisation taking up hospital beds but also by staff shortages. Staff absenteeism has increased, mainly driven by COVID-19 infections and requirement to isolate. Studies have shown that patient-facing healthcare workers are at increased risk of infection due to on-the-job exposure with an odds ratio of between 1.5 and 2.5 compared to non-patient facing NHS staff[28], and that during the second

wave of the pandemic in England, the odds ratio of infection for NHS staff working on an inpatient ward or emergency department were between 1.5 and 2.1 (SIREN study).[29] In England alone, from March 2020 to February 2022 a monthly average of 279,214 FTE days were lost due to COVID-19.[30] The last 2 peak losses were in January 2021 (637,734 FTE days) and January 2022 (862,085 FTE days). Data from Wales and Scotland shows a similar pattern with staff absence due to COVID-19 sickness ranging from 0.3%-2.5%.[31,32] Multiple other studies from across the globe present further evidence of the increased risk of developing severe COVID-19 among healthcare workers and the impact of this to healthcare systems.[33-36] We believe community treatments have a key role to play in reducing duration of staff absence to ensure sufficient resourcing on the health and care system. This would help to enable the clearing of the care backlog and alleviate winter pressures.

Unpaid Carers

Unpaid carers provide care to those affected by disability, physical or mental health illness, or frailty, presenting a significant cost saving to the NHS every day.[37] We believe the potential costs of absenteeism of unpaid carers due to severe COVID-19 should not be overlooked. Community treatment of unpaid carers could reduce the duration of absenteeism, and in turn reduce the cost of emergency temporary care for those with often complex care needs.

2. Derivation of clinical effectiveness evidence

The AG adopted a pragmatic approach to identifying and collating evidence on COVID-19 treatments in the community setting in order to provide evidence for decision making in an efficient manner. To this end, third-party sources of evidence identification and synthesis were used, instead of conducting a systematic literature review (SLR) and network meta-analysis (NMA). Limited methodology is available, and no critical appraisal of these sources is presented by the AG.

When reviewing the methods for deriving the clinical evidence, Pfizer acknowledges the time constraints faced by the AG, while noting the inherent limitations in this approach.

2.1 Systematic literature review

The COVID-NMA initiative[38,39] was used as a third-party source to identify relevant trials. The appropriateness of the evidence could not be assessed due to limited methodology and the omission of absolute numbers of outcomes.

2.2 Indirect comparison

The clinical effectiveness section of the AG report (section 2) does not provide detailed methodology of the Indirect Treatment Comparison (ITC) analysis, and this is not readily available on any of the third party source websites. This omission

presents a significant limitation to assessing the robustness and suitability of the data used to inform the economic modelling, which would not be acceptable in any standard NICE HTA. Detailed methodology should be presented by the AG to allow for a comprehensive review to address these various uncertainties.

The following considerations should be taken into account:

- **The methodology for evidence synthesis requires clarification by the AG**. It is unclear if a Network Meta Analysis (NMA) has been conducted by the AG or the third-party source, or if only extracted relative treatment effects from relevant studies are included. It appears that these relative treatment effects are compared naively, applied in the economic model using the RECOVERY trial as representation of SoC. However, this lack of clarity makes it difficult to assess whether the comparison was undertaken effectively and according to the relevant best practice guidelines, which would not be considered appropriate during a standard NICE HTA.

- **The appropriateness of pooling this data from multiple studies should be thoroughly evaluated by the AG**. Regardless of the methods used for evidence synthesis (naïve comparison, NMA or meta-analysis), a full assessment of the appropriateness of synthesis is required according to NICE best practice. A naïve comparison implicitly assumes that there are no underlying differences between studies in terms of study design, baseline characteristics or SoC, while an NMA is only appropriate if these differences are not considered to impact on outcomes. However, it does not appear that any assessment has been undertaken, although this is unclear.

- **The results of the NMA require additional context, as these are not clearly presented or explained**. This makes it difficult for readers to understand the results, which may lead to differing conclusions on the robustness of the results and suitability to inform decision making. In particular, no methodology for ranking the therapies is given, reducing the opportunity for comment on this aspect. It appears the probability rank is used to compare the relevant performance of treatments, but alternative methods such as the surface under the cumulative ranking curve (SUCRA) should be considered. These alternative methods may show more obvious patterns for different treatment performance by visual inspection.

It would also be useful to clarify how robustly the two living systems, COVID-NMA and metaEvidence, carry out the unattended NMA analysis based on the living systematic review; for example, whether any diagnostics checks for transitivity and consistency between direct evidence and indirect evidence are performed. As per guidelines, reproduction of the results from COVID-NMA and metaEvidence using the raw data from each trial and NICE published computer codes would go a distance to validating the two pre-existing systems utilised in this assessment.

2.3 Appropriateness of clinical evidence for synthesis

Based on the assessments of the identification and synthesis of evidence, described above, the following points regarding the appropriateness of the clinical evidence used for evidence synthesis should be considered:

- The report acknowledges study heterogeneity attributable to changes in SoC, vaccination status, prior COVID-19 infections, and SARS-CoV-2 variant as a main factor of uncertainty in the review findings. Although a brief description of each included RCT is provided in Appendix 1, no details are given on those variables within each trial to permit assessment of the potential impact of this heterogeneity.

- In particular, the report states that it is assumed that "all relative treatment effects were transportable to different settings". This meant that the naïve comparison included no assessment or adjustments were made to account for relevant covariates, including: SoC at the time of the clinical study; age; disease severity; vaccination status; history of SARS-CoV-2 infection; geographical location; dosage of relevant interventions. Given that COVID-19 severity and, in turn, patient outcomes, will be affected by these factors – particularly vaccination status, which is highly time-specific – this may have a significant impact on the relative treatment effects.

- It is acknowledged that there are data limitations across the COVID-19 evidence base when considering high-quality data sources, principally due to low clinical trial recruitment rates, which make adjustment unfeasible and lead to the aforementioned uncertainty. Regardless of the associated uncertainty, Pfizer agrees with the AGs approach to consider only the highest quality clinical evidence from randomised trials; broadening of the scope of evidence would only increase uncertainty further.

- Currently, the results report the relative risk (RR) for the following outcomes in outpatients: hospitalisation or death, and all-cause mortality at 28 days. However, the absolute number of the outcomes is omitted. In some studies, these outcomes are relatively rare in both arms (for example, the three casirivimab+imdevimab studies report 0/156, 1/838, 1/1,529 deaths in the treatment arm, and 0/158, 1/840, 3/1,500 deaths in the placebo arm), therefore the RR is very sensitive to event numbers and may be misleading. The raw data, including absolute numbers of outcomes, should be presented in order to aid interpretation.

3. Cost-effectiveness model approach

3.1 Design of cost-effectiveness model

The AG model for evaluation of the high-risk, non-hospitalised (community setting) population does not fully capture all relevant aspects of COVID-19 natural history, treatment pathway, treatment effects and outcomes necessary for decision making. As a result, it does not fully explore the value of treatment in the community setting, so that cost-effectiveness outcomes are vastly underestimated.

In particular, the following omissions are of concern:

- **The residual effect of community treatments once patients are hospitalised should be captured in the model:** The AG economic model assumes that community treatments are followed by current SoC when a patient is hospitalised. While the treatment algorithms for COVID-19 are unclear, it is unlikely that community patients who are hospitalised would immediately transition to receive only current SoC. As stated in the report, community treatments are expected to have a residual effect, which should be captured in the economic model in the form of a long-term impact, reducing costs and improving outcomes. By contrast, patients with declining status are likely to receive the most effective treatment options for hospitalised patients, which are likely to include treatments recommended as a result of this MTA. Thus, this assumption does not reflect the likely treatment pathway for hospitalised patients who have received treatment in the community setting. However, Pfizer agree that the studies assessing community- and hospital-setting treatments are not interchangeable and evidence from each population should not be compared.
- **Disease severity for hospitalised patients should impact on disease progression, mortality or subsequent costs**: In the PSM module, different severity levels should be captured in separate health states/events. While the model does use an 8-point ordinal scale for severity, occupancy on this scale is used to associate with supplemental oxygen and other management requirements and the subsequent impact on health-related quality of life (HRQoL) and costs. However, it does not capture the impact on progression of the disease and other outcomes (i.e. hospitalisation, discharge, mortality) and subsequent costs.

- **Viral load suppression should be reflected in the economic model:** Although viral load suppression was included in the scope of this evaluation, it has not been included in the economic model. Viral load suppression is a key endpoint for many virologic diseases, with impacts on clinical outcomes and disease transmission, and is the surrogate endpoint of interest for economic models, including for HIV modelling.[40] As a result, this decision requires justification by the AG.

- **The economic model should reflect the broader value of new antimicrobial treatment:** Previous assessments of the value of novel antimicrobials have noted that there are additional attributes of value for new antimicrobials that are

not typically included in standard HTA evaluations: diversity value; transmission value; enablement value; spectrum value; and insurance value.[41,42] These values remain relevant to novel antiviral therapies, particularly for COVID-19, where further outbreaks remain likely in the near future. **In particular, it is essential that the following attributes are captured:**

- **Transmission value**: The economic model does not capture the impact of treatments on preventing the transmission of the SARS-CoV-2 virus to non-infected people. The JCVI routinely includes transmission value in assessment of vaccines against other transmittable diseases. Whilst this would add a level of complexity in the model, it has long been established that the transmissible nature of infectious diseases is the critical characteristic that sets them apart from other diseases, with ISPOR-SMDM guidelines on incorporating transmission into economic models published in 2012.[43] Community treatments in particular have a crucial effect on transmission dynamics. The infection rate is a key consideration for the burden of disease of COVID-19, and we recommend that at least a simplistic approach is taken to include this component. The model could follow an approach similar to that used in other communicable disease areas such as HIV[40], through the use of a multiplier to be applied to the cohort, simulating the growth of an "Infected" compartment. This multiplier would reflect the effect of treatments on transmission dynamics and the model could be calibrated for this parameter against published studies.
- **Enablement value**: Enablement value is defined as the value of the benefits of being able to perform medical procedures because of new antimicrobials. This was deemed as a significant area of value in the NICE HTA assessment for antimicrobials. A key value benefit of Paxlovid® is the ability to ensure patients are not in hospital, occupying resources (beds, staff, etc) that could be used to enable other procedures to go ahead. This has not been accounted for in the model. Where possible, and to align with the NICE HTA assessment for antimicrobials, the cost-effectiveness model should look to capture the benefits of releasing hospital resources, that would otherwise be used for treating infections to enable healthcare and procedures in other patients. Where this is not possible, due to time and resource constraints, or lack of data, additional considerations should be made to the level of enablement value that exits.
- **Insurance value**: this refers to the value of having effective therapies available in case of an increase in the prevalence of infections. In the case of COVID-19, where future outbreaks are likely in the near future, the value should be reflected in the economic model.

3.2 Cost-effectiveness model inputs

- **It is critical than a PSA be conducted to assess the full impact of uncertainties within the model and would request that the AG present this**

analysis for further interpretation: The level of uncertainty associated with the majority of the efficacy measures is very high. Most efficacy measures were derived from small sample sizes and highly heterogeneous populations. For treatments in the community setting, the RRs for hospitalisation and death at 28 days have wide confidence intervals (CIs). For the RR for death at 28 days, all CIs crossed 1, except for molnupiravir and nirmatrelvir/ritonavir. As detailed in section 3.3 of this response, no probabilistic sensitivity analysis (PSA) has been presented, making it difficult to assess the impact of these uncertainties.

- For the decision tree, it is unclear how valid the admission rates used in the model are. For SoC, the model used an adjusted rate of admission for a general COVID-19 population, multiplied by 2, to account for the high-risk nature of the population, based on data used for the QCovid3 risk algorithm and clinical advice; however, it is unclear how the published data and advice were used to arrive at the multiplier. Nonetheless, we agree the admission data from *Nyberg et al*. is an appropriate source given the relative certainty that admissions are COVID-19 related. We also agree that it is important to consider the impact of a higher hospitalisation rate, as indicated by alternate data sources, through sensitivity analyses.
- Long COVID was defined in the model as at least 4 weeks of COVID symptoms. The model assumes that 10% of community patients not hospitalized will experience long COVID, based on the prevalence of long COVID in different populations based on vaccination status. Additionally, the AG estimated a mean duration of long COVID by fitting parametric distributions to published Office for National Statistics data. However, both elements fail to capture the differentiation between patients based on their vaccine history and severity of disease – where data allows, scenarios should be run to account for this variance in the population. We are not currently aware of treatments which impact the prevalence of long-COVID. It would be useful to test this assumption in scenario analyses and account for the potential residual effect that community treatments can have on the manifestation of long COVID.

- **The AG should clarify how model inputs were identified and the criteria used to select the most appropriate data from the identified sources:** The AG did not undertake an SLR to identify costs and healthcare resource use associated with the management of COVID-19 in the high-risk population. For infectious disease It may be more appropriate to model opportunity costs for hospitalisation (bed days)[44,45] – this should also be considered. No formal SLR was conducted to identify the most appropriate utility and disutility values to inform the economic model.

- **We suggest more appropriate sources be considered for the utility decrements applied in the model:** We acknowledge that EQ-5D data on COVID-19 are scarce and proxies would be acceptable. While an effort is made

to use values from influenza, the use of HRQoL for hospitalisations not requiring interventions is not appropriate. Values used were obtained from patients with severe diarrhoea and colitis due to *Clostridium difficile* bacterial infection.

- **More appropriate sources for unit costs by ordinal scale applied in the model should be considered**: VC40Z, the code used for ordinal scale 4, corresponds to rehabilitation post respiratory related admission and would be more appropriate to use for long-COVID costs. We suggest non-intensive care unit (ICU) hospitalisations be approximated with ICD-10/HRG codes for other viral pneumonia (J12.8 [Other viral pneumonia], J12.9 [Viral pneumonia, unspecified], DZ11 [other viral pneumonia). Considering the length of stay due to COVID-19 is at least 2 days, the use of non-elective long stay costs would be most appropriate. This approach was used by the UK Health Security Agency (UKHSA) in their cost-effectiveness analysis of vaccination and social distancing measures.[46] The complexity of care level and number of interventions allow for an alignment with the ordinal scores for non-ICU admissions, for example DZ11R-V could be mapped to Ordinal score 3; DZ11N-Q could be mapped to Ordinal score 4 and DZ11K-M could be mapped to Ordinal score 5.[47]

3.3 Model outputs and analyses

It is essential that a PSA be conducted to assess which inputs are causing uncertainty in the model and address this uncertainty: Deterministic sensitivity analyses can only inform the range of values (extremes) expected based on uncertainty, but do not provide a clear picture of the distribution of results according to uncertainty. As many of the estimates used in the model are either based on small sample sizes, heterogeneous populations and/or assumptions, it is crucial that this is tested.

4. Conclusions

Whilst we appreciate the time constraints the AG had to work with during this assessment and the uncertainties that are to be expected as a result, we believe there are some critical issues that should be addressed before this assessment is used to inform the NICE technology appraisal. Primarily: thorough assessment of the current evidence base to define ‘high risk’, which is currently over restrictive and excludes at-risk patients who would benefit from treatment (older age, hypertension, smoking, health care workers, carers etc.), provision of detailed indirect comparison methodology to allow the appropriateness of the clinical evidence informing the model to be assessed, inclusion of a PSA to assess the impact of uncertainties within the model and incorporation of transmission value within the model.

Checklist for submitting comments

- Consultation responses must not be longer than **10 pages**, excluding the references.
- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
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National Institute for Health and Care Excellence
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Pro-forma Response

Executable Model

Therapeutics for people with COVID-19 [ID4038]

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You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. If asked, you must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

July 2022

Issue 1 Reproducibility of low/high efficacy sensitivity analysis

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Reproduction of the low/high efficacy sensitivity analyses is not intuitive. As it stands, to reproduce these analyses you need to change to the 'Low/high efficacy setting' in the Results sheet, then click 'Run results', which runs the macro to change the efficacy. Finally, in the 'Baseline mortality outpatients' sheet, due to a broken macro in the 'Recalculate RRs' button, you need to copy the multipliers from the table to the right into column C (e.g. for the low setting you'd copy J15:J19 into C15:19) to reproduce the results from the report.	To allow these analyses to be easily reproducible the 'recalculate RR's' macro should be fixed to pull the correct multipliers from the 'baseline mortality outpatients' sheet.	NA

National Institute for Health and Care Excellence
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Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. Deadline for comments **5pm** on **Friday 29 July**. **Please submit via NICE Docs**.

Your name	[redacted]
Organisation name	Roche
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Please comment on the assessment report
We appreciate the efforts in producing such a broad Assessment Report and recognise the challenges linked to such an endeavour. Nonetheless we believe some analyses and consequent limitations would benefit from more clarity. As an example, differences in mean efficacy results often are marginal, due to the available evidence. In such cases not only the incremental analyses, but also the variation of ICERs can be uninformative. Priority comments 1. page 48 - 3.2.9 Long Covid *"The EAG was not aware of any evidence on the impact of community treatment on the incidence of long COVID and thus it was assumed that this was independent of treatment."* Jovanoski et al. 2021 (1) show that patients on more invasive oxygen support are more at risk of developing health issues after infection. Thus, given that the interventions lead to an improvement in the 8 point ordinal scale, it is to be expected that long-COVID would be more prevalent in patients who received SOC. (1) https://pubmed.ncbi.nlm.nih.gov/34893488/ *2. pg 53 - 3.3.4 Costs associated with COVID-19 for outpatients or following discharge.* It is unclear why no difference between treatment arms was assumed. As per point 1 above, the lack of differentiation should be highlighted as a key limitation, if not accounted for. The way long term impact and cost are modelled seem to penalise effective treatments. 3. pg. 39 - 3.1.2 *General model structure for non-hospitalised patients:* "*The proportion of hospitalised patients requiring supplemental oxygen was estimated from an ISARIC report where the requiring oxygen of any level on admission was calculated at 81% (55% high flow oxygen, 16% non-invasive ventilation, and 10% invasive ventilation)."* It is unclear how this accounts for the effect that interventions have on this outcome. In the absence of this differentiation, this should be pointed out as a key limitation. 4. *pg. 45 - 3.2.4.3 Movement between ordinal scales between day 0 and day 14: "for simplicity these proportions were assumed to remain constant after day 14."* We would welcome more granularity on this assumption or an explanation that it does

not capture treatment benefits beyond day 14 on this outcome, as well as between day 1 and 14. It is unclear what impact this assumption has.

Other comments:

5. For scientific accuracy purpose only, we suggest amending where appropriate the definition of 'mAb (monoclonal antibody)' as applied to casirivimab/ imdevimab to 'neutralising mAb' and of 'immunomodulator' as applied to tocilizumab to 'immunomodulating mAb' respectively. This would also impact sotrovimab and lenzilumab, respectively 'neutralising mAb'and 'immunomodulating mAb'.

6. Pg.8 "plain English summary…"*However, the value for money of these treatments have not been estimated."*

Published studies do exist that analyse the cost-effectiveness of some of the interventions. Suggest making this statement more setting specific.

7. Figure 4 pg. 29 "*The probability that the intervention used in hospital is associated with increased mortality based on the lognormal distribution derived from the living systematic reviews".* It is unclear how this information was produced, how the probabilities are calculated and why that method was chosen and how to interpret it.

8. Pg. 31 *"These wide CIs mean that there is a considerable probability (of more than 0.1) that all interventions except molnupiravir and nirmatrelvir/ritonavir could increase the risk of death, although this is a frequentist interpretation of the distribution and does not consider any correlation between reduced hospitalisation rates and the reduced probability of death."* Hospitalisation and death are competing risks and it is unclear how this was accounted for. The interpretation that there is considerable probability for interventions to increase risk of death seems questionable without further clarifications.

9. *pg.41 Table 8 "Hospital Admission and Death weekly numbers and percentages by age band compared to the whole population (mid May 2022)"* Use of external sources to inform models can lead to issues if differences exist between trial and external source populations. It is unclear as to how this may impact the ages calculated for the model, and thus, impact the results.

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Your name	[redacted]
Organisation name	Down's Syndrome Association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Please comment on the assessment report

The Down's Syndrome Association is a national charity focusing on all aspects of living successfully with Down's syndrome. Established in 1970, we have more than 20,000 members throughout England, Wales and Northern Ireland. The Association is in contact with over 130 affiliated local support groups and a range of professionals from different agencies. The aim of the organisation is to help people who have Down's syndrome lead full and rewarding lives.

We are the lead provider of information, advocacy, support and training to anyone with an interest in Down's syndrome. We are a membership-led organisation, with our membership comprising primarily the family-carers of children and adults with Down's syndrome and a growing membership of adults with Down's syndrome aged 18+. We are well placed to reflect the needs and views of people we seek to serve.

We have a commitment to inclusive participation and work closely with a diverse group of individuals who have Down's syndrome called "Our Voice", who come together regularly to help shape and inform our work.

Down's syndrome is a genetic condition, caused by the presence of an extra chromosome 21 in the body's cells. Everyone with the condition will have some degree of learning disability. In addition, there are a number of associated medical conditions, which affect some, but not all, people who have Down's syndrome, meaning the services that they access from the NHS (and social care settings) are of paramount importance to their wellbeing.

The number of people in England and Wales with the condition was estimated as 37,0901 in 2013.

The Down's Syndrome Association provides lifelong support, in the form of information and advice for people who have Down's syndrome and their parents and carers.

Individuals who have Down's syndrome and their experience of COVID-19

Individuals who have Down's syndrome were identified as being Clinically Extremely Vulnerable to COVID-19, following the publication (in the BMJ) of the *Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study* in October 2020.This study showed that adults who have Down's syndrome were up to 13 times more likely to die from COVID-19 than individuals, of a similar age, without Down's syndrome.

People who have Down's syndrome aged 16 and over were prioritised for COVID-19 vaccination at priority group 4 in the initial vaccine roll-out and younger children were prioritised for early access to COVID-19 ahead of the general population of children.

A minority of individuals who have Down's syndrome and have an additional health condition (e.g. a blood cancer) or are receiving a treatment, such as steroid medicine, biological therapy, chemotherapy or have had an organ or bone marrow transplant means they meet the criteria to be classed as immunosuppressed, have been offered a 4th (spring) booster

[1] Wu J, Morris JK The population prevalence of Down's syndrome in England and Wales in 2011 Eur J Hum Genet 2013 Sep; 21(9):1016-9. doi: 10.1038/ejhg.2012.294. Epub 2013

dose. All individuals who have Down's syndrome aged 5 and over will be eligible for an autumn booster from September 2022.

The experience of the COVID-19 vaccination programme has generally been extremely positive for people who have Down's syndrome. Uptake has been high and the performance of the vaccine (amongst those who are not immunosuppressed) appears to have been good. However, anxiety levels remain high, the fear of becoming unwell, should an individual who has Down's syndrome be infected with COVID-19 is ever present. Access to COVID-19 therapeutics have, therefore, been fundamental in the confidence of people who have Down's syndrome to begin to resume normal patterns of living.

From the autumn of 2021, anyone who has Down's syndrome aged 12 and over been eligible for a COVID-19 therapeutics assessment and this has been a crucial additional mechanism in the protection being afforded to this patient-group.

We realise the focus of this report is on appraising the relative costs and benefits of the range of therapeutics for people with COVID-19. We are not health economists, nor are we clinicians, but we wish to offer here, in our response to this important investigation, the experience of a patient-group and in so doing, indicate that **many of the potential benefits of antivirals and other licensed treatments are being missed because the system of facilitating access to these appears to have significant flaws.**

We were initially fearful that stopping asymptomatic community testing for COVID-19 across England in the spring of 2022 might significantly impede the ability of people who have Down's syndrome to keep themselves safe. However, letters sent to families outlining how relevant individuals can continue to access tests and the process of continued access to free tests appear to be effective.

The initial step towards identifying an eligible person who has Down's syndrome for COVID-19 therapeutics (i.e. a positive test being communicated to the NHS and this being flagged) seems to be effective. However, from this point onwards, the system appears to be broken.

Since the autumn of 2021, our helpline has received very many calls from families telling us the process, outlined in the letters sent to them about being eligible for COVID-19 treatments, is not being followed.

Typically, individuals are on day 4 or day 5 following a positive test and have failed to receive a call back to facilitate contact with a COVID19 Medicine Delivery Unit. The particular failures are:

1. NHS111 staff being unaware of their role in the system. They do not seem to have to hand any information relating to the agreed pathway for referral to a CMDU.
2. Once more than 48 hours from a positive test has elapsed, families who follow the advice given in the NHS letters they had last year about COVID19 therapeutics, call their GP and are met with opposition. Primary care staff invariably tell families to call 119 (which is not the agreed protocol). Other GPs refer families back to NHS111 and there is frequently a stand-off that can last several days.
3. The majority of eligible patients in these scenarios get "timed out" and find themselves on day 6 or 7 following a positive COVID-19 test, meaning they are too late for the treatments to be effective
4. Additionally, there are a series of difficulties for families of *children* who have Down's syndrome being able to access a CMDU with the capacity to prescribe for anyone under the age of 18. Many ICBs have not commissioned a paediatric CMDU facility. For example, a family in Hull (who were on day 5 of waiting for a CMDU assessment) eventually discovered that their nearest paediatric facility was in Leeds – an hour and half away.

These issues are not localised to a particular area or isolated in their occurrence and have occurred in the North, South, East and West regions of England (and are replicated in their frequency across Wales, too).

We have fed-back these operational issues to relevant policy leads at NHS England and Wales and to the DHSC, but make these comments in our feedback on the NICE commissioned report here, as we feel these significantly impact on the potential benefits being experienced by patients.

In initial discussions with DHSC, it was noted that there were plans to increase the range of clinicians able to prescribe the COVID-19 therapeutics. We would be supportive of that and if possible, would suggest that primary care teams are given a more direct role in this pathway.

Returning to the narrative of the report, it is disappointing, but understandable (given the timing and numbers of patients who participated in the study), that there are no differentiated recommendations of the relative suitability of different COVID-19 therapeutics for specific patient-groups. If, in time, it were possible to interrogate data to ascertain this, it would obviously be beneficial to have the additional intelligence on whether a specific therapeutic was more effective for individuals who had Down's syndrome (or any of the other conditions which make an individual eligible).

We would highlight that, for a significant proportion of individuals who have Down's syndrome, a venous route for a medication can be more problematic, due to the willingness of the individual to submit to this process. These issues can frequently be overcome with the right approach, but the skill level of clinicians working in settings differs greatly, as does the availability of specialist learning disability nurses, who can provide additional supports and advice on strategies to assist compliance and minimise distress. For this reason, there seems to be an inherent advantage to those therapeutics that can be administered orally and ideally in the community, removing the need for an individual to attend a clinical setting.

Finally, in assessing the benefits of the COVID-19 therapeutics, we would emphasise:

1. Individuals who were originally designated Clinically Extremely Vulnerable felt the effects of the pandemic earlier than the general population (as they began to 'shield' as a way of mitigating their risk of being infected and to deal with anxieties) even before this became established advice.
2. Even though formal shielding advice and the CEV patients list was wound-up many months ago, many individuals previously designated CEV still experience very high levels of anxiety and some people are still 'shielding'. Ensuring there is ready access to COVID-19 therapeutics, is one way of providing reassurance to affected individuals, especially during periods when community transmission remains so high.
3. The value to individuals who have Down's syndrome to be able to return to paid work, education and reengage socially is hard to overestimate – it is of paramount importance, as these freedoms have been very hard won.
4. The detrimental emotional and psychological impact of hospitalisation must be noted. For individuals who have a learning disability, being in a hospital setting, especially a critical care setting, can be very stressful. Difficulties in staff being able to make reasonable adjustments (especially around investing time in finding appropriate ways to communicate with a patient) can make these experiences very traumatic. The value of preventing a hospital admission for someone who has a learning disability should therefore be given greater weight in these cost / benefits calculations.
5. The cost to family-carers of a hospital stay for an child or adults who has Down's

syndrome (both emotional and monetary e.g. a parent missing work) should also be noted. Any therapeutic which prevents a hospital stay has a value that extends beyond just the patient.

By way of illustration, we end our submission with two anonymised (but real examples) of families' accounts of accessing COVID-19 therapeutics. These examples are typical of many and both are from June 2022

Firstly from a mum to a 17 year old who has Down's syndrome:

"Wed 15th : M tested positive. Reported at 10am via my NHS log in. Selected boxes for entitled to treatment. Selected vulnerable patient. Received texts, emails and phone calls to confirm receipt of notification of positive test. Track and Trace phoned and I made sure I checked with them that I am to expect contact re anti-viral treatment and if nothing in 48 hours to ring 111.

Fri 17th : Phoned NHS 111 as still had not been contacted about antivirals. Referral was made to anti-viral service. Mid-afternoon - phone call from CMDU. They took relevant information, but then said as he is under 18, NHS111 should have referred through to paediatric service. I thought she said she was putting me through, so I did not hang up. Call was ended and I had expected someone to ring back, but nothing.

Sat 18th : 11am - phoned 111 (half hour wait to speak to someone). Explained situation, someone to ring me back. Phone call from 111 to take a new referral to CMDU. Explained we had this far the day before and that I had been told they should have referred to paediatric team. 111 operator did not know where to refer a child. By this point, the CMDU team had closed for the day, so they could not be contacted. I kept this person on the phone for ages, at one point she even suggested I phone the children's ward at the hospital; she seemed to think our consultant would be the person to contact. I explained about the letter we had received, and I therefore didn't think it was the consultant who had hand picked him as eligible. She suggested I phone the Public Health Team. I did not think that would lead to anything on a Saturday afternoon! I suggested GP out of hours; she said they could not do anything. She went off to speak with a manager- who eventually made a referral to GP out of hours.

.

Sat evening : Phone call from GP. Gave her an overview and they arranged for on-call doctor to give a call back. Doctor phoned me and said she had just phoned our general hospital and asked them to find out what the procedure is, and to phone me back.

Sun 19th : Finally a phone call from the CMDU. Explained what had happened so far. She said she is hesitant to proceed, as M is under 18. Would discuss with her team and phone me back. Phoned me back and said she is emailing the anti-viral team and to expect to be contacted by them tomorrow.

Mon 20th : Phone call from one of the paediatric consultants at the hospital who was phoning in response to the ongoing GP out of hours enquiry. I explained what had happened to this point. Consultant was in the process of speaking with pharmacy and finding out how to proceed. Phoned me back lunchtime asking me to bring M to the ward. This is where she explained that they have never done this treatment, he was the first. (Why am I not surprised - everyone else probably gave up)"

Example 2 – a parent of a 16 year old (mum happened to be a clinician herself):

"Our GP surgery is xxx I called them after waiting for 111 to call me back to no avail. The receptionist had no idea what I was talking about, even when I read her both the letter we

had received from NHSE/I and the email to GP practices from the NHSE/I website. I asked for an appointment with a GP to discuss it, which was made and then an hour later cancelled by the practice manager.

I finally (through further calls to 111 and a friendly local infectious diseases consultant taking pity on my Tweet) got through to our CMDU. They said there is no local provision for children (anyone under 18) and that children would usually get referred out of region, to Leeds. I knew the CMDU Lead, as I used to work with her, so she was able to discuss the risks/benefits with me, but I know ours was not an isolated situation"

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Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

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Your name	[redacted]
Organisation name	Kidney Care UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a

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Please comment on the assessment report
1.4.5 We note that there was not time to explore the impact of immune system competence on the assessment of clinical and cost effectiveness. However, we recommend that the committee consider whether additional time should be provided to carry out this assessment. As you'll be aware, studies such as Octave have found a much lower response to vaccines among people who are immunosuppressed and it is likely that post-infection treatments are more important among this group. Given the potential lack of protection from vaccines it is important to accurately understand the value of the Covid therapeutics over usual care at preventing severe illness, hospitalisation and death in this vulnerable group. This would enable properly informed decisions can be made about how to provide the best protection possible. Future work: We also note the authors statement that "Contemporary information related to the probability of hospital admission and death for patients at high-risk in the community would improve the precision of the estimates generated as would ascertaining the average age of this population." Kidney Care UK have been calling for better information relating to outcomes for people in the high-risk group for just this reason and we hope that NICE strongly recommend this data is made available. We have noted that the prophylactic treatment Evusheld (which can also be used post-infection) is not included in this review although it was authorised in March 2022 by the MHRA and has been used on patients in some studies e.g. TACKLE. There are a large group of patients who have asked for wider access to it and we wonder whether consideration can be given to including a research recommendations for further research into its clinical and cost effectiveness.

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Your name	[redacted], [redacted]
Organisation name	Long Covid SOS
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Please comment on the assessment report

This report concerns the use of eight therapeutic agents use in acute hospitalised COVID and is primarily based on the large drug platform trials.

There are three knowledge gaps which will be addressed by ongoing research which will affect the findings and the interpretation of this report.

First, it is important to note that the scope for efficacy in the hospital and those at high risk in the community of being hospitalised may need to be revisited at a further date as the impact on Long Covid, i.e. the chronic disease resulting from a Covid infection, becomes more understood.We need to know who these individuals are (especially those who will experience the greatest impact) and how to identify them. Hopefully research studies such as CONVALESCENCE will narrow this gap. However, a key limitation is the collection of data in the community and the follow up that occurs.

Second, the impact of these agents across different waves of the pandemic in different vaccination scenarios needs to be updated in an ongoing manner.

Third, the impact of these agents on Long COVID is not known and barely assessed to-date. This can be addressed by longer term follow-up for long COVID in existing trials for acute COVID such as RECOVERY and PRINCIPLE trials, but also by dedicated Long COVID drug platform trials like STIMULATE-ICP (https://www.stimulate-icp.org/).

This is important as the assumption made is that the treatment in the acute COVID-19 phase has no impact on the development of Long Covid within the model (report section 3.2.9). The PANORAMIC study, assessing treatment in the community, has measurement points at 3 and 6 months, so should be able to provide information on the numbers going on to develop Long Covid. One of the current theories for Long Covid is that of viral persistence which would mean that these treatments would be expected to lower the probability of developing Long Covid, if this is the case.[1]

There have been several assumptions made for the measurement of Long Covid within this model, which may under-represent the health and social care cost.

First, the estimate of age at the midpoint (65) will highly skew the HRQoL measurement out of the working age bracket and into that for retirement/ nearing retirement (report p41 para 2). This may not be reflective of those in the community at risk of being hospitalised who may represent a lower age bracket similar to that reported in Long Covid studies.[2][3][4]

Second, a paper for the treatment of Chronic Fatigue System (CFS) which was looking at fatigue and the use of physiotherapy and occupational therapy was used for the management cost of Long Covid (report section 3.3.4.2, ref 55). Long Covid is a multi-organ condition and can present with

[1] https://www.science.org/content/article/what-causes-long-covid-three-leading-theories
[2] https://ifs.org.uk/uploads/BN346-Long-COVID-and-the-labour-market.pdf
[3] https://www.nature.com/articles/s41591-022-01909-w
[4] https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00299-6/fulltext#seccesectitle0027

cardiovascular, respiratory and neurological symptoms in the clinic.[5] There may, therefore, be more costs expected to be associated with management and investigations required.

[5] https://bmjopenrespres.bmj.com/content/8/1/e001041

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Your name	[redacted]
Organisation name	British Thoracic Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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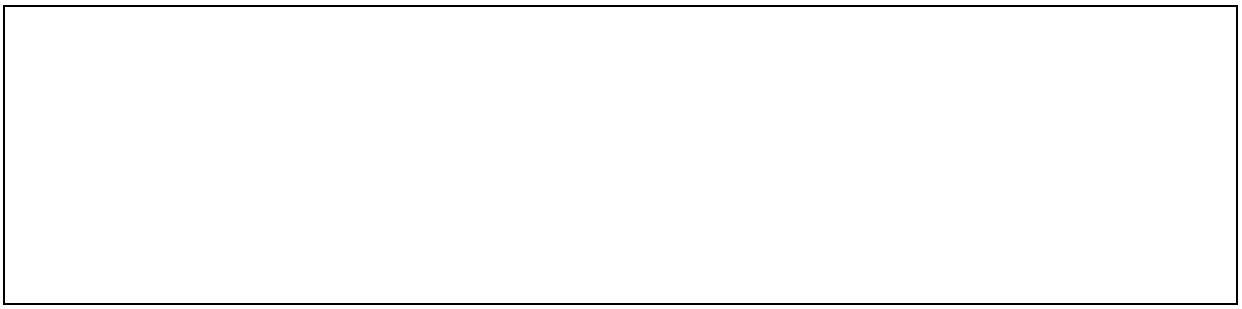
Please comment on the assessment report

1. We question the inclusion of Ronapreve given that it does not work for Omicron and has not been used clinically for a year or so.

2. The manuscript acknowledges pandemic phase and circulating variant is key to interpreting the data – yet then analyses the data as one set anyway. Is it valid to attribute data collected in April 2020 to management going forward? Even if this is noted as a limitation?

3. Why no dexamethasone? The headline from a study such as this should be that the most cost effective drug is dexamethasone.



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National Institute for Health and Care Excellence
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Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. Deadline for comments **5pm** on **Friday 29 July**. **Please submit via NICE Docs**.

Your name	[redacted]
Organisation name	Faculty of Pharmaceutical Medicine
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Please comment on the assessment report

Comments on NICE assessment report – Therapeutics for people with Covid 19

Overall comments

Overall

We welcome the fact that the report states that interventions in COVID-19 are cost effective. This a brave attempt at the impossible. We know this is a huge challenge for treatment of acute infections, though we are a little confused as to why there are anti-inflammatories widely used for supportive treatment for respiratory failure in the same report.

Timing

The analysis seems premature given that the NHS is not offering a 'normal' service to the public currently and repetitive waves of 'endemic' strains of COVID-19, leading to very high community infection rates is still proceeding and is resulting in sustained high levels of hospitalisation during waves, continuing to disrupt usual activities within hospital care.

With a backlog of more than 6 million people awaiting care for 'non urgent' conditions, disrupted cancer care and reduced access to cardiac surgery one might reasonably think that the ongoing costs of the disruption might be reason enough to consider an altogether different approach when weighing up the cost benefit of active vs passive management of covid rather the simplified individual QALY approach.

Key issues

FPM has identified:

- Issues related to actively deciding not to take differences in variants into account
- Assumptions have been made that anti-inflammatory outcome can be aligned and compared to antiviral treatment even though they are used in totally different groups of patients
- Trial data has not been validated or had a quality review and used data from incomparable sources and use of 8 point WHO data throughout the clinical outcome and costing model is no longer appropriate.
- Pre- and post- exposure treatments are not included and are as important to reducing hospital burden in some elderly and immunocompromised patients as vaccines
- Unlicensed treatments have been included
- Pricing data is only valid for tocilizumab
- No consideration of the serious long covid issues were factored in, especially re-hospitalisation
- Using May 22 data as the pricing benchmark, the lowest incidence data between waves is not helpful going forward to further waves or even the event incidence today (hospitalisation is currently (29.7.22) >3 times what it was in May).

The report cites need for speed, lack of time, need to compromise from using best or even good practise, using a lot of assumptions, variability of data, caution with interpretations and conclusions.

This failure to account for the variants in circulation in different settings at different times and the subsequent assumption of transportability of the treatment effect is a fundamental flaw within the study.

We believe that, as it stands, the paper may actually be harmful to public health, especially as we are currently at the peak of another wave and will no doubt face significant waves again in the near future.

Abstract and Scientific Summary

Abstract

Methodology and Results

The abstract does not emphasise enough the limitations of the study all listed by the authors in the methodology and results and is therefore misleading. For example

"*analyses indicated that baricitinib may be the most cost-effective treatment in a hospital setting and that nirmatrelvir with ritonavir (at an estimated price) may be the most cost-effective treatment in the community setting*"

These two treatments cannot be compared they are different mechanism of action and different patient populations.

"*many assumptions were required that limit the accuracy of the estimates of clinical- and cost-effectiveness*"

The statement includes a mention of variants but not that the impact of a new variant may render a particular therapeutic ineffective. If this variant becomes dominant within the population, the effectiveness of prescribing an ineffective therapeutic would be severely limited. Unless testing for specific variants is available at point of care, any cost-effectiveness model must include a variable relating to variants over time.

It should also be noted, as new variants emerge, any analysis will need to be redone with efficacy data against the particular variant.

Conclusions

"The results produced should be informative to decision makers, although conclusions regarding the most clinical—and cost-effective intervention in these settings should be tentative given the heterogeneity between studies, the evolving nature of the decision problem and the uncertainty in the costs of interventions."

This assessment is not robust enough to be informative as it stands. It could even be misleading and does not encourage effective management by treating clinicians, who generally know oral treatments are more cost effective than parenterals.

Future work

"Research assessing the relative clinical effectiveness of interventions within head-to-head studies would be beneficial. Contemporary information related to the probability of hospital admission and death for patients at high-risk in the community would improve the precision of the estimates generated as would ascertaining the average age of this population. Value of information analyses may efficiently direct future research."

For anyone involved in research in COVID-19 outcomes for both hospitalisation and non-hospitalised studies this is very simplistic and probably not achievable. There are many other things that could be done that would have more value in specific subgroups.

Scientific Summary

Comments in the scientific summary reflect those in the table for the report.

Report

Background

Page	Issue	Comment
Page 16 1.1 Background	Variability of ascertainment of cases	Since the 'Living with COVID' strategy was launched it has been worse – impact number of cases since LFTs stopped is unreliable
Page 16 1.1 Background	Should the risk of death following COVID-19 remain at low levels and SARS-CoV-2 becomes endemic in society, then treatments for patients with COVID-19 may no longer be treated differently to interventions for other conditions such as breast cancer or heart disease. If this above were the case, then it could be considered logical and acceptable that pharmacological treatment for COVID-19 would be appraised by the National Institute for Health and Care Excellence (NICE) using its standard methods	The conditions quoted here are completely different. The analogy would be other treatment for acute infections for antivirals and anti-inflammatories for ARDs. Antibiotics for pneumonia are the obvious analogy for antivirals and have always been considered a real challenge due (as with COVID) to the number of healthy young who get pneumonia and recover for many years of healthy life. Thus, in the past it has been considered that the use of "standard methods" needs a fairly stable and predictable disease with a consistent pathophysiology and treatment response. COVID is not showing signs of entering a phase of stability with another wave, with new variants, underway at the time of writing. Therefore, consideration of standard methods is not necessarily appropriate at this time.
Page 17 1.4.1 NICE scope	Following discussions with NICE, the definition for patients at high-risk was aligned to that … of (PANORAMIC) clinical study, with the exception that being aged 50 years or over was not considered to be a high-risk factor.	This would only apply to antivirals. Unfortunately, although it may have seemed pragmatic at the time, it removed all older people from the analysis and does not align with the licensed conditional labels, the remaining criteria are very limited e.g. a 90 year old with acute kidney failure would not be included as only CKD is an inclusion.
Page 17 1.4.1 NICE Scope	The aim of treatment differs between each group. For patients hospitalised due to severe or critical COVID-19, the aim of treatment is to reduce the immunoinflammatory response of the body and prevent clinical deterioration.	Some hospitalised patients also need to receive antivirals depending on when they were infected.
Page 17 1.4.1 NICE Scope	For non-hospitalised patients, the aim of treatment is to prevent viral replication and damp inflammation, thus reduce the probability of the development of severe symptoms that could lead to hospitalisation and death.	The aim for non-hospitalised patients, as stated in the report, is not accurate for any patients and particularly not immunocompromised. In non-hospitalised patients in the first phase of disease inflammation is upregulated and anti-inflammatories should not be used and there is data from RECOVERY showing it makes the outcome worse. This is why immunocompromised patients are at risk. Therefore, in non-hospitalised only antivirals should be considered.
Page 17 1.4.1 NICE scope	Missing comments	There is no comment here about timing of infection and onset of symptoms. There is a clear trajectory of viral load determining when antivirals are most valuable. The antiviral studies all include this data.

Page 18 1.4.2 Interventions	Multiple interventions are indicated for the prevention of severe COVID-19.	None of the treatments are indicated for "prevention of severe disease" except sotrovimab.
Page 18 1.4.2 Interventions	Severe disease in adults is defined as ….	This definition is a non sequitur here and is misleading, as none of the endpoints of the trials used this as an endpoint – this definition is the current adapted one for clinical use, which has changed over time.
Page 18 -21 1.4.3 Comparators	The eight treatments used for the treatment of COVID-19 in hospital or used in the community in patients with COVID-19 at high-risk of hospitalisation.	How were the treatments chosen? Why have antivirals been mixed with anti-inflammatories The two treatments are used in completely different stages of disease (anti-inflammatories for example being contraindicated in moderate disease). They have completely different outcomes not like oncology where a longer-term outcome of survival might be applied to treatments with different MOAs. Why are pre- and post- exposure prophylactics missing? Several organisations repeatedly raised the need to include therapies for prophylactic and post exposure prophylactic use at the engagement workshop and were repeatedly informed this was not in scope for this assessment, yet it also has a conditional license. Evusheld has a conditional license and should have been included. FPM strongly recommends these therapies administered for prophylactic use should be included within the scope of the assessment. Why is Ronapreve included? It is currently inactive against any VOCs and sotrovimab also has a major question of concern regarding efficacy for Omicron BA.5. Why have non-indicated treatments been included? Evusheld has conditional approval and baricitinib and lenzilumab are not licensed for the indication in any type of license. Errors in the tables 1 & 2 The allocation to full license and conditional approval is incorrect, which is important as conditional approvals generally are not given a price.
Page 18 1.4.3 Comparators	SoC has evolved throughout the COVID-19 pandemic, which means that randomised controlled trials (RCTs) conducted comparing interventions against SoC may not be directly comparable as SoC has improved over time.	It is correct that RCTs conducted at different times are not comparable. This means most remdesivir early trials are not comparable with Paxlovid or even molnupiravir. This statement should clearly be made in the limitations.

Page 22 1.4.4 Outcome measures	The cost-effectiveness of the eight treatments were expressed in terms of incremental cost-effectiveness ratios (ICERs) which were reported in terms of cost per quality-adjusted life year (QALY) gained. A patient lifetime horizon was used to take differential mortality between treatments into account	We believe QALYs are a challenge in acute infection (especially in the community) and were not traditionally used for antibiotics due to the variability of patients in the population, so patient lifetime horizon may be unreliable especially as older patients without comorbidities were excluded which would have distorted the model.
Page 22 1.4.5 Subgroups	Due to time constraints, the only subgrouping considered was related to whether oxygen was required upon admission to hospital entry	SOC giving oxygen on hospitalisation varied hugely both over time and geographically and in many countries all patients are routinely given nasal prongs on admission. There are many other subgroups that could be relevant.
Page 23 2.1.1 Rationale for using living reviews	COVID-19 clinical research has accelerated dramatically worldwide, with over 5000 registered trials investigating therapeutic interventions for COVID-19.8	This is misleading – there are very few trials on the treatments being studied.
Page 23 2.1.2 Selection of living reviews	Several living systematic reviews that incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple COVID-19 treatments, have been robustly developed and published.	Whilst the robustness of these reviews is excellent, they were not designed primarily to assess cost effectiveness. The problem here is the quality of data - as rigorous audited pharma trials are the only ones conducted on Paxlovid and a huge mixture of academic and pharma for remdesivir and tocilizumab, some inadequately powered. There is a limited number of trials overall. It might have been better to extract the reliable trials and run the usual Quality review. The analysts appear to be sacrificing a robust analysis for speed, is speed of pricing such a high priority? Given the high levels of uncertainty that the authors describe, the authors must look to refine their methods to include a literature review, before making conclusions that will directly affect patients' lives. This is illustrated by the statement "Double checks of the extracted data against the original RCT publications for accuracy could not be undertaken within the deadlines of the project".

Page 24 2.1.3 Assumption of transportability of relative treatment effects	Transportability of relative treatment effects and Adjustments made for changes.. "Across time SoC has changed markedly, most particularly with reference to the widespread use of corticosteroids such as dexamethasone and change in SARS-CoV-2 variants… Ideally there would be attempts to establish the impact of different circumstances on the observed clinical effectiveness of interventions in studies, although this was not possible within the timescales of the project. As such, the EAG had to make a simplistic assumption that none of the changes were treatment effect modifiers	Impact of variants A failure to understand the variants in circulation in different settings at different times and the subsequent assumption of transportability of the treatment effect is a fundamental flaw within the study. The variability caused by consecutive variants and changes in inclusion selection and outcome measurements, SOC and many aspects of trial design and clinical treatment is a characteristic that makes managing COVID challenging. The failure to recognise this within the study render the results extremely crude telling us oral treatment are, on the whole cheaper than expensive parenterals rather than measuring full impact. An exemplar is: If the incidence of hospitalisation falls by >50% and all-cause mortality by >75% mortality even more then there can be no transportability of HE from non-hospitalised treatments – whilst the sensitivity analysis takes some of this into account, it does not take into account the huge challenge of running and analysing very large studies. Impact of vaccination Many of the studies were conducted prevaccination – this should not impact patients with severe respiratory consequences and ARDS needing but markedly impacts outcomes of trials conducted pre and post vaccination.
Page 26- 32	Hospitalised data	Time to death and other measures of outcome – for hospitalisation is an unreliable comparison between antivirals and anti-inflammatories. Remdesivir and Ronapreve tend to be used in a different patient set to the anti-inflammatories. These two groups are not comparable as the treatments work in completely different ways in different patient subsets. This applies through all the hospitalised data sets.
Page 26-32	Non hospitalised data	This data is all impacted by that fact that by then the studies were complete. An exemplar is the death rate is so low for studies of molnupiravir, Paxlovid and Sotrovimab means this data is not comparable and SOC very different for remdesivir the studies were a different design and different timeline.
Page 36	Table 7	Patients in category 1 who had pneumonia would not have no limitations of activities and in reality could only be =>2 also sotrovimab must be symptomatic so also =>2 also tocilizumab tends be started at least at ICU or CPAP.

Methods

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The cost-effectiveness of the eight treatments were expressed in terms of incremental cost-effectiveness ratios (ICERs) which were reported in terms of cost per quality-adjusted life year (QALY) gained. A patient lifetime horizon was used to take differential mortality between treatments into account	The QALY may be more appropriate for treatment of ARDs, and related conditions may be relevant for a QALY because the life expectancy of the patients in immediately pre HDU and ICU may be more standardised. There have been alternative methods used for acute infections where QALYs for antibiotics have been recognised to be a challenge. There is a high probability that industry modellers will have constructed a Markov model already which could be populated with UK 'live' data - this at least will give baseline data from current SOC.	Consider discussing with relevant companies appropriate models to use and how comparisons might be made. Also recognise the limitations.
Use of concomitant treatments and comparing anti-inflammatory treatment in critical patients with antivirals in patients recently hospitalised.	The treatments fed into the model should not be considered separately as in a hospital setting some are used concurrently and overlap with some SOC which will include in later studies for hospitalised antivirals, tocilizumab, for example and vice versa for antivirals.	Separation of antivirals from anti-inflammatories would be more informative
Use of 8-point scale	Whilst 8-point scale was originally proposed and used in ACTIV I it was replaced in June 2020 by a 10 scale because grades 3 and 4 (patients	Drop 8-point scale and use, hospitalisation, discharge, or progression to ICU/HDU or mortality. Community studies can use

	symptomatic and not given O2 don't go into, or stay, in hospital) meaning only 3 points are used in hospital. Its use out of hospital has been almost useless due to difficulty of collecting reliable data.	scales to measure when the patient is recovered, and several are available or duration of shedding and LFTs.
The modelling did not assess the logistics of treatment in the community, but the EAG notes that this could be a large factor in deciding which treatments could be preferred, as oral treatments could be more acceptable to patients and healthcare systems than treatments that are given intravenously or subcutaneously.	Take logistics into account	The difference between oral and parenteral will be further stretched and you could then include less risky patients than the very limited group included and illness duration rather than simply hospitalisation. It would, however, imply the route of administration (oral) was the deciding factor for which treatment is used, a concern that treatments decisions should be on more effective / suitable treatments rather than ease for the "healthcare system".
Using Omicron data for from May 22 for clinical application	ONS data shows that hospitalisation and infections data in May 22 were the lowest in the UK since the start of the outbreak – this should be stated much more clearly – BA 5 hospitalisations with a longer time since vaccination shows hospitalisation of more than 3 times that in May and we have no reliable infection rates. Reinforce sensitivity analyses the 5% is not high enough	The data will be more useful for forward planning of future waves
Page 54 3.3.4.2 Costs associated with long COVID - The EAG assumed that management costs for long COVID was similar to the management of chronic fatigue syndrome. For time constraints, the EAG pragmatically searched for literature and found an economic evaluation study evaluating multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome in the Netherlands.55 Healthcare resource use included GP care, mental healthcare specialist, paramedical care,	We consider this to be huge underestimate – the authors have not considered thrombosis and other conditions more serious than "chronic fatigue," which may require (re)admission to hospital or mental health illnesses. There are AHA studies and the Swedish registry showing significant rates of	The impact of hospitalisation on cost to future care has been considerably underestimated

medical specialist care, hospital care, medications, alternative healers, company physicians, and the evaluated interventions. The EAG substituted the company physician cost with GP care and noted the similarity in costs between arms when intervention costs were excluded. An average of the two costs was used, which resulted in an annual cost of €1195. After conversion using the average of the HMRC rates56 published in January and December 2016, and inflation using NHS cost inflation index pay and prices indices,54 an annual cost of £1013 was estimated for patients with long COVID	myocardial infarction and stroke up to approximately 5% and many predict DM long term consequences. As stated in the report sepsis (in ICU) has many downstream consequences not least, suicide.	
The average age of people in the community with COVID-19 at high-risk of hospitalisation also had a marked impact on the ICERs, with younger people making the drugs more cost-effective the average age used is probably inappropriate in this model	Age over 50 was removed as a criterion for high-risk patients used. This may have lowered the age <60 and would have a big impact on the immunocompromised community especially for a future parenteral treatment. In this context parenteral should be evaluated separate to oral	This would make both parenteral and oral treatments potentially more cost effective
Assumption of Day 14 data for remdesivir	Remdesivir data was conducted at a completely different time making most outcome data used in this analysis inappropriate. The use of Day 14 data in this way just exaggerates this.	Remdesivir as the only parenteral ARV and one in which trials were conducted a different time should be analysed separately.
Conditional approval drugs don't have list prices as I understand it and therefore using US prices is not appropriate	Use only tocilizumab for pricing?	
WHO 8-point scale Table 13 levels 3 and 4 essentially do not exist in UK now so why give them a price?		

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Your name	[redacted]
Organisation name	Royal College of Physicians
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have no such connections or links past or present

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Please comment on the assessment report

This is a timely and thorough analysis of the value of therapeutics that have been shown to have some efficacy in the care of patients suffering from COVID-19

The premise of this commissioned work and what has been achieved:

1. Only Baricitinib, casirivimab/imdevimab, lenzilumab, molnupiravir, nirmatrelvir/ritonavir, remdesivir, sotrovimab, and tocilizumab were considered. The points of the analysis concern clinical outcomes and the value of these therapies both for community and hospital care.
2. The references on results of the major SoC comparison randomised controlled studies are included and given the continued change in standards for care over the period of the two major waves of COVID-19. This adds considerable to the complexity of the analyses. Despite the difficulties community therapies have undergone these analyses to provide a significant step to rationalising therapy to ensure value and efficacy are reported in an understandable fashion.
3. The NICE guidelines which also have changed are referred to enable clinicians and "purchaser" to make balanced decisions.
4. The categorisation of hospital admissions into those patients requiring O2 therapy or not, is particularly helpful. The phases of COVID-19 pneumonia are becoming clearer in terms of the pathobiological mechanisms. This approached has already been applied clinically to the use of steroids in those patients unable to sustain SaO2% > 93% on low flow oxygen.
5. The choice of outcomes for community care patients again is carefully based on the real issues bout outcomes.
6. As an old fashioned epidemiologist I am unable to critique all the details the analyses but am aware and support the intuitive assumptions used where information is limited. They are real and sensible without compromising the results.

The data derived from the randomised SoC appears to be robust and emphasises the wisdom of this style of drug development study. The authors provide a clear and convincing approach to adjusting the data and the comparison to take into account the impact of vaccines and the changing standards of care.

The pathobiology of the COVID-19 pneumonia remains unclear but the size of th impact of Baricitinib Jak 1 & 2 inhibitor and tocilizumab IL-6 inhibitor speaks to an innate immune response. Such an early response the viral invasion would normally contribute to recovery. But the impact seen mainly in the elderly and those with "immune" diseases including the metabolic diseases indicate support for an impaired antibody response that allows the virus to continue to replicate. Persistence and dysregulation of the terminal pathways of complements are a favour mechanism with reasonable evidence.

The power of the report strengthens of the evidence for such a mechanism.

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Your name	[redacted] & [redacted]
Organisation name	Renal Pharmacy Group
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Please comment on the assessment report

Description of problem

On page 50. 3.3.2 Administration costs. It was assumed that the costs associated with treatment administration whilst in hospital would be incorporated in the unit costs associated with hospitalisation (see Section 3.3.3). Additional administration costs were assumed for intravenous treatment in the community, but for simplicity, not for oral or subcutaneous treatments.

This statement does not take into account the time to reconstitute the nMAB with care and attention before administration, and therefore there is additional time. Some community patients will require a home visit for administration which isn't in the model.
It also doesn't consider the additional time for Paxlovid oral treatment to check for drug interactions to ensure safe use.
For all oral treatments the cost of delivering via courier to the patient has not been considered.

Description of proposed amendment

Time needs to be factored in for interaction checking for Paxlovid by the pharmacist, time for the nurse reconstituting and administering the S/C or IV formulation at the patient's home. Time and cost of travel to the patient's home by the nurse where home nMAB administration is required. The cost of delivery via courier (£50-£100) of the oral medication.

Result of amended model or expected impact on the result (if applicable)

I have not re-run the ICER, but the above will increase the cost of the treatment and will likely impact the cost effectiveness of Paxlovid and treatments administered in the patient's home by nursing staff.

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Organisation name	On behalf of UKKA
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Please comment on the assessment report

Summary: The assessment report attempts to evaluate the cost effectiveness of the various treatments for covid for pre hospitalised patients and those in hospital for treatment of covid pneumonitis.

The report is detailed and offers transparency about the many limitations -not least the impact of : variants, vaccinations and changing SOC. We would argue that the limitations not only detract from any usefulness of the appraisal in general but particularly for kidney patients and those with solid organ transplants.

The appraisal favours use of baricitinib in the hospital setting and paxlovid in the pre hospital setting. Neither can be used by the majority of the kidney patients at most risk.

Our major concern with this appraisal is that the patient groups who are most at risk of doing badly from COVID-19, will have very limited choices of appropriate treatment, either pre hospital or once admitted with severe COVID.

Sadly the appraisal completely fails to consider the cost effectiveness of Evusheld (approved for use for pre exposure prophylaxis by the MHRA in March 2022 and still not available).

Detail:

This appraisal fails to consider the kidney and transplant population who now can be considered the group at highest risk of severe COVID-19 and death from COVID-19. This is highlighted in the most recent output from the OpenSAFELY study – currently in pre print. ttps://www.opensafely.org/research/2022/covid-mortality-changes-over-time/ (abstract and lay summary below)

- Whilst it is encouraging that the death rates from COVID-19 have fallen overall with successive waves and variants, this is not the case for patients with severe kidney disease, with organ transplants, with blood cancer or those who are immunosuppressed.

- And importantly, the higher death rate is probably an underestimate of risk as many patients in these groups continue to shield – "freedom day" in July 2021 was not freedom day for them. Their protective behaviour, hugely intrusive on quality of life and ability to work and travel, is likely impacting on the results of studies such as these.

So not only are kidney and transplant patients at greatly increased risk from a bad outcome from COVID-19, many of the studies cited excluded patients with severely impaired kidney function (e.g. the RECOVERY baricitinib study excluded all those with an eGFR <15mls/min –

ie chronic kidney disease (CKD) stage 5) so the outcome data are not generalisable to those patients.

Importantly, many of the drugs reviewed by the appraisal are contra-indicated for kidney patients either because their kidney function is too poor (many exclude use even with eGFRs <45mls/min, CKD stage 3) or they are on drugs, eg to prevent transplant rejection, which interact and preclude use – for instance, paxlovid cannot be taken by transplant patients taking tacrolimus or cyclosporin – the vast majority of transplant patients in England.

We recognised that COVID vaccination has helped reduce the risk of severe outcomes from COVID-19 but it has not prevented transmission, certainly not in the current wave, and many kidney patients, particularly those taking immunosuppression for autoimmune kidney disease or to prevent transplant rejection, or those on dialysis, do not mount an effective immune response even after repeated vaccinations.
(for instance see:
Spensley K et al Kidney Int Rep. 2022 Jun;7(6):1406-1409. doi: 10.1016/j.ekir.2022.04.005. Epub 2022 Apr 13.PMID: 35434428;
Carr E et al Lancet. 2022 Feb 26;399(10327):800-802. doi: 10.1016/S0140-6736(22)00104-0. Epub 2022 Jan 20.PMID: 35065703;
Prendecki M et al Lancet. 2021 Oct 23;398(10310):1482-1484. doi: 10.1016/S0140-6736(21)02096-1. Epub 2021 Oct 4.PMID: 34619100;
Prendecki M et al Ann Rheum Dis. 2021 Oct;80(10):1322-1329. doi: 10.1136/annrheumdis-2021-220626. Epub 2021 Aug 6.PMID: 34362747).

The antibody response to vaccines in nearly 30,000 patients with either solid organ transplant patients, blood cancer or rare autoimmune diseases (enriched for those with kidney diseases who have been treated with rituximab) is being prospectively studied by the UKRI-MRC funded, CUE-Tip prioritised MELODY study (https://www.imperial.ac.uk/medicine/research-and-impact/groups/melody-study/) and will report within the next few months. We know that a significant proportion of patients have no detectable antibodies even after 4 vaccines.

Of the drugs reviewed in the appraisal, our recommendations would be:

Neutralising antibodies:

Ronapreve is not effective against omicron and no longer in use.

Sotrovimab needs to remain available pre hospital for patients with low eGFRs / known poor antibody responses (it is currently first line treatment for those with solid organ transplants).

Sotrovimab is probably not as effective against the latest variants as earlier ones and NICE need to rapidly approve use of newer nMABs as they become available.

Drugs:

Remdesivir can also not be used in patients with an eGFR <30mls/min not on haemodialysis. It should remain available for those whose eGFR permits as undoubtedly helps reduce viral load in the early stages of pre hospital infection and the immunocompromised patients admitted with severe infections.

Mulnopirivir offers far less optimal protection and should not be the default for kidney patients now - those at highest risk would be offered the least effective drug which is highly iniquitous.

Paxlovid offers excellent protection but as mentioned is not recommended for those with CKD stage 4 and 5 or those on dialysis due to lack of information on dosing; and c/I in those with solid organ transplants due to drug interactions.

Baricitinib – is not recommended for those with an eGFR <30mls/min

Tocilizumab – no information regarding use in impaired renal function but has been used widely in hospitalised kidney patients with COVID-19 pneumonitis requiring oxygen supplementation.

Conclusions:

What is clear is that patients with kidney disease are at increased risk, and increasingly so compared to the general population, from severe outcomes if they get COVID-19. Additionally, the majority of medicines available for pre hospital and in hospital treatment may not be able to be used due to concerns about kidney function or drug interactions. Limiting availability of the drugs that can be used based on the modelling in this appraisal would be wrong.

But our clear request is for access to pre exposure prophylaxis with Evusheld (or similar) before the next wave in order to allow kidney patients a real opportunity to reduce their risk and have the freedoms which the general population now enjoy.

Abstract OpenSafely study:

Objectives To quantify in absolute and relative terms how population-level COVID-19 death rates have changed in demographic and clinical subgroups.
Design Retrospective cohort study on behalf of NHS England.
Setting Linked primary care and death registry data from the OpenSAFELY-TPP platform, covering the first three pandemic waves in England (wave 1: March 23 to May 30, 2020; wave 2: September 7, 2020 to April 24, 2021; and wave 3, delta: May 28 to December 14, 2021).
Participants In total, 18.7, 18.8, and 18.7 million adults were included for waves 1, 2, and 3 respectively.

Main outcome measures COVID-19-related mortality based on linked death registry records.
Results The crude absolute COVID-19-related death rate per 1,000 person-years decreased from 4.48 in wave 1 (95%CI 4.41;4.55), to 2.70 in wave 2 (95%CI 2.67;2.73), to 0.64 in wave 3 (95%CI 0.63;0.66). The absolute death rate decreased by 90% between waves 1 and 3 in patients aged 80+, but by only 20% in patients aged 18-39. This higher proportional reduction in age- and sex-standardised death rates was also seen for other groups, such as neurological disease, learning disability and severe mental illness. Conversely, standardised death rates in transplant recipients stayed constant across successive waves at 10 per 1,000 person-years. There was also only a small decrease in death rates between waves in people with kidney disease, haematological malignancies or conditions associated with immunosuppression. Consequently, the relative hazard of COVID-19-related death decreased over time for some variables (e.g. age), remained similar for some (e.g. sex, ethnicity), and increased for others (e.g. transplant).
Conclusions COVID-19 death rates decreased over the first three pandemic waves. An especially large decrease was seen in older age groups and people with neurological disease, learning disability or severe mental illness. Some demographic inequalities in death rates persisted over time. Groups more likely to experience impaired vaccine effectiveness did not see the same benefit in COVID-19 mortality reduction.

Lay Summary

Background:

In the early stages of the COVID-19 pandemic, we learned that certain groups of the population were at greater risk of death due to COVID-19. Older age, belonging to a racially minoritised group, socioeconomic deprivation and learning disability were found to be associated with increased risk of death, as well as several pre-existing medical conditions such as diabetes, blood cancer, kidney disease, heart disease and having an organ transplant. However, as the pandemic has progressed, several strategies have been adopted to reduce rates of death. These include treatment for people who are sick enough to be admitted to hospital for COVID-19 (such as steroids), population-wide vaccination, and early community-based treatment with new drugs for people who are considered to be at high risk (such as sotrovimab).

In this study, we looked at whether risks have changed across different groups of the population over time, and which groups are at the highest risk at the current stage of the pandemic.

Using healthcare records and death registration data across England on the OpenSAFELY platform, we compared the risks of death due to COVID-19 across three time periods, each corresponding to COVID-19 waves:

- Wave 1 - 23 March 2020 to 30 May 2022
- Wave 2 - 2 September 2020 to 24 April 2021 and
- Wave 3 - 28 May 2021 to 14 December 2021

Each of the study periods included over 18 million adults. Our study largely does not include the Omicron wave of the 2021-22 winter.

Findings:

We measured rates of death for every 1000 person-years. If you followed 1000 people of the same age and sex with the particular condition for a year (while the risk of catching COVID-19 remained the same) this is the number of people we estimate would have died from COVID-19. We looked at the proportion of people who died of COVID-19 out of all of the adults in the study, not just those who had caught Covid.
The groups we considered included age, sex, ethnicity, BMI, geographical region and a number of medical conditions. Overall, for the whole study population, after taking account of age and sex, COVID-19 death rates decreased over time from 4.6 per 1000 person-years in wave 1, to 2.8 in wave 2 and 0.7 in wave 3. Reassuringly, the rates of death consistently fell over each wave in each of the groups we studied. Rates of death fell across waves considerably in people over the age of 80 years, those with brain conditions, learning disabilities and severe mental illness. The amount by which they fell was lower in people with severe obesity, kidney disease, blood cancers and other immunosuppressed conditions.

We also measured the relative risk of death in groups across each wave to allow us to compare the risk of death from COVID-19 for people with a condition compared to people without the condition. In some groups, relative risk remained roughly consistent across the waves (e.g. the risk of death in males compared to females was 1.7 times higher in wave 1, 1.6 times in wave 2 and 1.9 times in wave 3). In other groups, there was a decline: for example, in people aged over 80 years the risk of death was 42 times greater than people aged between 50 and 59 in wave 1, whereas it was 15 times greater in wave 3.

However, in several groups, there was an increase in the relative risk of death. [redacted]

The marked reduction in COVID-19 death rates across all groups, including in those who are immunosuppressed, is encouraging. This is likely to be due to high uptake of vaccination, which was introduced on 8 December 2020 in the middle of wave 2 as well as improved hospital treatments, with a contribution from immunity from those previously infected. [redacted]

Checklist for submitting comments

- Consultation responses must not be longer than **10 pages**, excluding the references.
- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Process and methods manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the pro-forma response document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Assessment Report

Therapeutics for people with COVID-19 [ID4038]

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. Deadline for comments **5pm** on **Friday 29 July**. **Please submit via NICE Docs**.

Your name	[redacted]
Organisation name	Healthcare Improvement Scotland
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Please comment on the assessment report
Healthcare Improvement Scotland welcomes this piece of work and look forward to it progressing to the next stage.

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Checklist for submitting comments

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Process and methods manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the pro-forma response document, please submit these separately.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Targeted company submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Your name	[redacted]
Organisation name	AstraZeneca
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

1. For this MTA the Assessment Group has already developed a model and drafted a report which you have had the chance to comment on.

Please provide any additional comments below – do not repeat comments submitted in response to consultation on the Assessment Report.

Our comments mostly focus on the outpatient treatment analysis (i.e. *people with mild COVID-19 at high-risk of progressing to severe COVID-19* – page 16), if not otherwise stated.

Comment 1. The risk of hospitalisation for the general population used in the current base case is inconsistent with the latest evidence. The risk of hospitalisation for COVID-19 in the general population is approximately 2.4%

Section 3.1.2 of the EAG's assessment report outlines the assumptions used to inform the hospitalisation rates for the general population. The EAG used a risk of 0.9% for the general population based on data presented in Nyberg et al.[1] The EAG noted that this risk was lower than the ~5% reported in the UK Coronavirus dashboard, which has a much larger sample size.[2] Despite the smaller sample size the EAG adopted the 0.9% due to concerns that the dashboard is less nuanced and that half of those cases reported in the dashboard may not have been hospitalised due to COVID-19. Assuming that this statement is correct, this would still result in a hospitalisation risk of ~2.5%, which is almost three-fold higher than the 0.9% used for the base rate in the general population.

AstraZeneca has recently commissioned third-party analysis of Hospital Episode Statistics (HES) data in England[3] which demonstrates that (in the 12-month period to 30th May 2022) nearly half (47.5%) of all COVID-19 related hospitalisations are due to COVID-19 infection (primary diagnosis). This data are consistent with the EAGs conclusion that '*it may be the case that half of patients with COVID-19 in hospital, were not hospitalised due to COVID-19'*.[2] Assuming that 47.5% of all COVID-19 admissions reported in the UK Coronavirus dashboard are due to COVID-19, this results in a hospitalisation rate of 2.4% across all patients in England.

As the base rate of hospitalisation is used to inform the risk in the population relevant to the MTA we request that the risk of hospitalisation in the general population is increased from 0.9% to 2.4% to reflect the data from the UK Coronavirus dashboard and HES, both of which represent contemporaneous data for the entire population of England.

Comment 2. The MTA should consider a separate analysis of cost-effectiveness for those who are deemed to be at highest risk of adverse outcomes from COVID-19

The MTA currently considers only one population in the outpatient setting; those not hospitalised and at high risk of adverse outcomes. This high-risk population is defined by the inclusion criteria of the PANORAMIC trial.[4] However, patients at the highest risk of

adverse outcomes have previously been determined by an independent advisory report commissioned by the Department of Health and Social Care (DHSC)[5], and this report does not identify some of the lower-risk groups included in the PANORAMIC criteria such as those with asthma, diabetes, and morbid obesity.

The EAG assessment report cites Hippisley-Cox *et al.*[6] as a publication that was reviewed to inform the multiplier of 2 for the high-risk population, however within this publication the adjusted hazard ratios for risk of hospitalisation vary greatly between the sub-groups. For example, the HR for renal transplant patients is 12.82 versus patients with no CKD whereas people with Type 2 Diabetes (HbA1c < 59mmol/mol) had a HR of 1.28 when compared to those without Type 2 Diabetes.

As the current analysis applies the same risk level to all patients (multiplier of 2) it vastly underestimates the risk in those identified as at the highest-risk. This population represents a clinically important and easily identifiable population who we request should be considered separately to reflect the inherent increased risk of adverse clinical outcomes and the disproportionate impact that COVID-19 continues to have on these individuals.

This disproportionate impact is highlighted by the OpenSAFELY Collaborative analysis[7] of over 18 million adults in England which concludes that whilst COVID-19 death rates in the general population have decreased over the first three pandemic waves, groups more likely to experience impaired vaccine effectiveness did not see the same benefit in COVID-19 mortality reduction. Specific groups where there has been only a small decrease in death rates between waves include people with kidney disease, haematological malignancies, conditions associated with immunosuppression and organ transplant recipients, all of whom are identified in the independent advisory report commissioned by the DHSC.[5]

Comment 3. The risk of hospitalisation for the highest-risk population used in the current base case is inconsistent with the latest evidence. The risk of hospitalisation for COVID-19 in the highest risk population is approx. [redacted]

The independent advisory report commissioned by the DHSC[5] identifies the highest-risk population as primarily comprising those who are immunocompromised due to either Primary Immunodeficiency (PID) or Secondary Immunodeficiency (SID). Therefore, the population of interest to the MTA are those identified in this report and in this population the risk of hospitalisation due to COVID-19 is inherently greater than that currently stated in the EAG assessment report (general population multiplied by a factor of 2).

A recent study undergoing peer review
([redacted]

The rates of hospitalisations during the omicron period
[redacted]

[redacted]

We understand from the analyses presented in the assessment report that the underlying risk of hospitalisation is a key driver of the cost-effectiveness, and therefore it is essential that the latest available data rather than assumptions are used to inform the underlying risk. We therefore request that the risk of hospitalisation for the highest-risk population is changed to [redacted]

Comment 4. The current approach adopted in the economic evaluation results in clinically implausible estimates of inpatient mortality, and therefore puts into question the robustness of the analysis. In the absence of an alternative solution, the RR for inpatient mortality should be set to 1.0 for all treatments.

AstraZeneca is concerned about the robustness of the approach adopted to model inpatient mortality, and therefore requests that either the model is adapted to implement an appropriate solution, or that all RR for inpatient mortality are manually set to 1.0.

The model currently applies a mortality multiplier in an attempt to align the trial-based and model-based estimates of all-cause mortality, and this is applied irrespective of whether or not a patient receives outpatient treatment with an antiviral or nMAB. This approach results in RR estimates of inpatient mortality greater than one – with the exception of molnupiravir – ranging from 1.14 to 4.61 for Paxlovid and sotrovimab, respectively. This modelling approach therefore assumes that patients who receive treatment with an antiviral or nMAB who subsequently end up in the hospital are a significantly greater risk of death compared with those who did not receive treatment. This is clinically implausible, particularly for treatments which have a statistically significant reduction in the risk of hospitalisation or death. Specifically, with reference to Evusheld, a Phase III, randomised, double-blind, RCT evaluating the efficacy and safety of IM Evusheld for early outpatient treatment of COVID-19 demonstrated a 50.5% RRR compared with placebo[9], and it is therefore perverse to assume that the inpatient mortality is greatly increased. It is therefore inappropriate for the EAG and NICE to accept this flawed modelling approach.

AstraZeneca are concerned to read the EAGs comments on this limitation[2], in which they stated: '*The EAG comments that it may be clinically implausible that treatments which have a statistically significant beneficial HR relating to hospitalisation or death would be associated with increased RR of death at 28 days, but this limitation could not be addressed in the timescales of the project'*.

The timelines of the MTA process should not negatively impact the robustness of the NICE process, and therefore undermine the rigor of the evidence-based decision making processes employed by NICE. Therefore, AstraZeneca requests that the EAG incorporates an appropriate update and fix to the model, or alternatively, that they manually set the RR for inpatient mortality to 1.0 for all treatments considered in the MTA.

Comment 5. In the absence of further data, the mean age of patients in the economic model should be reduced to reflect those enrolled in relevant RCTs

AstraZeneca recognises that there may be some limitations of the generalisability of the populations enrolled in clinical trials compared with UK clinical practice. However, without any further justification from the EAG, we firmly believe that data from the RCTs represent the most appropriate source of data to be used to inform the cost-utility analysis.

The current mean age of 65 years assumed in the base case is significantly greater than those enrolled in the outpatient RCTs where the mean age ranges from 42 to 53 years.[10-14] AstraZeneca is concerned that the mean age of 65 years currently used in the base case analysis is more reflective of the mean age of patients enrolled in the inpatient trials, such as the RECOVERY and ACTT-1, which represents a different patient population.[15-17]

Comment 6. Due to methodological limitations, it is inappropriate to compare the relative cost-effectiveness between treatments. The MTA should therefore focus solely on the assessment of each treatment relative to standard care.

AstraZeneca is concerned that the assessment report attempts to evaluate the relative cost-effectiveness of treatments compared with each other. Currently, there is no direct evidence to compare the relative efficacy of antiviral and nMAB COVID-19 treatments, and therefore a network meta-analysis and indirect treatment comparison would be required to evaluate the relative efficacy between treatments. The current estimates of efficacy have predominately been sourced from COVID-NMA, however, this is associated with significant limitations. Specifically, there are significant imbalances in the populations between the trials; particularly with respect to patients' age, disease severity, vaccination status, history of SARS-CoV-2 infection, and treatments available in the standard care arm of the trials. Despite the significant imbalances between the populations, the EAG assumed that none of these differences were significant effect modifiers. However, AstraZeneca firmly believes that most – if not all – of these are highly likely to be effect modifiers and therefore any naïve comparisons of treatment effects between treatments is significantly confounded, highly uncertain, and thus inappropriate for decision making.

In addition, reporting of efficacy outcomes is inconsistent between trials, such that hospitalisation outcomes were assumed using a combination of all-cause mortality and COVID-19 hospitalisation or all-cause mortality and all-cause hospitalisation across treatments. These outcomes cannot be directly compared, and therefore further demonstrates the limitations of any comparison and conclusion made with respect to the relative benefits of different treatments.

Direct comparisons of efficacy, and therefore relative differences in cost-effectiveness cannot be determined. The outputs of such analysis would be highly uncertain, methodological flawed, and inappropriate. It is therefore not possible to make any robust conclusions on the relative cost-effectiveness between treatments, hence conclusions from the MTA should focus solely on the cost-utility analysis of each treatment relative to standard care.

2. Please provide details of any additional evidence you wish to submit that is not included in the Assessment Report.

Please note:

- **If you wish to submit additional evidence, please contact TAteam4@nice.org.uk as soon as possible. Proposals to submit additional evidence must be agreed by the Associate Director or Programme Director before submission**
- **If academic in confidence data is submitted, NICE and the Assessment Group may choose to rely on published data in order to ensure transparency for all stakeholders.**

Additional Evidence 1. Data on the efficacy and safety for Evusheld for early outpatient treatment of COVID-19

Evusheld hasn't currently been included as a treatment for COVID-19 within the MTA. Therefore, AstraZeneca would like to provide a brief summary of the pivotal trial which informs the data on the efficacy and safety of Evusheld for early outpatient treatment of COVID-19, and the key efficacy data which should be considered to inform the MTA.

In summary, the key efficacy and safety data is informed from the TACKLE study; an ongoing Phase III, randomised, double-blind, placebo-controlled RCT.[9] Eligible participants were non-hospitalised adults aged ≥18 years with a documented laboratory-confirmed SARS-CoV-2 infection, as determined by RT-PCR or an antigen test collected 3 days or less before enrolment, and were randomised to (1:1) to receive Evusheld 600 mg or placebo. Participants had to receive treatment with the study drug 7 days or less from the onset of mild to moderate COVID-19 symptoms. Further inclusion and exclusion criteria are detailed in the publication.

The primary efficacy endpoint was a composite of either severe COVID-19 or death from any cause through to day 29, with severe COVID-19 being defined as a minimum of either pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltrates) or hypoxaemia (oxygen saturation <90% in room air, severe respiratory distress, or both), plus a WHO Clinical Progression Scale score of 5 or more. The primary safety endpoints were adverse events, serious adverse events, and adverse events of special interest throughout the study. Adverse events of special interest included anaphylaxis and other serious hypersensitivity reactions, including immune complex disease and injection site reactions.

Secondary endpoints at day 29 included the incidence of respiratory failure, levels of SARS-CoV-2 RNA in nasal swabs, and incidence of antidrug antibodies to Evusheld in serum. The key secondary endpoint was a composite of death from any cause or hospitalisation for COVID-19 complications or sequalae to day 169. Other secondary endpoints were whether Evusheld reduces the progression of participant-reported COVID-19 associated symptoms to day 29, the differences in symptom duration between Evusheld and placebo to day 29, and the single-dose pharmacokinetics of Evusheld. Efficacy outcomes were assessed relative to the time which elapsed between symptom onset and receipt of treatment.

The study has a follow-up period of 457 days. Therefore, data are presented from the primary data cutoff (Aug 21, 2021), at which time all ongoing study participants had completed at least 29 days of study follow-up.

Full details of the outcomes reported can be found in the key publication. For consistency with the analyses previously conducted in the MTA, we have presented the data from the TACKLE trial which are most relevant to inform the cost-utility analysis of the MTA below:

[redacted]

To support the EAG with its inclusion of the TACKLE data within the MTA, we have provided some further guidance below which outlines key considerations required with respect the reporting of outcomes, population, and time from symptom onset.

Outcome definition. As previously described, the primary endpoint of the TACKLE manuscript's primary endpoint is a composite of either severe COVID-19 or death from any cause. However, COVID-NMA – which the key source of the data used to inform the data used in the economic analysis for treatments currently included within the MTA – reports outcomes for either "COVID-19 Hospitalisation or Death" or "Hospitalisation or Death". As detailed in the study protocol for TACKLE, having severe COVID-19 is equivalent to a World Health Organization (WHO) Clinical Progression Scale (CPS) score of 5 or worse (i.e. higher). However, hospitalisation is equivalent to a WHO CPS score of 4 or worse. Therefore, it is not possible to directly compare the efficacy of Evusheld with all those reported in the COVID-NMA.

Population. The COVID-NMA initiative uses the ITT populations for the reporting of efficacy outcomes. However, the investigators of the TACKLE trials created a modified full analysis set (mFAS) which excluded 76 patients that were either hospitalised at baseline for isolation purposes (in Japan and Russia) or were randomised after 7 days of symptom onset.[9] The mFAS therefore satisfies the population inclusion criteria of being an outpatient at baseline. As such, data from the TACKLE trial should only be considered based on outcomes from the mFAS alone. This will ensure consistency with the study requirements and with the some of the outcomes reported for the other COVID-19 treatments considered within the MTA.

Time from symptom onset. Time from symptom onset to treatment administration is a key driver of the efficacy for nMABs. Patients treated within 5 days of symptom onset are considered to be aligned with the Assessment Report base case population because this time to treatment matched with the key comparator trials. Specifically, in Molnupiravir (MOVE-OUT[12]) trial, nirmatrelvir/ritonavir (EPIC-HR[11]) trial and sotrovimab (COMET-ICE[10]) trial, treatment was administered within 5 days of symptom onset. In the casirivimab / imdevimab[13] and remdesivir[14] trials, the inclusion criteria stated that treatment should have

been administered within 7 days. Nevertheless, in the casirivimab / imdevimab trial the median time from symptom onset to randomisation was 3 days. As such it is therefore pertinent for the EAG to adopt a similar approach for selecting data from the TACKLE trial to inform the economic evaluation for Evusheld within the MTA. Specifically, data for patients either treated within 3 or 5 days should be utilised within the analysis for the MTA.

Additional Evidence 2. Consistent with the existing approach adopted by the EAG, an administration cost of £0 should be assumed

Evusheld should be administered via an intramuscular (IM) injection and should be administered by a doctor or nurse in a healthcare setting with patients observed for 1 hour following administration18.

The EAG currently assumes there is no administration cost associated with the administration of casirivimab/imdevimab. Casirivimab/imdevimab is administrated via a subcutaneous injection, and again should be administrated by a healthcare professional and that patients should be observed for 1 hours following administration. As such, AstraZeneca believes that it is reasonable to also assume no cost of administration of Evusheld via IM injection.

3. If you are the manufacturer of one of the interventions, please provide details of your product(s):

- **GB marketing authorisation status/timing**
- **GB marketing authorisation wording**
- **Method of administration and dosage**
- **List price**
- **Any confidential arrangements that would apply in routine commissioning for this product.**

GB marketing authorisation status/timing

AstraZeneca made its submission to the MHRA in [redacted]. Marketing authorisation is expected to be granted by the MHRA in [redacted].

GB marketing authorisation wording

The anticipated wording of the licence is as follows:

[redacted]

Method of administration and dosage

List price

On the [redacted], the DHSC approved the following list prices for Evusheld, however, the list price has not yet been published:

- Evusheld Liquid 150mg vial 2 x 1.5ml: [redacted]
- Evusheld Liquid 150mg vial 4 x 1.5ml: [redacted]

[redacted]

- Evusheld Liquid 150mg vial 2 x 1.5ml: [redacted]
- Evusheld Liquid 150mg vial 4 x 1.5ml: [redacted]

Any confidential arrangements that would apply in routine commissioning for this product.

[redacted]

4. Are there any potential equality issues that should be taken into account when considering these treatments?

No

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Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Targeted company submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Your name	[redacted]
Organisation name	Eli Lilly and Company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

1. For this MTA the Assessment Group has already developed a model and drafted a report which you have had the chance to comment on.

Please provide any additional comments below – do not repeat comments submitted in response to consultation on the Assessment Report.

No further comments.

2. Please provide details of any additional evidence you wish to submit that is not included in the Assessment Report.

Please note:

- **If you wish to submit additional evidence, please contact TAteam4@nice.org.uk as soon as possible. Proposals to submit additional evidence must be agreed by the Associate Director or Programme Director before submission**
- **If academic in confidence data is submitted, NICE and the Assessment Group may choose to rely on published data in order to ensure transparency for all stakeholders.**

No additional evidence to be submitted.

3. If you are the manufacturer of one of the interventions, please provide details of your product(s):

- **GB marketing authorisation status/timing**
- **GB marketing authorisation wording**
- **Method of administration and dosage**
- **List price**
- **Any confidential arrangements that would apply in routine commissioning for this product.**

UK Regulatory timelines

[redacted]

[redacted]

Proposed indication

[redacted]

Method of Administration and dosage

Oral (4mg daily). Although the optimal duration is currently unclear, The COV-BARRIER study had a maximum duration on treatment for up to 14 days, however the results from the trial showed that (source data on file from CSR from COV-BARRIER) median days of exposure was 8.1 days.

List price

The NHS list price for a 28 pack of 2mg or 4mg tablets both cost £805.56 per pack.

Confidential arrangements

[redacted]

4. Are there any potential equality issues that should be taken into account when considering these treatments?

None identified.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Targeted company submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Your name	[redacted]
Organisation name	Gilead Sciences
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

1. Additional Comments

Summary

Gilead would like to reiterate our concerns expressed in our initial (pre-referral) response to the Assessment Report (AR), during Phase I, to ensure that these are properly recorded within the formal process of the MTA appraisal e.g., during Phase II. Gilead has significant concerns about the conduct of this technology appraisal, primarily with regard to robustness, fairness, and a lack of methodological transparency. Gilead believes that NICE have potentially failed to act fairly by breaching its own published process and methods for the development of guidance. For example:

- The Assessment Group (AG) were commissioned, and the AR was published without formally starting the technology appraisal process.
- The lack of transparency regarding data selection which is unsystematic and contrary to the normal NICE methods. We do not believe the most relevant or applicable data has been selected for many of the interventions, with key trials such as SOLIDARITY and CATCO (Canadian sub study of SOLIDARITY) excluded without a clear justification. Meanwhile, less methodologically robust trials, such as Wang *et al.* (2020) and Mahajan *et al.* (2021) were included.
- No other stakeholder submissions have been considered during Phase I of the technology appraisal (TA) process and companies were not permitted to submit their own *de novo* cost-effectiveness analyses.
- Companies have not been invited to submit an evidence submission before the development of the AR; it is unclear if and how evidence submitted during Phase I of the TA will be considered by the AG and the committee.
- It is concerning that companies were required to seek NICE approval to submit additional evidence during Phase II of the TA; contrary to normal NICE methods and processes.
- It is unclear if or how Gilead's response to the AR will be taken into consideration.

- It is also unclear if, how and when commercial in confidence patient access schemes (PAS) net price discounts will be considered in the technology appraisal process, which in turn may limit patient access to effective treatments.
- It is unclear if there will be any mechanism to appeal, rectify or otherwise meaningfully contribute to the development of robust guidance on the use of COVID-19 therapeutics.

Gilead believes that NICE have potentially exceeded its powers by 'resequencing the steps of the MTA'. Companies have potentially been treated unfairly during phase I of this TA. While challenges such as changing vaccination status, COVID-19 variants, and rapidly evolving evidence landscape are inherent to a TA of COVID-19 therapeutics and which complicate this TA, we would respectfully request amendments regarding the following specific elements of the AG's analysis.

1. **The incremental cost-effectiveness analysis included in Section 4.1. is unhelpful and potentially obfuscating for decision-making**

The incremental analysis undertaken by the AG, which includes all comparators within each of the populations, is inappropriate and methodologically flawed. Therefore, Gilead is of the opinion that any recommendation based upon the incremental analysis may be unreasonable given the substantial deviation from normal NICE process and methods.

Typically, incremental analyses are used to assess comparators that could in practice displace each other; however, this is not the case for the treatments compared. Anti-virals are beneficial during the viral shedding stage because they inhibit viral replication, and remain applicable from the early stages of disease course all the way to severe disease, as there can be ongoing viral replication during the "inflammatory" phase of the disease course.

In contrast, other drug classes play different roles in the disease course and therefore are useful in different settings. Although treatments can be broadly split into anti-viral and anti-inflammatory, there are subgroups within these groups that relate to different populations. Broadly speaking, subgroups include:

- Antivirals targeting the virus to stop viral replication;
- Neutralising monoclonal antibodies that target the outer virus receptors to neutralise the virus and prevent entry into cells; and
- Anti-inflammatories (including monoclonal antibodies working as anti-inflammatories).

Therefore, the therapies being assessed are not mutually exclusive. For example, in clinical practice remdesivir, baricitinib, tocilizumab or lenzilumab cannot be used interchangeably. This is due to their very different but complementary mode of actions in the treatment of COVID-19: remdesivir targets viral replication while tocilizumab, baricitinib and lenzilumab act against the inflammatory phase.

As such, remdesivir can be viewed as a backbone treatment for patients in hospital. This is clearly evidenced by the fact that remdesivir is used as a component of SoC in a number of trials for other medicines included in the MTA. There is a growing body of literature supporting the positioning of remdesivir as a backbone therapy, particularly in the clinical trials of other treatments being studied for use in hospitals, for example:

- The US National Institute of Allergy & Infectious Diseases ACTT and ACTIV platform trials:
    - ACTT-2: evaluated the combination of baricitinib and remdesivir compared to remdesivir alone.
    - ACTT-3: evaluated the combination of interferon beta-1a and remdesivir compared to remdesivir alone.
    - ACTT-4: evaluated the combination of baricitinib and remdesivir compared to dexamethasone and remdesivir.
    - ACTIV-3: evaluating the combination of ACTIV-3 investigational treatments and remdesivir compared to remdesivir plus placebo.
    - ACTIV-5 (BET-A): evaluated the combination of remdesivir and Risankizumab compared to remdesivir plus placebo.
    - ACTIV-5 (BET-B): recruiting to evaluate the combination of lenzilumab and remdesivir compared to remdesivir plus placebo.

    - ACTIV-5 (BET-C): recruiting to evaluate the combination of danicopan and remdesivir compared to remdesivir plus placebo in patients younger than or older and equal to 70 years old.
- ITAC trial (NIAID, NIH and INSIGHT): evaluating the combination of hyperimmune immunoglobin to SARS-CoV-2 (hIVIG) and remdesivir compared to remdesivir plus placebo.
- Casirivimab and Imdevimab for Treatment of Hospitalized Patients With COVID-19 Receiving Low Flow or No Supplemental Oxygen.

Remdesivir is also currently established clinical practice, and represents a backbone to the treatment regimen, across a broad spectrum of COVID-19 disease for these patients as set out in 3 existing Clinical Commissioning Policies:

- Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised with COVID-19 (adults and adolescents 12 years and older) (Version 4) focuses on the use of remdesivir for hospitalised COVID-19 patients requiring supplemental oxygen(1).
- Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies in the treatment of hospital-onset COVID-19 (Version 7) focuses on the use of remdesivir (alongside other options) for patients with hospital onset COVID-19 at high risk of progressing to severe COVID-19 disease but not yet requiring supplemental oxygen(2).
- Interim Clinical Commissioning Policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19 (version 6) focuses on the use of remdesivir (alongside other options) in non-hospitalised patients with COVID-19 at high risk of progressing to severe COVID-19 disease(3).

In this example, the pairwise analysis showed that all these treatments were cost-effective against SoC, but the incremental analysis suggested that all were dominated or extendedly dominated. The real-world comparators of remdesivir in combination with tocilizumab, baricitinib or lenzilumab are not considered due to lack of evidence, although their inclusion may have theoretically altered the results of the incremental analysis.

While current NICE guidelines recommend that ideally a full incremental analysis is carried out, in this instance, inclusion of the incremental analysis in the main body of the report encourages decision-making based on flawed evidence. We suggest the incremental analysis is removed or reported within the appendices for information purposes only, with further cautionary notes.

2. **The analysis does not appropriately segment patient in the 'in hospital' setting by oxygen use, and should do so**

The AG fails to segment the patient population according to oxygen use within the hospital setting. This split does not reflect sequencing in clinical practice or recognise the key stages of disease progression. It also does not reflect the correct wording of the regulatory labels of the various interventions.

The use of these therapies at different stages of their disease progression is important to understand. For example, the use of therapies with an immunomodulatory mode of action too early (such as in a patient not yet requiring supplementary oxygen support) can be detrimental to a patient's outcomes as outlined in the RECOVERY trial for dexamethasone. The AG seem to discount this clinically important note when assessing clinical and cost effectiveness of the therapies, even though NICE's living guidelines for the management of COVID-19 splits patient groups in hospital by oxygen usage.

Therefore, we request that the model used in the appraisal appropriately reflects the various patient groups within the hospitalised setting: people who require low flow supplemental oxygen in hospital, people require high flow oxygen in hospital, and people who require mechanical ventilation / ECMO.

3. **The model structure excludes the impact of more severe disease on longer-term outcomes**

The existing AG model structure assumes that a proportion of patients experience 'long COVID', with an associated reduction in quality of life (QoL) and higher mortality risk. This approach currently does not differentiate between hospitalised patients with lower-intensity oxygen requirements and those with more severe disease requiring admission to ICU and/or need for mechanical ventilation or ECMO.

The Sheinson *et al.* (2021)(4) economic evaluation of treatment for patients hospitalised with COVID-19 applies a disutility for patients requiring mechanical ventilation for a period of 5-years post-discharge based on evidence that even relatively young patients who survived acute respiratory distress syndrome (ARDS) had persistent exercise limitations and a reduced physical quality of life 5 years after their critical illness.

The same model applied a hazard ratio for post-discharge mortality for ventilated patients vs. general population for 5 years based on evidence that there is an increased risk of death (33%) and hospital readmission rate (22%) in patients surviving an episode of intensive care compared with hospital control subjects in the 5 years after discharge from hospital, after adjusting for important confounders. These structural additions would be expected to increase QALY gain and therefore reduce the ICER for comparators demonstrated to reduce the need for mechanical ventilation or ECMO.

4. **Rationale for selection of certain sources of evidence and studies are unclear and should be more fully justified by the EAG**

It is not clear which sources of evidence the EAG has chosen to include and exclude. Equally, where some sources of evidence were excluded, the reasons for this are not described in detail.

Regarding extraction of particular studies, the AG states that all data extractions were undertaken by the end of May 2022. However key studies which one would reasonably expect to be included, such as the SOLIDARITY study, were not. The AG provide no explanation of the reasons for excluding such studies. In addition, NICE has recently updated the living guidelines for the management of COVID-19, and the conditional use of remdesivir, using the SOLIDARITY data set which confirms the relevance of this evidence source.

Furthermore, on the studies selected to estimate the efficacy of each treatment, the AG notes how many studies were used but does not indicate which studies these were. The approach to identifying and selecting key sources of clinical evidence and

lack of transparency regarding data selection is unsystematic and contrary to the normal NICE methods.

It appears that the selection of interventional studies, and therefore the appraisal of the benefit, is inequitable and unbalanced. For example, the AG's assessment of nirmatrelvir/ritonavir is based on only one study (EPIC-HR) despite the fact that there are multiple additional sources of evidence to consider such as EPIC-SR.

As for the studies that were specifically selected for remdesivir, the AG gave no clear rationale for why certain outcomes were chosen from these studies. An example is the inclusion of the pivotal study ACTT-1 (Biegel *et al.,* 2020)(5) - this study had a clear primary endpoint of time to recovery, however the EAG only looked at the outcome of time to death. If the AG had included SOLIDARITY in their assessment, this outcome would make more sense to be retrieved from this study given the primary endpoint of investigating mortality in a much larger population. The AG discounted the outcome of time to discharge for remdesivir, which is an outcome that could easily be retrieved from ACTT-1.

Furthermore, the AG have chosen to include Wang *et al.* (2020) a study that was halted early due to the lockdown in China and led to a study that could not be completed efficiently and gave an underpowered trial, which taken alone, gives inconclusive findings. Given that this study was selected to assess the outcomes time to death and clinical improvement, both ACTT-1 and SOLIDARITY amongst others are far more robust data sets from which to retrieve these outcomes for assessment. Equally, The AG have chosen to include the Mahajan *et al.* (2021) study, which had a small patient pool of only 81 patients, from which it is difficult to derive reliable and robust results from. This study had been included to look at the outcome of clinical improvement which could have been retrieved from ACTT-1, a justifiably robust clinical trial. Gilead is of the opinion that the AG's arbitrary selection of studies and outcomes may lead to unreasonable recommendations in light of the evidence that is available. Therefore, Gilead is of the opinion that the Wang *et al.* (2020) and DISCOVERY (more detail is provided on this trial in section 2) trials should be replaced with SOLIDARITY, which is far more methodologically robust.

Gilead strongly recommends that the AG conduct a fully systematic review of all literature (clinical, humanistic and economic), and fully describes the rationale for inclusions and exclusion of sources of evidence and the studies themselves as well as rationale for selecting certain outcomes from each study selected. The information should be presented in a PRISMA diagram and the appraisal should adhere to the NICE Reference Case.

2. Additional Clinical Evidence

The following section presents key evidence which the AG has not considered, and which NICE has agreed Gilead may submit as new additional evidence. It should be noted that NICE refused Gilead's request to submit a *de novo* cost-effectiveness analysis (CEA) of remdesivir for the treatment of COVID-19. The Company's *de novo* CEA was developed as per the NICE methods guide and therefore adheres more closely to the NICE Reference Case than the AG's analysis.

SOLIDARITY

Gilead believes that NICE should consider evidence from the World Health Organization (WHO) SOLIDARITY(6) study in the appraisal of therapeutics for the treatment of COVID-19.

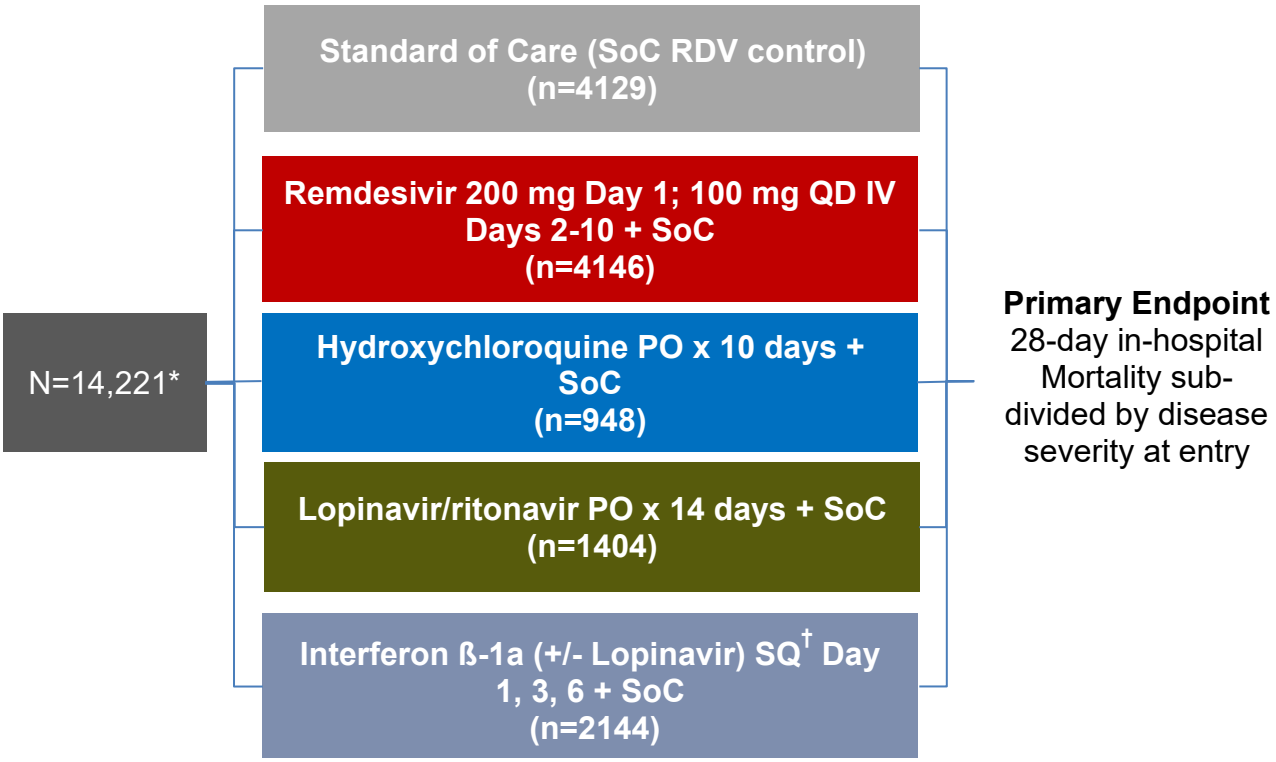
SOLIDARITY was a master study that has a number of sub-studies as part of its overall evaluation of investigational COVID-19 therapeutics. These sub-studies operate under the guidance of the WHO and are informed by the WHO master protocol, often evaluating the same treatments, sharing common endpoints and design, and reporting results back to the WHO for inclusion in the overall findings of SOLIDARITY.

The Assessment Report (AR) considers the sub study, DisCoVeRy, but fails to consider the larger WHO SOLIDARITY trial, with no rationale provided for the exclusion. The Assessment Group (AG) states that all data extractions were undertaken by the end of May 2022, however, the final publication associated with SOLIDARITY was published on the 2nd of May 2022, and an interim report was published in February 2021. Therefore, this study should have been included in the evidence base considered by the AG and would have been identified if a full systematic literature review was conducted in accordance with the NICE methods guide and established best practice for an HTA(6,7).

Clinical evidence for remdesivir has been presented from the SOLIDARITY trial, a phase 3 open-label international multi-centre randomised trial of treatments for hospitalised patients receiving standard of care for COVID-19(6).

Eligible patients were randomised equally between the 5 treatment arms: standard of care, Remdesivir +SoC. Hydroxychloroquine +SoC, Lopinavir/ritonavir + SoC, Interferon ß-1a (+/- Lopinavir) + SoC (**Error! Reference source not found.**)(6).

Figure 1: SOLIDARITY Trial Design(6)



Data from Mar 2020 – Jan 2021
*14,304 patients enrolled; 14,221 patients left in ITT analysis after no/uncertain consent to follow-up
Participants were randomly assigned in equal proportions to locally available study drug or control (up to 5 options: 4 active and local standard-of-care).
HCQ: 200 mg, 4 tabs PO (hour 0, 6), 2 tabs BID (hour 12 and beyond); LPV/r: 200/50 mg 2 tabs PO BID
†IFN: 44 mcg SQ on day 0, 3, 6 or 10 mcg IV daily for 6 days for patients on high-flow oxygen, ventilators, or ECMO
HCQ, LPV, IFN discontinued on June 18, July 14, Oct 16 respectively

A summary of the SOLIDARITY study design and associated key details is provided in Table 1(6).

Table 1: Clinical effectiveness evidence: SOLIDARITY(6)

Trial identifier	ISRCTN83971151
Study	World Health Organization (WHO) COVID-19 Solidarity Trial for COVID-19 Treatments (SOLIDARITY)
Study design	A Phase 3, open label international multi-centre randomised trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care.
Population	Hospitalised adult patients with COVID-19
Location	454 hospitals in 35 countries
Eligibility Criteria	Key inclusion criteria of SOLIDARITY • Consenting adults (age ≥18) • Hospitalised at a collaborating hospital with COVID-19 • Not known to have received study drug • Patients without anticipated transfer within 72 hours to a non- study hospital. • No expected transfer within 72 hours • No contraindication to study drug in the physician's view Exclusion Criteria • AVAILABLE study drugs are contra-indicated (e.g., because of patient characteristics, chronic liver or heart disease, or some concurrent medication). • Declined to participate in the study

Study periods & trial drugs	The trial assessed Remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon ß-1a (+/- lopinavir), versus control (local standard of care). The trial begun in March 2020 and is ongoing.
	
	The study aimed to randomise participants equally to each of the 5 study arms (where they are locally available):
	
	• Local standard of care only
	• Local standard of care **AND** one of the following:
	  ○ Remdesivir.
	  ○ Hydroxychloroquine
	  ○ Lopinavir/ritonavir
	  ○ Interferon ß-1a (+/- Lopinavir)

Primary Outcome	• In hospital mortality, subdivided by disease severity at study entry. Palliative discharge was assessed as an in-hospital death.
Secondary outcomes used in the model /specified in the scope	• Initiation of ventilation (yes or no) • Length of hospital stay (study entry to discharge).
Pre-planned subgroups	Pre-planned subgroup analyses included those with and without severe disease at entry. To this end data on oxygen use and ventilation at the time of randomisation was collected. Separate analyses are provided for those receiving supplementary oxygen at entry, and those ventilated at entry, vs those who were not.

Summary of Baseline Characteristics of Trial Participants

Beginning in March 2020, 14,304 patients across 454 hospitals in 35 different countries entered the study(6). Of these, 0.6% (83) patients lacked clear consent for follow-up, or their COVID-19 diagnosis was refuted, resulting in a total of 14,221 patients included in the intention-to-treat (ITT) analysis(6). In the remdesivir arm only 7 patients (<0.1%) of patients had their diagnosis refuted(6). **Error! Reference source not found.** describes further the characteristics of the trial participants(6).

The trial was conducted across all 6 WHO regions including Western Europe and The Americas, with 454 hospitals in 35 different countries participating(6). The trial enrolled patients in Latin America, Asia, and Africa (69% overall, and 60% of the remdesivir arm)(6). It is important to note that geographic differences in patient population and healthcare practice was not addressed as part of the study. Furthermore, the variation in standard of care, implementation, and availability (of high flow oxygen or ventilation) is important to note particularly in under-resourced settings. Time to treatment following symptom onset was also unknown(6).

Across the 5 trial arms, 4,169 were assigned to receive remdesivir, 956 to hydroxychloroquine, 1,414 to lopinavir, and 2,154 to interferon. (Interferon randomisation was to interferon plus lopinavir vs lopinavir until July 4, 2020, then to interferon vs no study drug). A total of 8,605 patients were allocated to standard of care control groups (**Error! Reference source not found.**)(6). Although the study aimed to randomise patients equally to each arm, the local availability of treatments resulted in an unequal allocation.

11,214 (79%) were younger than 70 years of age, 8851 (62%) were male, 3,685 (26%) were diabetic, 1,141 (8%) had already been ventilated, and 8500 (60% were randomised on either day 0 or day 1 of their hospital stay(6).

Of those assigned to remdesivir, 95.5% were still adherent midway through the trial period. 67.1% of those on remdesivir were also receiving corticosteroids(6).

The protocol was designed to be simply conducted in countries with over-stressed hospitals, therefore trial procedures were minimal with no form filing and other

reporting required after randomisation, except online reporting of death in hospital or discharge alive and suspected unexpected serious adverse reactions(6).

As a result, several important baseline patient characteristics were lacking, including level of oxygen support (low-flow vs. high-flow), number of days a patient received RDV prior to ventilation or death, and duration of symptom onset prior to randomisation(6).

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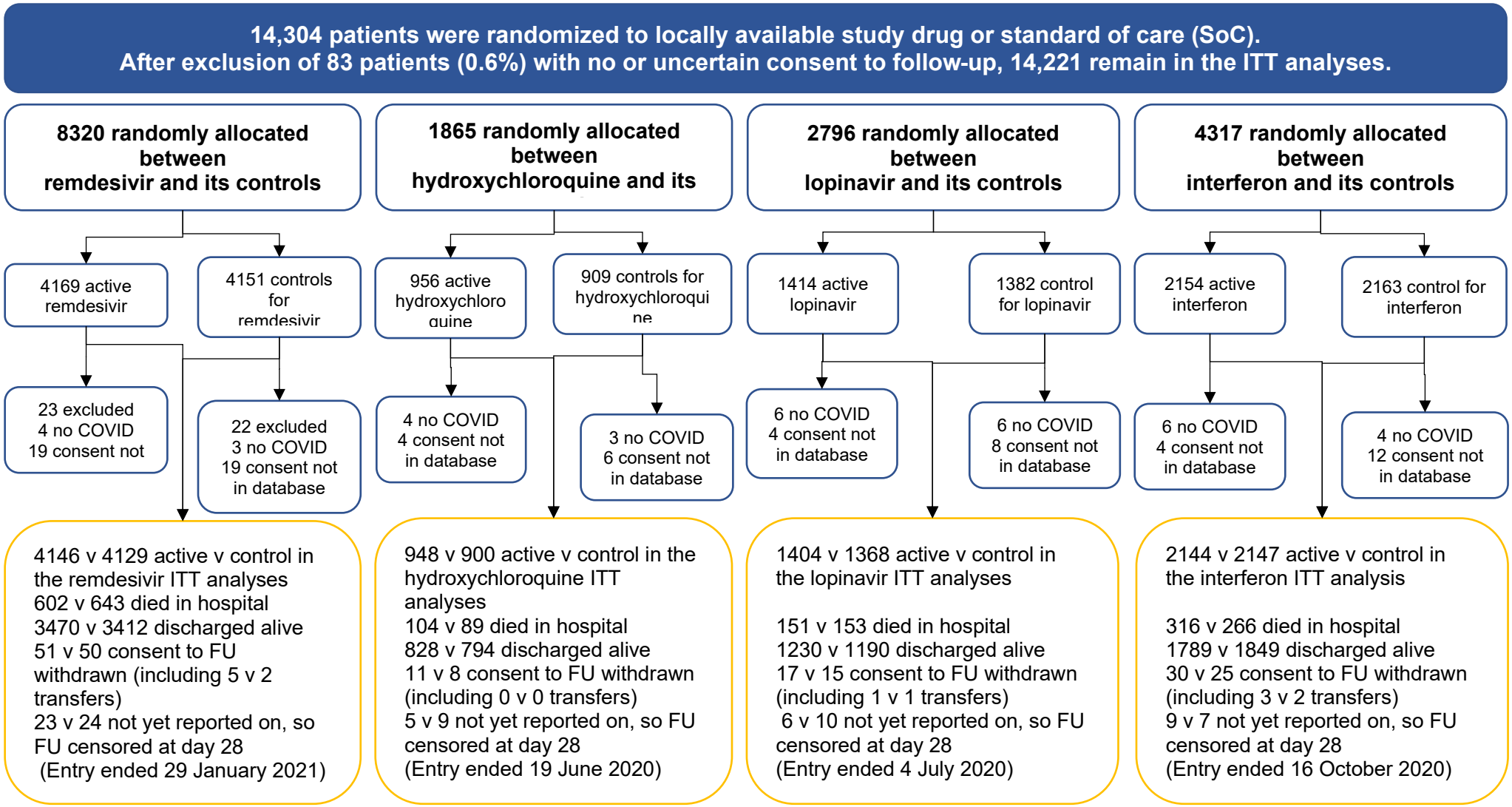
Table 2: Baseline Demographics and Adherence(6)

		Any ITT analysis (N=11,266)			RDV vs Its Control	
		Entered Trial No. (%)	Died in Hospital No.	28-Day Mortality %	Active (n=2743)	Control (n=2708)
Entry characteristics	**Age (years)** <50 50-69 ≥70	3995 (35) 5125 (45) 2146 (19)	237 618 398	6.2 12.8 20.4	961 1282 500	952 1287 469
Respiratory support	No supplemental O_2 at entry On supplemental O_2 at entry Already receiving ventilation	3204 (28) 7146 (63) 916 (8)	78 844 331	2.5 12.8 39.0	661 1828 254	664 1811 233
Lesions in both lungs	No Yes Not imaged at entry	1266 (11) 8832 (78) 1168 (10)	49 1043 161	3.7 12.7 14.9	287 2175 281	259 2153 296
Previous days in hospital	0 1 ≥2	3289 (29) 3713 (33) 4264 (28)	319 384 550	9.8 10.8 14.6	724 917 1102	712 938 1058
Geographic location	Europe and Canada Latin America Asia and Africa	2488 (22) 1941 (17) 6837 (61)	188 400 665	7.8 22.7 10.3	715 470 1558	698 514 1496
Other Characteristics	Male sex Current smoker Diabetes Heart disease Chronic lung disease Asthma Chronic liver disease	6985 (62) 830 (7) 2768 (25) 2337 (21) 635 (6) 529 (5) 135 (1)	852 93 379 319 102 6 21	13.0 11.8 14.7 14.7 17.2 11.5 17.2	1706 178 707 571 151 139 36	1725 161 666 567 145 139 41
Adherence to assigned treatment	% taking trial drug midway through scheduled duration	-	-	-	96	2
Use of non-study drugs	Corticosteroids Convalescent plasma Anti-IL-6 drug Non-trial interferon Non-trial antiviral	-	-	-	1310 (47.8) 52 (1.9) 133 (4.9) 3 (0.1) 65 (2.4)	1288 (47.6) 58 (2.1) 143 (5.3) 25 (0.9) 152 (5.6)

Figure 2: Randomisation between trial arms and controls in further detail(6)



Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

There was no protocol-specified sample size due to the uncertainty in predicting the progression of the COVID-19 pandemic at the time of its writing. Analyses were conducted according to the assigned treatment group and did not follow actual treatment. Patients with refuted COVID-19 diagnosis or unclear consent were excluded(6,8).

In regard to sample size, both the protocol and final publication stated, “The larger the number entered the more accurate the results will be, but numbers entered will depend on how the epidemic develops […] it may be possible to enter several thousand hospitalised patients with relatively mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial”(6,8).

Primary analyses specified by the protocol were in-hospital mortality split by disease severity at entry. Records of ventilation and oxygen use at study entry were used to stratify severity; however, no distinction was made between high and low oxygen flow use. Mortality risk ratios (RRs) and hazard ratios (HRs) and their associated p values were calculated using log-rank or cox analyses. These were analysed according to three age groups: ≥70 years, 50-69 years; and <50 years, and according to three levels of respiratory support: ventilated, oxygen only, and none(6).

RRs for mortality only describe proportional reductions in risk, however, the absolute risk reductions are additionally dependent on background risks. Unstratified Kaplan-Meier methods were modified to assess in-hospital mortality over time. As such Kaplan-Meier denominators across each time point include already previously discharged patients(6).

The risk on a given day (day N) was calculated through first excluding patients with entry less than N days prior to dataset closure or without a reported outcome. Patients were also excluded if consent to follow-up was withdrawn, or the patient was transferred before day N. Subsequently, the total in hospital deaths as of day N were divided by the number of patients in the hospital at day N, or discharged alive

prior to day N. The risk set was further utilised in the calculation of the contribution of day N to the Cox and Log-rank analyses for in hospital mortality. Patients with no reported follow-up were included for denominators for day 0 deaths but were not included for later days (as deaths on day 0 were likely to have been reported(6).

Log e RR (with variance 1/V and a normal distribution) was calculated as (O-E) / V, where the stratified log rank observed is O, the expected number of deaths is E and variance is V. Confidence intervals were 95% with no allowance for multiple comparisons despite the data-dependent focus on particular subgroups. Forest plots used in this analysis included x^2 statistics based on $(O-E)^2/V$ in order to test for discrepancy between RRs. V roughly denotes the weight of each stratum(6).

Clinical effectiveness results of the relevant trials

Key findings of the trial were as follows(6):

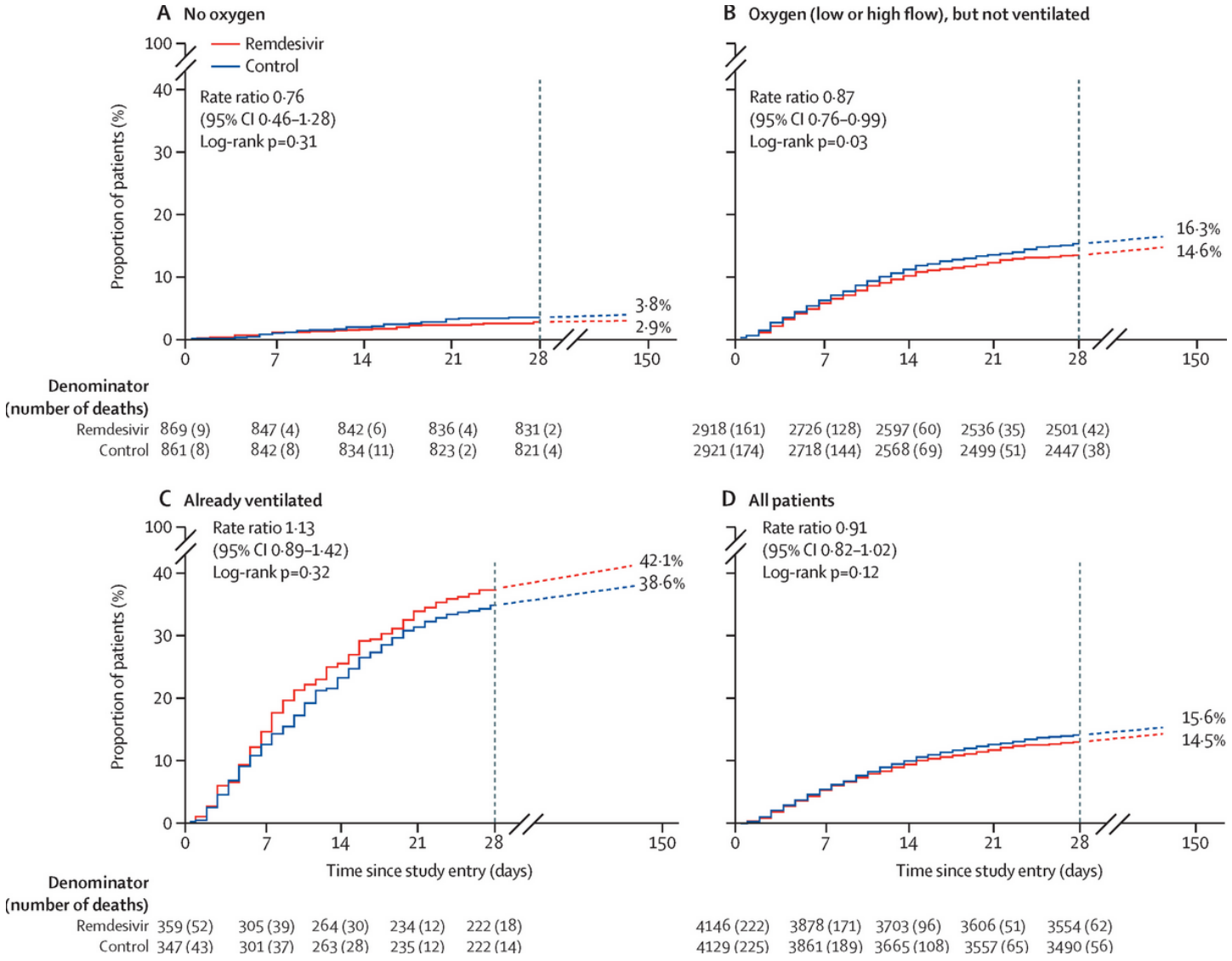
- There was no difference in the primary endpoint of in-hospital mortality at Day 28 between RDV and control [RDV 14.5%, control 15.6% (RR 0.91; 95% CI 0.82-1.02, P=0.12)]
- A significantly lower mortality in those assigned to remdesivir (14.6%) vs standard of care (16.3%) in patients who were receiving oxygen but were not ventilated (RR 0.87 [0.76-0.99], p=0.03).
- Of those not initially ventilated, significantly fewer patients (11.9%) died in the remdesivir group vs those assigned to the control group (13.5%) (RR 0.86 [0.76-0.98], p=0.02).
- Similarly, within this group, 14.1% of patients progressed to ventilation in the remdesivir group compared to 15.7% in the control group (RR 0.88 [0.77-1.00], p=0.04).

The interpretation of these results by the WHO SOLIDARITY Trial Consortium was that remdesivir “has a small effect against death or progression to ventilation (or both)”, in COVID-19 patients who are not already ventilated(6).

Primary Efficacy Endpoint: In-hospital mortality

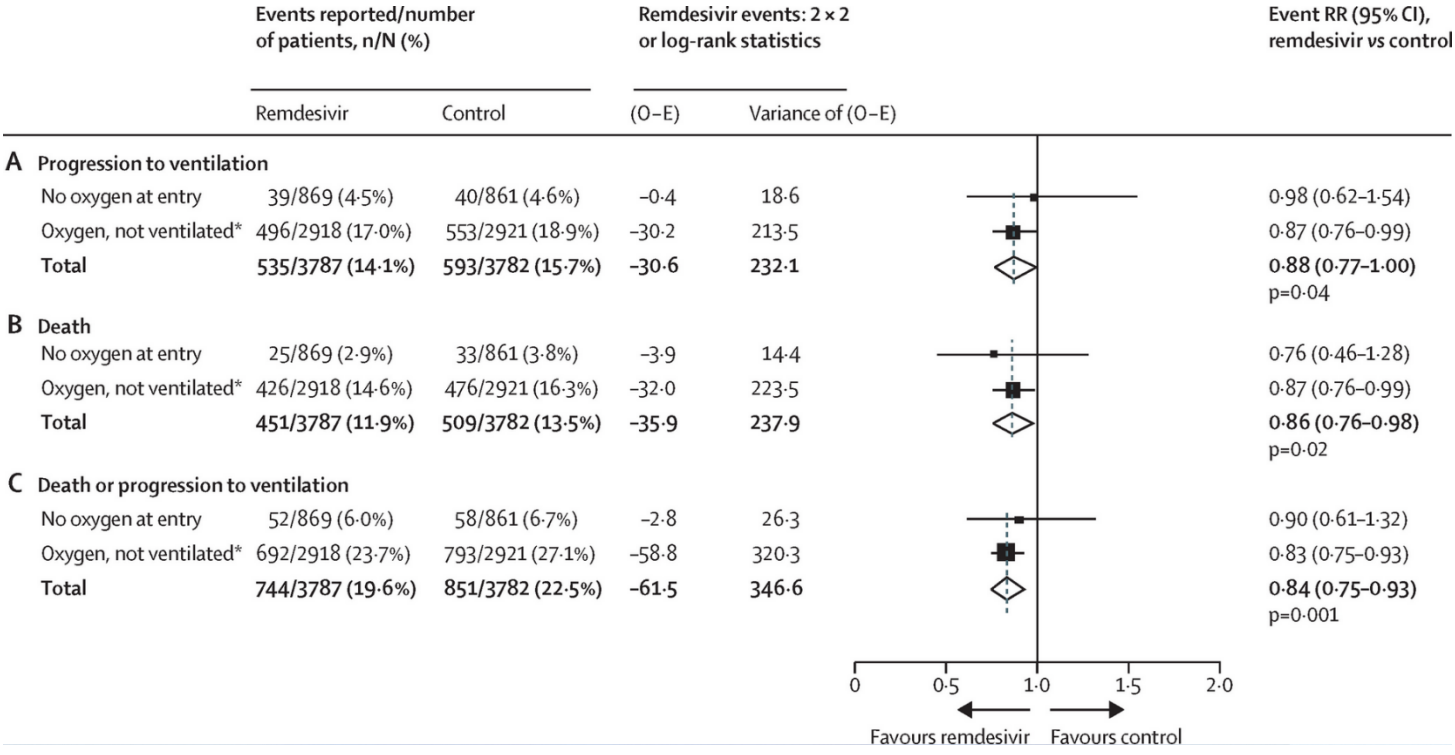
The primary outcome was in-hospital mortality, which was further subdivided by disease severity (oxygen use, ventilation) at trial entry. In-hospital mortality over time is shown in Figure 3**: Primary endpoint - 28-day mortality stratified by disease severity**. Overall mortality findings exclude substantial harm or substantial benefit but do not exclude either a moderate impact on mortality or zero impact. 602 (14.5%) of the 8,275 patients in the remdesivir analysis and 643 (15.6%) of the 4,129 assigned to control groups died. (RR 0.91 [95% CI 0.82-1.02], p=0.12). This analysis included 15 and 11 palliative discharges from the remdesivir and control groups, respectively(6).

Figure 3: Primary endpoint - 28-day mortality stratified by disease severity(6)



When subdivided by disease severity, the RR appeared less favourable in severe disease groups (trend test x^2_1=3.9, p=0.05). Among those 1,730 individuals assigned not on oxygen at trial entry, 25 of the 869 (2.9%) assigned to the remdesivir group died. In the same substratum, 33 of the 861 (3.8%) in the control group died (RR 0.76 [0.46-1.28], p=0.30) (Figure 4)(6). 5,839 patients entered the trial without ventilation but receiving either low or high flow oxygen. Of those in this group who were assigned to remdesivir 426 of 2,918 (14.6%) died, while 476 of 2,921 (16.3%) in the control group died (RR 0.87 [0.76-0.99], p=0.03). There was also a significant reduction in deaths for all non-ventilated patients with 11.9% dying in the remdesivir group and 13.5% dying in the control group (RR 0.86 [0.76-0.98] p=0.02). Among those 706 who were ventilated at the start of the trial, 151 of 359 (42.1%) in the remdesivir group died, while 134 of 347 (38.6%) assigned to the control group died (RR 1.13 [0.89-1.42], p=0.32])(6).

Figure 4:Relative Risk ratios for death and progression to ventilation stratified by disease severity at trial entry(6)



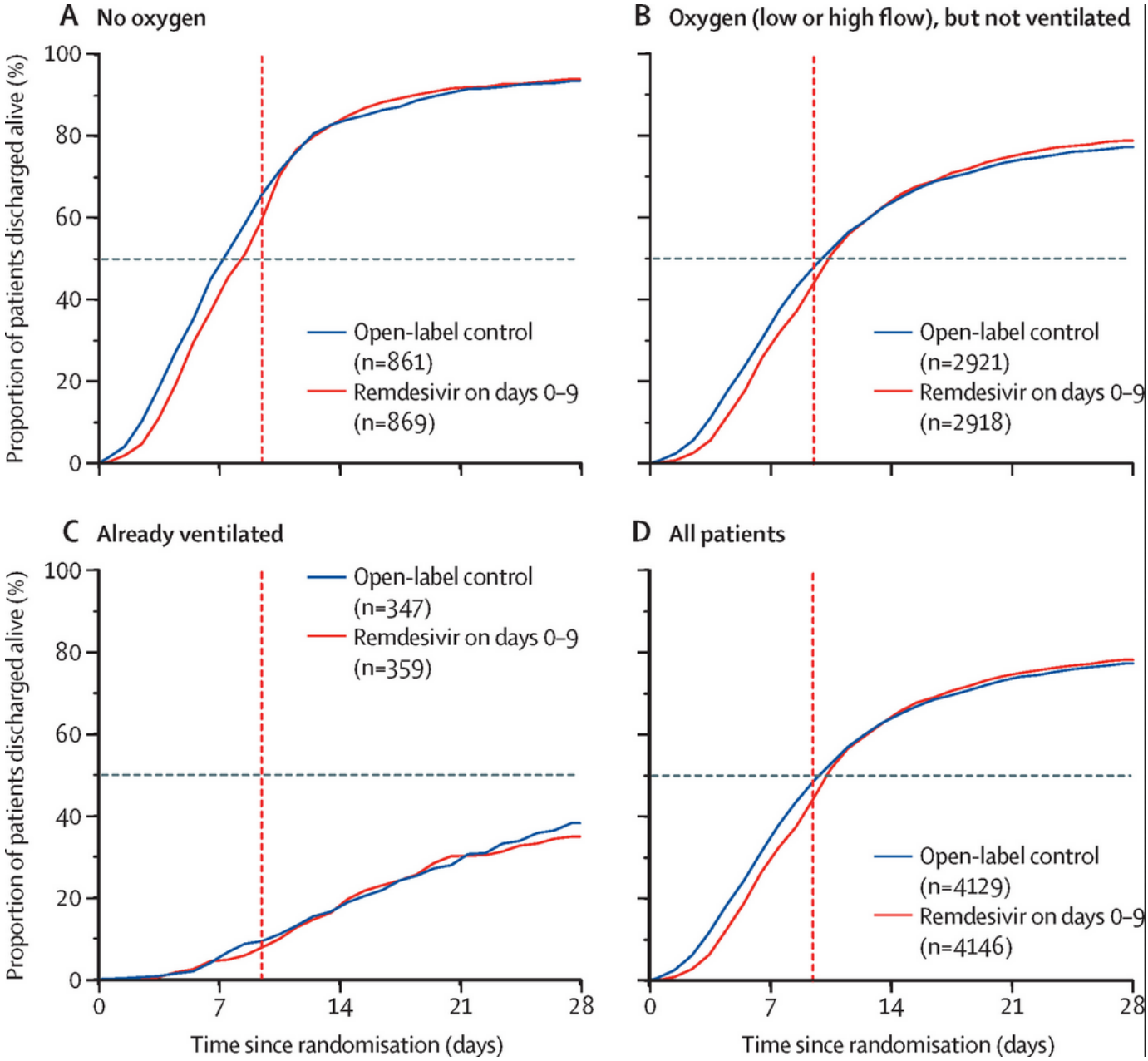
Secondary outcomes: Progression to Ventilation and Time to Discharge

Progression to ventilation and length of hospital stay were the defined secondary endpoints. Overall progression to ventilation was 14.1% (535 of 3787) in the remdesivir group and 15.7% (593 of 3782) in the control group (RR 0.88 [0.77-1.00], p=0.04) (Figure 4). These outcomes were stratified by disease severity. 1,730 patients were not on supplemental oxygen at trial entry. Of those assigned to remdesivir 4.5% progressed to ventilation vs 4.6% in the control group. A total of 6.0% of the remdesivir group and 6.7% of the control group died or had ventilation initiated, respectively (RR 0.90 [0.61-1.32], p=0.59)(6).

5,839 were receiving high or low flow oxygen at study initiation. Of these 17.0% assigned to remdesivir, and 18.9% assigned to the control group required ventilation, while 23.7% of the remdesivir group, and 27.1% of the control group either died or had ventilation initiated (RR 0.83 [0.75-0.93], p=0.001)(6).

Error! Reference source not found. shows time to discharge stratified by disease severity. The overall impact of assignment to the remdesivir group compared to the control group was about a 1-day delay to discharge during the treatment period of 10 days. No impact was seen in the period following these 10 days(6).

Figure 5: Time to discharge stratified by disease severity(6)



Adverse reactions

This information was not reported in the main publication for SOLIDARITY or the interim report(6,9).

Interpretation of clinical effectiveness and safety evidence

The SOLIDARITY trial found there was no significant difference in in-hospital mortality at Day 28 between RDV and control [remdesivir 14.5%, control 15.6% (RR 0.91; 95% CI 0.82-1.02, P=0.12)]. However, there was significant mortality benefit associated with remdesivir in patients who were on oxygen (low or high-flow) but not ventilated [remdesivir 14.6%, control 16.3% (RR 0.87; 95% CI 0.76-0.99, P=0.04]; which is consistent with the findings in ACTT-1 of mortality benefit in the group on low-flow oxygen(5,6). No data was available to determine a difference between low and high flow oxygen outcomes. No significant differences in mortality were found for remdesivir vs. control in patients on no oxygen and those already ventilated. SOLIDARITY found that the defined secondary outcome of progression to ventilation was significantly reduced by assignment to remdesivir (p=0.04). The composite outcome of either death or progression to ventilation was also significantly reduced (p=0.001) though this was not defined prior to study initiation and can be considered subject to bias(6).

SOLIDARITY shows with some reliability that those assigned to remdesivir infusion groups did not have a largely reduced time to discharge. The open label nature of the trial, especially during a pandemic, may explain this through non-pharmacological effects, including the awareness that the patient was receiving a study drug. The reported data therefore includes this impact alongside the time to medical fitness to discharge. Given that there is a 1-day delay to discharge in the 10-day treatment period and not after, we can surmise that if remdesivir reduces time to discharge, the size of this impact is smaller than that of the mentioned non-pharmacological effects, IE, the effect is not likely to be large(6). This uncertainty around time to discharge is further compounded by the lack of data collection concerning time from symptom onset to treatment initiation in the SOLIDARITY trial. Due to this lack of data, there is no way to control for patients with a similar clinical course for whom discharge was delayed allowing for completion of their 10-day

course of remdesivir. Further to this, the 10-day clinical course has been proven to be clinically equivalent to a 5-day course(6,10). Thus, time to discharge data collected in this manner would not be applicable to current clinical practice. ACTT-1 may provide more insightful conclusions on the impact of remdesivir on time to discharge due to its double-blind design. Its secondary endpoint of clinical improvement (discharge or National Early Warning Score (NEWS) ≤2 for 24 h) found a significantly lower median time to discharge for remdesivir [remdesivir 8 days, placebo 12 days (RR 1.27; 95% CI, 1.10 to 1.46)](6,10).

SOLIDARITY has various limitations: Among these were the lack of confirmation of infection and unknown time from symptom onset to treatment initiation, both of which have the potential to introduce inaccuracy to the data(6,8). Likewise, patients in SOLIDARITY were randomised equally according to what drugs were locally available, and the open control, meaning that controls may have been treated in a completely different study location from those receiving the active comparator. A lack of data collection surrounding the reasons for oxygen administration, variation in resource limitation between countries and hospitals, leading to patients being ventilated in some settings and not in others despite similar circumstances(6). However, the validity of the secondary ventilation outcomes is unaffected by this. Furthermore, the variation between trial treatment settings by country and hospital does not introduce significant bias to the comparisons vs control as all could administer the allocated treatments and reliably report study outcomes(6,8). Conversely, time to discharge is biased by the requirement for patients to remain in the hospital for 10 days to complete their remdesivir treatment course. Additionally, trial recruitment took place before the spread of the omicron and delta COVID-19 variants and subsequent widespread vaccination of the global population. Due to the mechanism of action of remdesivir (acting via internal non-structural proteins NSPs), the drug effect is unlikely to be impacted by the emergence of new viral variants(5,6). However, the true mortality impact may be influenced be various factors for which data was not collected. These include infection with lower risk variants, vaccination status, treatment with other anti-viral or immune modulating drugs, or strong quality of supportive care. Furthermore, non-pharmacological effect is included in the mortality effect as no placebo infusion was included in the trial design (in order to

maximise the possible sample size)(6,8). There is uncertainty regarding conclusions drawn from the SOLIDARITY data, due in part to random error as can be seen by wide confidence intervals. Additionally, there is uncertainty around findings in specific subgroups and whether the focus should be on these over the overall data (specifically those patients not ventilated at randomisation)(6,11). Furthermore, the lack of data on high vs low flow oxygen makes it impossible to reliably extend any conclusions around ventilated patients to high flow oxygen patients(6).

Despite the impressive study size of ~8000 participants randomised to remdesivir and its control group, an insufficient sample size remains the largest limitation of SOLIDARITY. With this data a large impact on mortality can be refuted. However, a moderate effect cannot be shown, yet also cannot be ruled out, particularly in specific subgroups(6).

Although much larger than many trials, study size was the largest limitation of SOLIDARITY, with some ~8,000 individuals randomised to remdesivir and control groups. Despite this impressive number of participants, the sample size was still insufficient to refute moderate effects, especially if only present in specific subgroups. However, with this data a large impact on mortality can be refuted(6).

Given the results for the oxygen/non ventilated patients align with the findings of ACTT-1 (which is a randomised controlled trial), we can assume that these results are robust and reliable enough to assess clinical effectiveness in this specific population, supporting its inclusion as a source of data. Furthermore, given the inclusion of DisCoVeRy in the AR, the full dataset from SOLIDARITY is more applicable, as outlined in the next section.

Strengths and Advantages of SOLIDARITY compared to DisCoVeRy

This SOLIDARITY sample size represents a ~16-fold increase in sample size of remdesivir and remdesivir controls vs DisCoVeRy. SOLIDARITY incorporates not only data from DisCoVeRy, but also clinical outcomes data from a much larger patient pool including highly generalisable data from the Canadian CATCO sub study. The conclusions drawn from the SOLIDARITY data thus have markedly greater internal and external validity from a statistical perspective(6,12,13). Furthermore, while it could be argued that the western European patient group included in the DisCoVeRy sub study is more generalisable to the UK, no UK hospitals participated in the study(6,12).

SOLIDARITY also represents the most current data for remdesivir which are consistent with both the recent EMA label for remdesivir, NHSE commissioning, and provisional NICE guidance. Over a third (39%) of the DisCoVeRy cohort were classified as severe as they were receiving either high flow oxygen, invasive mechanical ventilation (IMV), or extra-corporeal membrane oxygenation (ECMO)(6,12). Patients receiving either IMV or ECMO are outside the scope of the guidance for remdesivir, making a potentially significant fraction of the DisCoVeRy sub study patient pool not relevant for the purposes of the MTA assessment. While these severe patients are also present in the SOLIDARITY dataset, they represent a much smaller fraction of the overall patients and thus have a much smaller influence on its outcomes(6,12).

3. Details of Remdesivir

This section presents details of the marketing authorizing associated with remdesivir (Veklury®), as well as the method of administration, dosage, list price and details of any commercial arrangements that would apply in routine NHS commissioning.

GB marketing authorisation status/timing

Veklury 100 mg powder for concentrate for solution for infusion:

- GB marketing authorisation: PLGB 11972/0036
- Date of first authorisation: 16/07/2021

GB marketing authorisation wording

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19):

- in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment),
- in adults with pneumonia not requiring supplemental oxygen.

Method of administration and dosage

Remdesivir is for administration by intravenous infusion after reconstitution and further dilution (see SmPC for further details). The recommended dosage of remdesivir in adults and adolescents (12 to less than 18 years of age and weighing at least 40 kg) is:

- Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion
- Day 2 onwards – 100 mg given once daily by intravenous infusion.

The total duration of treatment should be at least 5 days and not more than 10 days. Use of remdesivir is confined to healthcare facilities in which patients can be monitored closely (see SmPC for further details).

List price

The list price for VEKLURY is £340.00 for one vial of remdesivir 100mg powder for concentrate for solution for infusion (MIMS, 2022).

Any confidential arrangements that would apply in routine commissioning for this product.

None.

4. Equality Issues

This section presents a discussion of the equality issues that should be taken into account when considering therapeutics for the treatment of COVID-19.

There are multiple equality considerations that should be taken into account for this appraisal, given that Public Health England has reported the impact of COVID-19 on exacerbating existing health inequalities. Some of the disparities found were around age and sex, ethnicity and comorbidities (14). For the purposes of the appraisal the following equalities issues should be taken into account by NICE.

Patients with a weakened immune system

Immunosuppression, or being immunocompromised, are considered risk factors for more severe COVID-19. Patients with a weakened immune system may be at a greater risk of severe illness from COVID-19 due to impaired immune defences. This high-risk population includes patients with primary immunodeficiency which is caused by genetic defects and patients with secondary immunodeficiency which can be caused by many conditions and treatments, such as prolonged use of glucocorticoids or other immune weakening medications(15).

Vaccination status:

In addition, there is evidence to suggest that uptake of vaccination is substantially lower in specific groups of people including people from lower socioeconomic groups and ethnic communities, which could further heighten their risk of infection and/or disease progression compared to the general population(16,17). The dramatic impact of COVID-19 on these communities has both replicated and exacerbated existing health inequalities(14). Providing the option of treatment with remdesivir, particularly early in their hospital-based management, could help to address some of these inequalities by providing an effective treatment option for more susceptible patients who will not engage with vaccination, or potentially monoclonal antibody therapies.

As we outlined in our response to the scoping exercise, subgroups relating to these factors should be considered to avoid equality issues arising.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Targeted company submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Your name	[redacted]
Organisation name	GlaxoSmithKline
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted]

1. For this MTA the Assessment Group has already developed a model and drafted a report which you have had the chance to comment on.

Please provide any additional comments below – do not repeat comments submitted in response to consultation on the Assessment Report.

Other comments

Sotrovimab administration route:

The EAG reports says *"It was assumed that the costs associated with treatment administration whilst in hospital would be incorporated in the unit costs associated with hospitalisation (see Section 3.3.3). Additional administration costs were assumed for intravenous treatment in the community, but for simplicity, not for oral or subcutaneous treatments."*

In order to make sotrovimab more easily accessible and improve the ease of administration, GSK is in the process of applying for marketing authorisation (MA) for intramuscular administration (IM) for sotrovimab. [redacted] In the EAG report (section 3.3.2), it was stated, where an intervention, like casirivimab/imdevimab, can be administered by both multiple routes, intravenous (IV) and subcutaneously (SC), the assumption is that all administration will be by SC, which the EAG assigned no administration cost. GSK expects the same lever will be extended to sotrovimab when considering the administration route to be used in the EAG's analysis. Please refer to Section 3 for additional information on the IM license.

To support the IM application, GSK sponsored the COMET-TAIL clinical trial (Shapiro 2022), a phase-3, randomised, multicentre, open-label study which tested non-inferiority of 500mg IM administration to 500mg IV administration, using a 3·5% absolute non-inferiority margin. The trial enrolled a total of 983 patients up to seven days after onset of symptoms, who are randomly assigned 1:1:1 to receive a single 500mg IV infusion of sotrovimab or IM injection of sotrovimab at one of two doses (500mg or 250mg). The 250mg IM group was discontinued early due to a greater proportion of hospitalisation in that arm. The primary endpoint was a composite of progression to all-cause hospitalisation for more than 24 hours for the acute management of a disease or death due to any cause until day 29.

At day 29, the number of people in the IV and IM groups admitted to the hospital for more than 24 hours were 5 (1.3%) and 10 (2.7%) respectively, while numbers of deaths were 0 in the IV group and 2 (0.5%) in the IM group. These results yielded an IM vs IV risk difference of 1.11 (-1.24 to 3.45), establishing the noninferiority of IM to IV sotrovimab.

Similarly, low proportions of participants in the IV and IM groups had any adverse event related to study treatment, 2% and 1% respectively, any infusion- or injection-related reaction (under 1% in both groups), any grade 3 or 4 adverse event (2% in both groups), any serious adverse event (under 1% and 2%), any serious adverse event related to study treatment (0 in both groups), any disease-related event (4% and 3%), and death (0 and under 1%).

The sotrovimab 500mg IM injection was well tolerated and found to be non-inferior to IV administration. The option of IM administration of sotrovimab will expand the ease for outpatient treatment of COVID-19, reducing the burden of healthcare resource.

GSK believes the same logic employed in assuming a £0 (zero) administration cost of subcutaneous (SC) interventions in the EAG analysis, should also be extended to sotrovimab intramuscular (IM), which is even less complicated in comparison.

2. Please provide details of any additional evidence you wish to submit that is not included in the Assessment Report.

Please note:

- **If you wish to submit additional evidence, please contact TAteam4@nice.org.uk as soon as possible. Proposals to submit additional evidence must be agreed by the Associate Director or Programme Director before submission**
- **If academic in confidence data is submitted, NICE and the Assessment Group may choose to rely on published data in order to ensure transparency for all stakeholders.**

Additional Evidence

Due to the uncertainty around some of the inputs, especially the hospitalisation rate, in the EAG analysis, GSK has made efforts to generate evidence to inform a more accurate hospitalisation rate of covid infected persons.

Within the short period provided by NICE, GSK carried out a targeted literature review and has provided interim data from a database (Discover-NOW 2020) study. Please see below for more details.

Literature Review

Study identification: GSK conducted a review of published and pre-printed literature on hospitalisation following confirmation of COVID in patients from December 2021 to August 2022, searching the MEDLINE and EMBASE databases.

Selection process: Overall, 23 articles were identified for potential inclusion in the review. Further filtration for the dominant variant (omicron or majority omicron) and patients identified as high risk reduced the articles number to 5. Please see table below for the output of the search. Evidence tables were prepared for the articles that captured the hospitalisation rate in the previously mentioned search criteria. Table 1. below shows summaries of those articles and the outcomes reported. Please see GSK Appendix A for full details of the targeted literature review methodology and GSK Appendix B (search outputs) for full details.

Table 1: Literature Review Search Results

Source name	Author	Source type	Study type (if applicable)	Setting	Time period	Variant predominance period	Patient population	Could be classed as high risk?	Vaccination status of cohort	Numerator definition	Denominator definition	n	N	Proportion of patients hospitalised (%)
2022 update on the clinical outcome of coronavirus disease 2019 in haemato-oncology patients	Bradwell et al 2022	Letter	Retrospective cohort analysis	England	6th October 2021 - 26th January 2022	Majority Omicron (86%)	Haematological malignancy	Y	Unknown vaccination status = 63% Vaccinated = 36% Unvaccinated = 1%	Hospital admission for symptoms related to COVID-19	Positive PCR or a positive result on home rapid antigen testing.	14	53	26.42
COVID-19 vaccines elicit robust cellular immunity and clinical protection in chronic lymphocytic leukemia	Parry et al 2022	Letter	Cohort analysis	England	Jan 2021 - Feb 2022	Omicron	Chronic lymphocytic leukaemia	Y	Fully vaccinated	Unspecified	Unspecified	3	39	7.69
Humoral Response in Hemodialysis Patients Following COVID-19 Vaccination and Breakthrough Infections during Delta and Omicron Variant Predominance	Chinnadurai et al 2022	Published literature	Prospective observational cohort study	Salford, UK	21 December 2021 to 15 January 2022	Omicron	Haemodialysis Patients	Y	Fully vaccinated	COVID-19-related hospitalization was defined as hospitalization due to COVID-19 and was adjudicated by two clinician co-authors	Positive PCR COVID-19 cases	0	23	0.00
Kidney Transplant Recipients and Omicron: Outcomes, effect of vaccines and the efficacy and safety of novel treatments	Glesson et al 2022	Pre-print literature	Prospective observational cohort study	London. UK	17th Dec 2021 to 31st March 2022	Omicron	Kidney transplant recipients, all immunosuppressed	Y	1 dose = 2.1% 2 doses = 18.8% 2 doses + booster 68.7% 2 doses + 2 boosters = 10.4%	Hospital admission	Symptomatic COVID-19 patients who declined treatment even though they were eligible	10	48	20.83
Outcomes of SARS-CoV-2 omicron infection in residents of long-term care facilities in England (VIVALDI): a prospective, cohort study	Krutikov et al 2022	Published literature	Prospective cohort study	England	Dec 13, 2021– Feb 1, 2022	Omicron	Residents in long term care	Y	unvaccinated=12.29% 2 doses=12.66% Booster >1 week before positive test=75.05%	Hosp admission within 14 days following positive COVID-19 test	COVID-19 infections picked up by monthly PCR + LFD asymptomatic testing long term care facilities	84	1864	4.51

The search identified studies at different stages of publication (published and pre-printed). The patient populations vary in term of size and comorbidity, which includes haematological malignancy, chronic lymphocytic leukaemia, kidney transplant recipients, and immunosuppressed patients, all of which fall within the high-risk group patient population as defined in the Independent Advisory Group Report by the Department of Health and Social Care (DHSC 2022a).

Results: The populations in the search had differing vaccination status between cohorts. Collectively, 87% of the cohorts are confirmed vaccinated, in line with the high proportion of vaccination coverage expected in the high-risk patient population.

The hospitalisation rate recorded in these literatures varies from 0 to 26.4%. Pooling together the data across the five studies (N=2,027), the total number of all cause hospitalisation of confirmed COVID-19 patients is 111, resulting in "all cause hospitalisation rate" for the aggregated high-risk population of 5.48%. Of those five studies, three studies (N=1940) reported COVID related hospitalisation only in 98 patients, resulting in COVID related hospitalisation rate of 5.05%.

Conclusion: Findings from the most recent and relevant literature suggest that the hospitalisation rate of COVID-19 is higher in the high-risk patient group than the 1.8% assumption used by the EAG in its original analysis.

Discover-Now Database

GSK is currently undertaking a number of studies to gain more insight into patients at highest risk of developing severe outcomes for COVID-19. One such study available for sharing in the United Kingdom is a data analysis of the Discover-NOW database in North-West London(Discover-NOW 2020).

The Discover-NOW dataset holds depersonalised primary, secondary, acute, mental health, community health, and social care data of 2.3 million participants, who have consented via their GP in North-West London.

The study includes non-hospitalised patients who have been diagnosed with COVID-19 from 1st December 2021 onwards, who were eligible to receive either antiviral or neutralising monoclonal antibody treatment, according to NHS Interim Clinical Commissioning Policy (DHSC 2022b). The high-risk conditions considered in this analysis are the same as those defined as the highest risk group in the Department of Health and Social Care commissioned Independent Advisory Group Report (DHSC 2022a): Down's syndrome, solid cancer, haematological diseases (including cancers), renal disease, liver disease, immune mediated inflammatory disorders, immune deficiencies, HIV/AIDS, solid organ and stem-cell transplant recipients, and rare neurological conditions.

The core objectives of the study included estimating the proportion of high-risk COVID-19 patients who did not receive treatment (antiviral or monoclonal antibody (mAb)) and experienced a COVID-19-attributable hospitalisation within 29 days of their initial diagnosis. A COVID-19 attributable hospitalisation was defined as a hospitalisation with a primary diagnosis of COVID-19.

Analysis results (GSK Data on File) included data on 3,865 high risk non-hospitalised patients with a COVID-19 diagnosis or positive PCR test between 1st December 2021 and 30th April 2022 and who did not receive treatment with an antiviral or mAb for COVID-19 (the control group). This cohort of patients had a median (IQR) age of 52 (25) years, 1,755 (45.4%) were female, and 3,321 (85.9%) had received two or more vaccinations. The most frequent high-risk comorbidities were immune deficiencies (1,027 [26.6%]), HIV/AIDS (949 [24.6%]), and renal disease (833 [21.6%]). A total of 234 (6.1%) patients had an inpatient hospital admission due to any cause within 29-days of being diagnosed with COVID-19. Of these patients, 108 (2.8%) had an inpatient admission with a primary diagnosis code for COVID-19 within 29 days of being diagnosed with COVID-19. The analysis will be refreshed as data for patients diagnosed between 1st May 2022 and 31st July 2022 becomes available in the coming weeks. Based on these initial analysis findings, the proportion of high-risk COVID-19 patients in North-West London hospitalised due to COVID-19 within 29 days of diagnosis was 2.8%.

It is important to emphasise here that evidence generated from the Discover-Now database analysis demonstrates a higher hospitalisation rate in the high-risk group than the 1.8% rate used in the EAG analysis.

The information provided above is from an interim analysis of the Discover-Now data described earlier, GSK intend to release the final analysis results through a journal publication later in Q3-2022 or Q1-2023.

3. If you are the manufacturer of one of the interventions, please provide details of your product(s):

- **GB marketing authorisation status/timing**
- **GB marketing authorisation wording**
- **Method of administration and dosage**
- **List price**
- **Any confidential arrangements that would apply in routine commissioning for this product.**

Sotrovimab Intravenous

- **GB marketing authorisation status/timing:** Conditional Marketing Authorisation
- **GB marketing authorisation wording:** Treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40kg) with acute covid-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe covid infection.
- **Method of administration and dosage:** IV, 500mg
- **List price:** £2209

Sotrovimab Intramuscular

- **GB marketing authorisation status/timing:** [redacted]
- **GB marketing authorisation wording (Proposed):** [redacted]
- **Method of administration and dosage:** IM, 500mg
- **List price:** [redacted]

4. Are there any potential equality issues that should be taken into account when considering these treatments?

Unmet need within the high-risk group in the absence of monoclonal antibodies

The absence of monoclonal antibodies (mAb) as a treatment option would cause an objective, clinically validated unmet need for some patients who fall within the high-risk group, where there is expressed demand for treatments in COVID patients who are contraindicated to treatment with oral antivirals (OAVs). We believe it is essential that NICE recognises that not all treatment-eligible high-risk patients are clinically suitable for OAVs, and mAbs should continue to be available for these patients to ensure equity in clinical care.

The Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies for non-hospitalised patients with COVID-19 (DHSC 2022b), advises that some of the OAVs could induce serious adverse effects due to interactions with other medicinal products. The potential adverse effects are well recognised in the Clinical Guide: Specialty advice for 'highest-risk' cohorts (DHSC 2022c), where OAV contraindications were expressly listed for some medical conditions and medications in patients at high risk of COVID-19 progression.

A very common example is the case with nirmatrelvir/ritonavir (Paxlovid), according to its Summary of Product Characteristics (SmPC) (Pfizer 2021), Paxlovid is a CYP3A inhibitor which should not be taken with other CYP3A metabolised medicinal products due to drug-to drug-interactions. These interactions could lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products
- Clinically significant adverse reactions from greater exposures of nirmatrelvir/ritonavir
- Loss of therapeutic effect of nirmatrelvir/ritonavir and possible development of viral resistance

A published observational study conducted by a team at University College London Hospital (UCLH), UK (Joshua Gahir 2022) and presented at the British Infection Association (BIA) provides an insight into the experience of clinicians at the frontline of COVID-19 management when considering the number of patients eligible for intervention that can take Paxlovid. The team assessed 872 COVID-19 treatment eligible patients that used North Central London (NCL), COVID Medicine Delivery Unit (CMDU) between 10th February 2022 and 2nd May 2022.

It was estimated from the study that 36% of high-risk patients eligible for COVID-19 treatments could not take Paxlovid due to contraindications and 5% of those who began treatment with Paxlovid had to discontinue the treatment.

Table 2: Patients Observations

Total considered for Paxlovid	872
Paxlovid Contraindicated	317 (36%)
Prescribed Paxlovid	555
Followed up	342
Completed course	305
Reported side effects	181
Discontinued Paxlovid	18 (5%)

Of the contraindications, 238 (75%) were due to DDIs, which could destabilise patients' existing long-term health states and impact prognosis. For example, 38 (12%) patients had severe renal impairment (CKD stage 4 and 5), a contraindication for Paxlovid. Further breakdown of the contraindications is provided in Table 3.

Table 3: Reasons Paxlovid was not prescribed if considered otherwise eligible

Category	N (%)
Drug-drug interaction	238/317 (75)
Anticoagulation	55/317 (17)
Tacrolimus	71/317 (22)
Antiplatelet	19/317 (6)
PDE5 Inhibitor	4/317 (1)
Other	79/317 (25)
CKD stage 4 or 5	38/317 (12)
Pregnant/trying to conceive	5/317 (2)
Patient choice	8/317 (3)
Liver Disease	6/317 (2)
Previous Paxlovid	5/317 (2)
Unable to swallow tablets	5/317 (2)

Other*	12/317 (4)
*including: clinician error, poor gastric absorption, paediatric, hospital admission	

While the above contraindications focus on Paxlovid, it is important to note that other COVID antivirals such as molnupiravir and remdesivir are also contraindicated in some high-risk groups (SPS 2021). It is important to note that patient groups identified as having unmet needs are those most likely to suffer from a severe outcome due to COVID progression.

The population size in the study is small and limited to North-Central London, increasing the confidence interval for the estimates. We acknowledge that further analysis is needed in the area of antiviral contraindications in COVID high-risk patients, but it is clear that the absence of mAbs such as sotrovimab would create significant inequality that could have a detrimental impact not just on the patient and the NHS but also to society at large.

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Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Targeted company submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Your name	[redacted]
Organisation name	Merck Sharp & Dohme (UK) limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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1. For this MTA the Assessment Group has already developed a model and drafted a report which you have had the chance to comment on.

Please provide any additional comments below – do not repeat comments submitted in response to consultation on the Assessment Report.

The Company would like to take the opportunity to expand on some areas that were already raised within our pro-forma response to the Assessment Group's (AG) report. The targeted submission response therefore focuses on the following areas;

- Hospital discharge disutility
- IV administration disutility
- The impact of drug-drug interactions

The targeted submission below may assist the Appraisal Committee (AC) in contextualising the impact of the aforementioned points on decision-making.

Hospital discharge disutility –post-hospitalisation for COVID-19

The AG model disaggregates quality-adjusted life-years (QALYs) into QALYs acquired during patients' stay at hospital and QALYs acquired after discharge. The disutility associated with long COVID is applied as a total disutility decrement in the first cycle. The current approach does not accurately capture how health-related quality-of-life (HRQoL) for patients following hospitalisation for COVID impacts the cost-effectiveness results, which may lead to an inefficient use of the National Health Systems resources.

Currently, the model assumes that when patients are discharged from hospital, their utility is equivalent to patients with a clinical status of 2 on the 8-point ordinal scale: "not hospitalised, with limitation of activities, home oxygen requirement, or both". The model does not apply a utility decrement to this clinical status and is, therefore, equivalent to clinical status 1, "not hospitalised and no limitations of activities". This is unlikely to reflect patients' actual HRQoL upon discharge, considering disease severity and patient testimonies, thereby overestimating QALYs within the economic model.

A UK study, conducted by Halpin *et al.* (2021), assessed the post-discharge symptoms and rehabilitation needs of survivors of COVID-19 and found that there was a clinically significant drop in HRQoL post-hospital discharge relative to patients prior to COVID-19 infection; the utility of patients, measured using EQ-5D, dropped further for participants who were admitted to the intensive care unit (ICU) group, compared with participants who were only ever in a hospital ward.[1] The mean change in EQ-5D-5L index value from pre-COVID to post discharge was higher for the ICU group than the general medical ward group at -0.155 and -0.061, respectively.[1] This demonstrates that QALYs after discharge from hospital are dependent on the severity of patients' COVID-19 infection whilst in hospital.

The Company believe that utility decrements should be applied post-hospital discharge dependent on whether the patient required oxygen whilst in hospital or not. Using the Halpin *et al.* (2021) study, the post-discharge utility decrements should be applied to the clinical statuses as presented in the table below. This

assumes that all patients that receive oxygen for their COVID-19 infection are treated in the ICU. However, we recognise as a limitation that in the real world some patients may receive supplemental oxygen whilst being triaged prior to formal hospital admission.[2]

Table 1: Halpin et al. (2021) reported post-discharge utility values.1

Ordinal scale	Clinical status	Post-discharge utility decrement
3	hospitalised, no longer requiring ongoing medical care	0.061
4	hospitalised, not requiring supplemental oxygen	0.061
5	hospitalised, low-flow oxygen	0.155
6	hospitalised, high-flow oxygen or non-invasive ventilation	0.155

IV administration disutility

The EAG model does not currently capture the utility decrements associated with the administration or injection site reactions (ISRs) associated with IV antibiotics.

To adequately capture the decrement associated with this mode of administration for the community drugs under evaluation, the Company suggest implementing a disutility for an IV administration and a disutility for an associated ISR within the EAG model.

An example of a disutility that could be utilised can be found in Davies *et al.* (2017)[3], which aimed to elicit disutility values associated with different routes of administration of drugs on the prostacyclin pathway. The study concluded that there are quantifiable HRQoL differences between different modes of administration of drugs.[3] Furthermore, a study by Matza *et al.* (2015)[4] aimed to estimate the utility associated with treatment administration and adverse events of hepatitis C; the study found that more complex and burdensome treatment regimens, including the addition of injectable treatments, were associated with lower utilities.[4] Matza *et al.* demonstrated that a utility decrement of 0.02 could be applied per day of IV therapy.[4] The Company requests scenario analyses are conducted to understand the impact of administration route to test the generalisability of the aforementioned source. While data are limited, we consider it important to test the impact of individuals' preferences for effective non-IV treatment options.

The Company considers that the current benefit of molnupiravir over community treatments that require an IV administration has not been fully considered. As molnupiravir is a simply administered, oral drug, applying a disutility for IV administration and ISR's would provide a more realistic representation of a patient journey in the model, and therefore a more accurate estimate of the incremental

cost-effectiveness of molnupiravir compared to standard of care (SoC). This is especially true when applying the disutility to community drugs that require multiple days of IV administration.

Impact of DDI on costs and health resource utilisation

In addition to the points mentioned in the Company response to the EAG report, acknowledging the disutilities and costs associated with drug-drug interactions (DDIs), GP and pharmacist costs, and hospital visits should also be included in the economic model. Potential unit costs for GP and pharmacist time and ambulatory services can be sourced from the National Schedule of NHS Costs and the Unit Costs of Health and Social Care 2021 Personal Social Services Research Unit (PSSRU), as demonstrated in Table 2 **Error! Reference source not found.**below.[5,6] This would be required for selected community drugs under evaluation and further highlight a key benefit of molnupiravir compared to other available COVID-19 treatments and SoC.

Cost should be applied according to the time health care professionals (i.e., GPs and community pharmacists) need to minimise the risk of the DDIs. Cost should also be applied to the percentage of patients treated that consequently experience a negative DDI that requires treatment.

A study by Johnell *et al.* (2007)[7] highlighted the correlation in the number of drugs dispensed in the community and the frequency of DDIs. A strong relationship among people aged ≥ 75 years registered in the Swedish Prescribed Drug Register was shown. Additionally, many patients who need treatment for COVID-19 may have pre-existing renal or hepatic disease.[8] Drug concentrations of some COVID-19 medications altered renal or hepatic function at lower dose, due to impaired drug metabolism and excretion, resulting in increased drug toxicity or reduced efficacy.[9–12]

Unless resolved quickly, DDIs may have an impact on the health-related quality of life of patients, particularly those in hospital. The impact of DDIs on patient health-related quality of life is highlighted within the US study by the Lown Institute (2019)[13], which highlights the impact of medication overload and the associated side effects on patient quality of life. We provide the AG with potentially relevant cost inputs (Table 2**Error! Reference source not found.**).We have been unable to identify a robust source of disutilities associated with DDIs for the purposes of this submission. We request the AG tests the impact of DDIs on health-related quality of life through further scenario analyses, to understand the impact on cost-effectiveness estimates for treatments available in the community setting. This element should be noted as an area of further research.

Table 2:Indicative unit costs from public sources that may be applicable for costing of arising Drug-Drug Interactions

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Service	Unit Costs (£)	Reference
GP consultations		
GP cost per hour of patient contact, excluding direct care staff, with qualification costs	£223	Unit Costs of Health and Social Care 2021, PSSRU[6]
Pharmacist consultation		
Non-consultant led, Clinical pharmacology, non-admitted, face-to-face, first (WF01B)	£352.49	National Schedule of NHS Costs 2019/2020.[5] Inflated to 2021 using the inflation index from Unit Costs of Health and Social Care 2021, PSSRU.[6]
Ambulance services		
Hear and treat and refer	£48	Unit Costs of Health and Social Care 2021, PSSRU[6]
See and treat and refer	£215	
See and treat and convey	£265	
Average of all	£134	

2. Please provide details of any additional evidence you wish to submit that is not included in the Assessment Report.

Please note:

- **If you wish to submit additional evidence, please contact TAteam4@nice.org.uk as soon as possible. Proposals to submit additional evidence must be agreed by the Associate Director or Programme Director before submission**
- **If academic in confidence data is submitted, NICE and the Assessment Group may choose to rely on published data in order to ensure transparency for all stakeholders.**

The Company does not wish to submit any additional evidence that is not already included in the assessment report.

3. If you are the manufacturer of one of the interventions, please provide details of your product(s):

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- **GB marketing authorisation status/timing**
- **GB marketing authorisation wording**
- **Method of administration and dosage**
- **List price**
- **Any confidential arrangements that would apply in routine commissioning for this product.**

Pricing information

Product information for molnupiravir can be found in **Table 3**. For further prescribing information, please refer to the Summary of Product Characteristics (SmPC) for each product.

Table 3: Lagevrio (molnupiravir) product information

Product Information	Details
GB marketing authorisation status/timing	Conditional marketing authorisation on 4th November 2021
GB marketing authorisation wording	Lagevrio 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.
Method of administration and dosage (SmPC):	The recommended dose of Lagevrio is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days. Lagevrio 200 mg capsules can be taken with or without food. The capsules should be swallowed whole with a sufficient amount of fluid (e.g., a glass of water). The capsules should not be opened, crushed or chewed.
List Price (£):	Refer to separate document
Confidential arrangements	Refer to separate document

4. Are there any potential equality issues that should be taken into account when considering these treatments?

Compared to molnupiravir, other community treatments for COVID-19 do not have simple administration regimens and require travel to hospital for administration or pharmacological assessment in order to receive the drug. Molnupiravir is easy to

prescribe in the outpatient setting and is given as a single, oral tablet to be taken every 12 hours over 5 days. Therefore, infectious patients do not need to travel to hospital to receive treatment.

Subsequently, a recommendation to withhold molnupiravir in mild-moderate COVID-19 will have a greater negative impact on patients in rural areas or who are unable to easily travel to hospital, such as the elderly and those with disabilities.[14]

As there are no known clinically meaningful DDIs associated with the use of molnupiravir, it is unlikely to cause an adverse reaction when administered concomitantly with other medications.[15] Conversely, other treatments are associated with several drug-drug interactions, including interactions with anticoagulants, anticonvulsants and antiarrhythmics,[16,17] which are common treatments for the comorbid conditions defining high-risk patients. Furthermore, drug concentrations of some COVID-19 medications can be significantly affected in patients with altered renal or hepatic function due to impaired drug metabolism and excretion, resulting in increased drug toxicity or reduced efficacy.[9–12]These drug-drug interactions may prevent or complicate the use of treatments other than molnupiravir in a substantial proportion of patients at high-risk of COVID-19.

Therefore, a recommendation to withhold molnupiravir in mild-moderate COVID-19 will have a greater negative impact on people with concomitant conditions that will be effected by the DDIs.

A UK study reported that race, social background, gender and age are all key risk factors associated with death from COVID-19.[18] Subsequently, a recommendation to withhold community treatments in mild-moderate COVID-19 will have a greater negative impact on people of Asian and Black ethnic origin, people from deprived social backgrounds, men and people of older ages.[18]

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Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Targeted company submission

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Your name	[redacted]
Organisation name	Pfizer
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

1. For this MTA the Assessment Group has already developed a model and drafted a report which you have had the chance to comment on.

Please provide any additional comments below – do not repeat comments submitted in response to consultation on the Assessment Report.

There are four key topics for which additional comments are provided:

- **Value of reducing viral load and COVID-19 transmission:** Paxlovid had a significant impact on viral load during EPIC-HR.[1] Impact on viral load is within the scope of the current assessment[2] and is a key endpoint for many virologic diseases, with impacts on clinical outcomes and disease transmission for economic models in other indications.[3] Thus, viral load and disease transmission should be considered in the present assessment.

- **Value of reduced hospitalisations:** Paxlovid is associated with a reduction in hospitalisation risk.[1] Reduction in the number of COVID-19 patients in hospital will impact on costs and may help relieve the pressure on the NHS, reducing costs and releasing hospital resources to enable procedures in other patient populations. These benefits are not currently reflected in the economic model.

- **Residual impact of community-based treatment during hospitalisation**: The residual effect of community treatments once patients are hospitalised should be captured in the model. Community treatments are expected to have a residual effect, which should be incorporated in the economic model in the form of a long-term impact, reducing costs and improving outcomes.

- **Supportive network meta-analyses**: Evidence from a contemporary systematic review and network meta-analysis (NMA) supports the conclusions of the Assessment Group's (AG) treatment comparison. However, this study does not address the uncertainties in the AG's model and several factors make it unsuitable to directly inform decision making within the context of this appraisal.

In summary, this submission provides clinical evidence to demonstrate that Paxlovid offers several additional elements of value that are not currently captured in the economic model. If this value is not incorporated into the assessment, the overall benefits to the NHS provided by this treatment will be underestimated.

Value of reducing viral load and COVID-19 transmission

It is extremely likely that the reduction in SARS-CoV-2 viral load and the acceleration of negative RT-PCR respiratory SARS-CoV-2 conversion observed with Paxlovid

treatment will reduce virus transmission in both the community and hospital setting. Although impact on viral load is within the scope of this assessment, the economic model does not reflect this benefit.[2]

- Impact of Paxlovid and viral load: During EPIC-HR, Paxlovid reduced viral load at day 5 by an additional 0.868±0.105 $\log_{10}$ copies/ml (95% confidence interval [CI]: –1.074 to –0.6615; P<0.001) when treatment was initiated within 3 days after symptom onset, a decrease in viral load by a factor of 10 relative to placebo.[1]

- Impact of viral load on transmission: The relationship between SARS-CoV-2 viral load and its infectiousness is yet to be fully characterised; however, by modelling SARS-CoV-2 viral dynamics, Marc et al.(2021)[4] found that larger viral load levels were associated with an increase in the probability of transmission. Similarly, in a cohort study that analysed factors associated with transmission of SARS-CoV-2 from index cases to their contacts, the viral load of the index case was strongly associated with the risk of onward transmission (adjusted odds ratio per log10 increase in viral load: 1·3; 95% CI: 1·1–1·5).[5] Thus, it is likely that decreased SARS-CoV-2 viral load may lead to decreased transmission of the virus in the community.

- Impact of Paxlovid on negative respiratory conversion of SARS-CoV-2: In a cohort study conducted in high-risk patients with mild-to-moderate COVID-19, The median time for patients who converted from positive to negative RT-PCR was 10 days (interquartile range [IQR]: 7-12 days) in patients treated with Paxlovid ≤5 days after symptom onset and 17 days (IQR: 12-21days) in non-treated patients, respectively.[6] The proportions of patients with a negative conversion at day 15 were 89.7% and 42.0% in Paxlovid- treated patients and non-treated patients (hazard ratio [HR]:4.33; 95% CI: 3.31-5.65).[6] Although there is currently no ideal surrogate marker for infectiousness, a negative respiratory RT-PCR is likely indicative of non-infectiousness.[7] Thus, it is likely that accelerating negative RT-PCR respiratory SARS-CoV-2 conversion might reduce infectiousness and subsequent risk of viral shedding and disease transmission.

- Impact of fewer COVID-19 hospitalisation on hospital transmission: Data from EPIC-HR indicate a reduction of approximately 90% in the relative risk (RR) of hospitalisation or death at 28 days in patients receiving Paxlovid.[1] By reducing the number of patients hospitalised due to COVID 19, following treatment with Paxlovid, it would be logical to expect a reduction in transmission in the hospital settings. This is of particular relevance if we consider the health economic impact of in-hospital exposure to SARS-CoV-2

of healthcare workers and susceptible patients, where exposure to an infectious patient has a considerable increase in risk of infection.[8]

Taking into consideration the limited timescale of the present assessment and the limited evidence base, a pragmatic approach is suggested, similar to those used in the recent assessment of novel antimicrobials.[9,10] However, full assessment of the impact of viral load and transmission in the economic model would be recommended for future assessments of COVID-19 therapies.

Value of reduced hospitalisations:

Paxlovid is associated with a reduction in hospitalisation risk and shorter time to discharge, which may help relieving the pressure on the NHS, reducing costs and releasing hospital resources to enable procedures in other patient populations. These benefits are not currently reflected in the economic model.

- Impact of COVID-19 on health systems: Non-COVID-19 health service outputs suffered a substantial decline in 2020 with elective care procedures and GP visits in Q3 being less than one-quarter, and at 62% of their level, respectively, in final quarter of 2019.[11] These declines are envisioned to have lasting effects on health outcomes due to reduced screening, late diagnosis and delayed treatment, among other factors.[11] Of note, a recent cohort study showed that decreasing median values of viral load were paralleled by a reduction in the proportion of COVID-19 patients requiring intensive care.[12]

- Impact of reduced COVID-19 hospitalisations on health systems: Availability of effective treatments that reduce risk of developing severe COVID-19 and hospitalisation needs is highly valuable to the NHS. By reducing viral load, hospital bed occupancy, and the overall risk for hospitalisation,[1] use of Paxlovid may alleviate pressure on the NHS, enabling procedures in other patient populations (e.g., cancer patients etc.), and mitigating the impact of late diagnosis and treatment initiation. Enabling these additional procedures would translate into an additional QALYs gain that is beyond the scope of the current model but should be taken into consideration.

Residual impact of community-based treatment after hospitalisation

The AG economic model assumes that treatments received in the community setting, such as Paxlovid, impact only the rate of hospitalisation. However, there is evidence in the clinical trial, EPIC-HR, and elsewhere which shows that use of Paxlovid is beneficial beyond its impact on hospitalisation requirement. Residual effects have been shown in the form of improved hospital outcomes and reduced health care resource usage in Paxlovid treated patients that are hospitalised:[1,13]

- Impact of viral load on clinical outcomes: As noted previously, Paxlovid significantly reduced viral load versus placebo by day 5 of treatment during EPIC-HR.[1]
  In patients with SARS-CoV-2 infection, higher upper respiratory tract (URT) viral load has been associated with higher likelihood of developing COVID-19 (86.4% vs. 67.6%), longer intensive care unit (ICU) stay (6.76 ±12.99 vs. 3.21 ±8.30 days) being intubated (11.3% vs. 6.40%), and dying compared to patients with moderate or low URT viral load (p-values= <0.001, 0.01, 0.05, and 0.03, respectively).[14] These findings have been confirmed in other studies, in which high viral load was associated with an increased risk of hospital admission[15] (adjusted odds ratio [aOR]: 1.57; 95% CI: 1.11–2.26), ICU admission[15] (aOR, 7.06 [95% CI, 2.15–43.57]), intubation[16] (aOR, 2.73; 95% CI, 1.68-4.44).and mortality[16] (aOR: 6.05; 95% CI: 2.92-12.52). Viral load suppression is a key endpoint for many virologic diseases, with impacts on clinical outcomes and disease transmission for economic models in other indications,[3] and should thus also be considered in the present assessment.

- [redacted] intensive care unit (ICU) visits: [redacted] patients in the Paxlovid arm of EPIC-HR reported ICU visits, compared with [redacted] patients in the placebo arm (CSR Table 17). [13] This observation would [redacted] costs for patients receiving Paxlovid.

- [redacted] medical visits: In addition to [redacted], [redacted] patients in the Paxlovid arm of EPIC-HR experienced COVID-19-related medical visits ([redacted] versus [redacted]; [redacted] visits versus [redacted] visits; CSR table 22), including [redacted] emergency room visits and [redacted] visits to general practitioners.[13] This is supported by a RWE study which suggested that in addition to reduced likelihood of emergency room visits, hospitalization or death, Paxlovid was also associated with a decrease in complications and overall resource utilization.[17] If translated to clinical practice, these outcomes should translate to [redacted] costs in the community and hospital setting.

- [redacted] time to alleviation of symptoms: [redacted] in the median time to sustained alleviation of each considered COVID-19 sign and symptom were observed with Paxlovid treatment compared with placebo (CSR Figure 17 and Figure 18).[13] This indicates a potential quality of life benefit for patients receiving Paxlovid.

Supportive Network Meta-Analyses

In our response to the AG report, we noted the various uncertainties within the modelling approach, in particular around the treatment comparison used by the AG to inform relative treatment effects. Due to the lack of detailed methodology, it was

not possible to assess the robustness of their analysis. Since the submission of our response, we have identified a systematic review and NMA which supports the conclusions of the AGs comparison. This study by Pitre *et al*.[18] compares the efficacy and safety of antivirals in the treatment of COVID-19; all treatments included are compared to standard of care or placebo, but also indirectly to each other with pairwise estimates for relative and absolute risk reductions. This is a very comprehensive study which utilises contemporary randomized controlled trials as evidence and frequentist NMA. The conclusions are that nirmatrelvir–ritonavir and molnupiravir probably reduce the risk of hospital admissions and death among patients with non-severe COVID-19, and that nirmatrelvir–ritonavir is probably more effective than molnupiravir for reducing risk of hospital admissions. Whilst this study does not address the uncertainties within the AG's treatment comparison, it does provide strong supportive evidence that the AG's conclusions around treatments used in the community setting can be considered robust. However, whilst this study may be considered supportive of the AG's analysis, there are several factors that make it unsuitable to directly inform decision making within the context of this appraisal:

- Whilst NICE's appraisal is focussed on patients at high-risk of progression to severe disease (within the community setting), Pitre *et al*. does not stratify studies by risk level; hence, data for patients at low risk of progression are included within the relative effectiveness estimates.
- In addition to including data from low-risk populations, interim analyses are included for EPIC-SR[19]; this data has not yet undergone peer review and was taken from a press release. The inclusion of such data increases the uncertainty around effectiveness estimates for some treatments, resulting in large confidence intervals.
- Where more than one study is available to inform clinical effectiveness of a treatment, the results are pooled and averaged with weighting for sample size. In terms of the NMA's relevance to the decision problem in NICE's appraisal, doing so does not account for the relative uncertainty and inappropriateness of including studies such as EPIC-SR. As a result, effectiveness estimates will be biased against some treatments where less robust or relevant data is factored into their relative effectiveness.

As a result of these points, we believe this study should be considered as no more than supportive evidence within this appraisal.

2. Please provide details of any additional evidence you wish to submit that is not included in the Assessment Report.

Please note:

- **If you wish to submit additional evidence, please contact TAteam4@nice.org.uk as soon as possible. Proposals to submit additional evidence must be agreed by the Associate Director or Programme Director before submission**
- **If academic in confidence data is submitted, NICE and the Assessment Group may choose to rely on published data in order to ensure transparency for all stakeholders.**

There are three key areas where additional evidence is provided:

- **High risk patient groups not included in the assessment scope:** the definition of patients with mild COVID-19 at high risk of progressing to severe COVID-19 is overly restrictive and excludes patient populations at high risk of severe COVID-19. Hence, the scope of the current assessment excludes relevant vulnerable subgroups who would benefit from treatment. This submission provides evidence to describe the elevated risk in these populations.

- **Additional populations that would benefit from treatment:** evidence is presented to describe the impact and potential benefits of treating COVID-19 in front-line healthcare workers, who are at high risk of exposure to COVID-19 infection, and unpaid carers, who play a significant role in supporting the healthcare system. Treatment of these populations supports an early return to work, helping to protect the health service.

- **Additional evidence to support the efficacy of Paxlovid**: The AG's report notes that areas of uncertainty include vaccination status, SARS-CoV-2 variant and the evolution of standard of care over time. Additional evidence is presented to support the effectiveness of Paxlovid, with the aim of informing this uncertainty.

High risk patient groups not included in the assessment scope

As described in the response to consultation on the Assessment Report, the definition of high-risk patients used in the AG's assessment is considered overly restrictive and excludes patient populations that would benefit from Paxlovid treatment. Here we provide additional evidence that describes the impact of COVID-19 on patients with these risk factors.

The key independent risk factor for consideration is age; additional risk factors that should be considered in this appraisal are hypertension, BMI (<18.5 and ≥ 25 kg/m^2), smoking, patients receiving cancer treatments and patients with splenectomy. Cost-effectiveness in this broader cohort needs to be explored as the

base case. The population currently included in the assessment exclude relevant vulnerable subgroups who would benefit from treatment.

Age is an independent risk factor

As discussed in the AG report response, there is a substantial UK and international evidence base that has demonstrated age as an independent risk factor for hospitalisation and mortality. We further request that consideration be given to the inclusion of age ≥ 50 years as a high-risk population and an independent risk factor in this assessment.

In one of the largest cohort studies conducted on the topic, data from primary care records of over 17 million adults was examined for factors associated with COVID-19-related death.[20] The study was conducted using OpenSAFELY, a secure health analytics platform that holds data on 40% of all patients in England.[20] Risk of death was evaluated by age range compared to age 50-59 (reference range) and reported as adjusted hazard ratios (HR) and 95% Confidence Internals (CI) for COVID-19-related death. Increasing age was strongly associated with risk of COVID-19-related death, with a fully adjusted HR of 2.40 (2.16–2.66) for age 60-69, rising to 6.07 (5.51–6.69) for age 70-79, and 20.60 (18.70–22.68) for age 80 and over, compared to 50-59-year-olds.[20]

In a large systematic literature review and meta-analysis of 42 studies and over 400,000 patients, older age was associated with increased risk COVID-19 mortality with a pooled odds ratio (OR) and pooled HR of 2.61 (95% CI 1.75–3.47) and 1.31 (95% CI 1.11–1.51), respectively.[21]

Further, the living risk prediction algorithm QCOVID, comprising 1205 genera practices in England with linkage to covid-19 test results, Hospital Episode Statistics, and death registry data, has demonstrated the association of increasing age on the risk of COVID-19 death (Figure 1) and hospitalisation (Figure 2).[22]

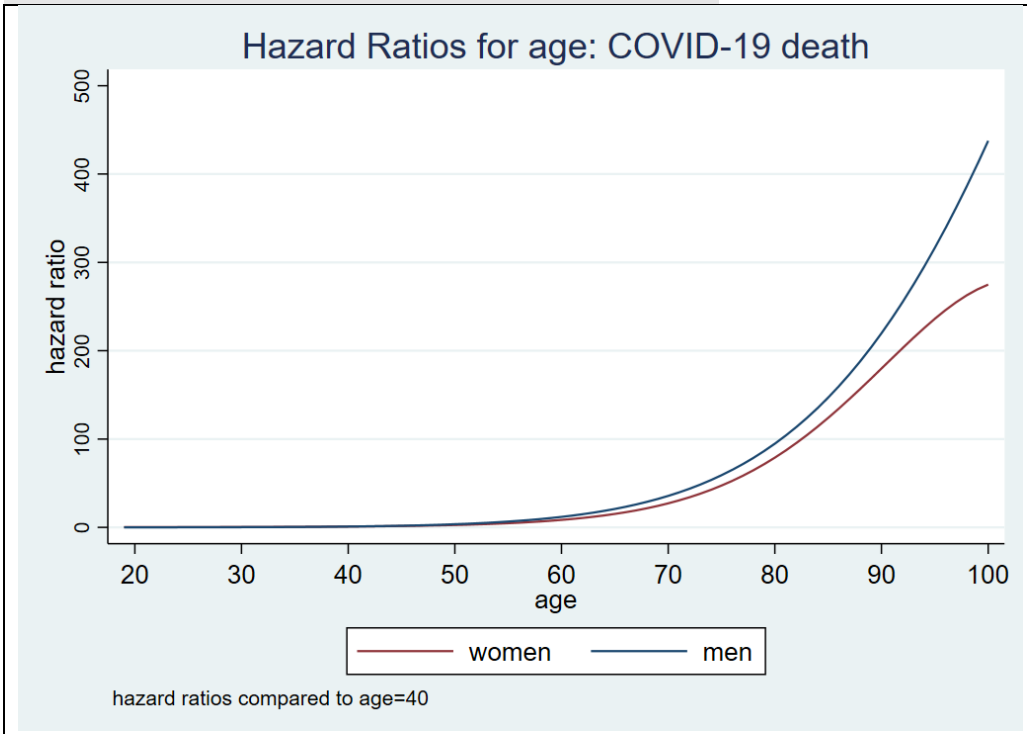

Figure 1. Adjusted hazard ratios for age and risk of COVID-19 deaths derived from the living risk prediction algorithm QCOVID[22]

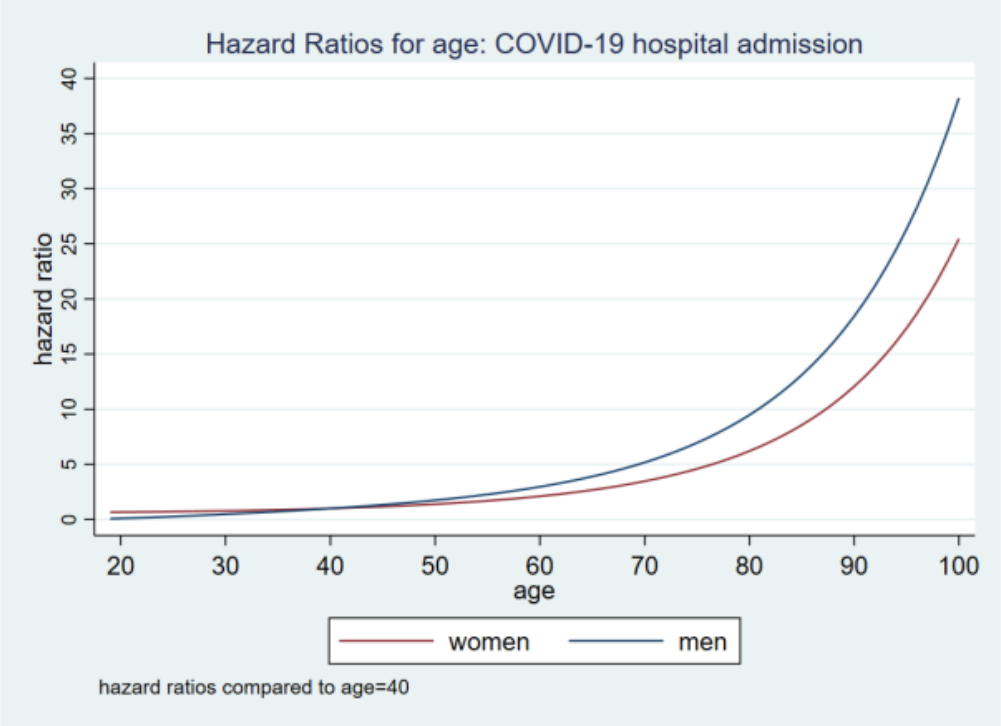

Figure 2. Adjusted hazard ratios for age and risk of COVID-19 hospitalisation derived from the living risk prediction algorithm QCOVID[22]

The PANORAMIC study[23] includes patients aged ≥ 50 years as a risk factor. Additionally, reputable institutions including the International Severe Acute

Respiratory and emerging Infections Consortium (ISARIC) and the Centre for Disease Control (CDC), have linked age of the range ≥ 50 years to increased risk of COVID-19-related death,[24] and hospitalisation,[25-27] respectively.

The EAG report notes that the definition of patients at high risk in the decision problem aligns with the population of the PANORAMIC study,[23] which enrols patients aged ≥ 50 years. However, the definition applied in the appraisal excludes age ≥ 50 years as a high-risk factor. Adoption of a broader definition would ensure these patients have rapid access to treatment in order to reduce risk of COVID-19-related hospitalisation and mortality and protect the NHS from increasing hospitalisations in this vulnerable group.

Additional risk factors

Hypertension

Evidence in support of hypertension as a risk factor of hospitalisation due to COVID-19 was included in the AG response report.[28-31] Further evidence is provided to describe the impact of this risk factor on COVID-19 outcomes.

A large-scale systematic review and meta-analysis including 127 observational studies over 900,000 patients with COVID-19 demonstrated increased risk of COVID-19-related mortality among patients with hypertension (summary relative risk: 1.42; 95% CI 1.30 to 1.54).[32] Another large systematic literature review and meta-analysis using data from over 6 million COVID-19 patients in Europe reported an association between hypertension and either hospital admission (OR 2.139 [95% CI 0.896-5.106]) or a composite of death or ICU admission (OR 1.39 [0.941-2.053]) among COVID-19 cases within the community setting.[33] Further systematic reviews and meta-analyses have reported an association between hypertension and increased risk of hospital re-admission (OR 1.734 [1.404–2.140]),[34] and COVID-19-related death.[21,35]

Body mass index (BMI) <18.5 and ≥ 25 kg/m^2

Additionally, a number of systematic literature review and meta-analyses have reported an association between obesity and COVID-19-related outcomes. A large systematic review and meta-analysis evaluated BMI and mortality risk among over 800,000 patients with COVID-19, from 54 observational studies.[32] The reported summary relative risk (SRR) was 1.45 (1.31 to 1.61) for obese (BMI ≥30 kg/m^2) versus non-obese (BMI <30 kg/m^2) patients, with an increase of 12% and 45% in risk of absolute and relative death, respectively. Additionally, the study reported a 1.5–2-fold increase in risk of death for a BMI of 40–45 kg/m^2 versus 22–24 kg/m^2. Certainty of the evidence was rated high.[32] Furthermore, greater risk of COVID-19-related death has been associated with increasing levels of obesity; with the fully

adjusted HR increasing from 1.05 (1.00-1.11) for a BMI of 30-34.9 kg/m^2, to 1.40 (1.30-1.52) for a BMI of 35-39.9 kg/m^2, and further again to 1.92 (1.72-2.13) for a BMI of ≥40 kg/m^2.[20]

Further systematic reviews and meta-analyses have similarly reported an association between obesity and COVID-19-related death. The systematic literature review and meta-analysis by Constantine *et al*.[33] also reported an association between obesity and risk of mortality, specifically in the community setting (OR 1.138 [0.925-1.399]).[33]

Data from the living risk prediction algorithm QCOVID have highlighted the association of increasing BMI on the risk of COVID-19 death (Figure 3) and hospitalisation (Figure 4), with an impact on patients from BMI 25 kg/m^2.[22]

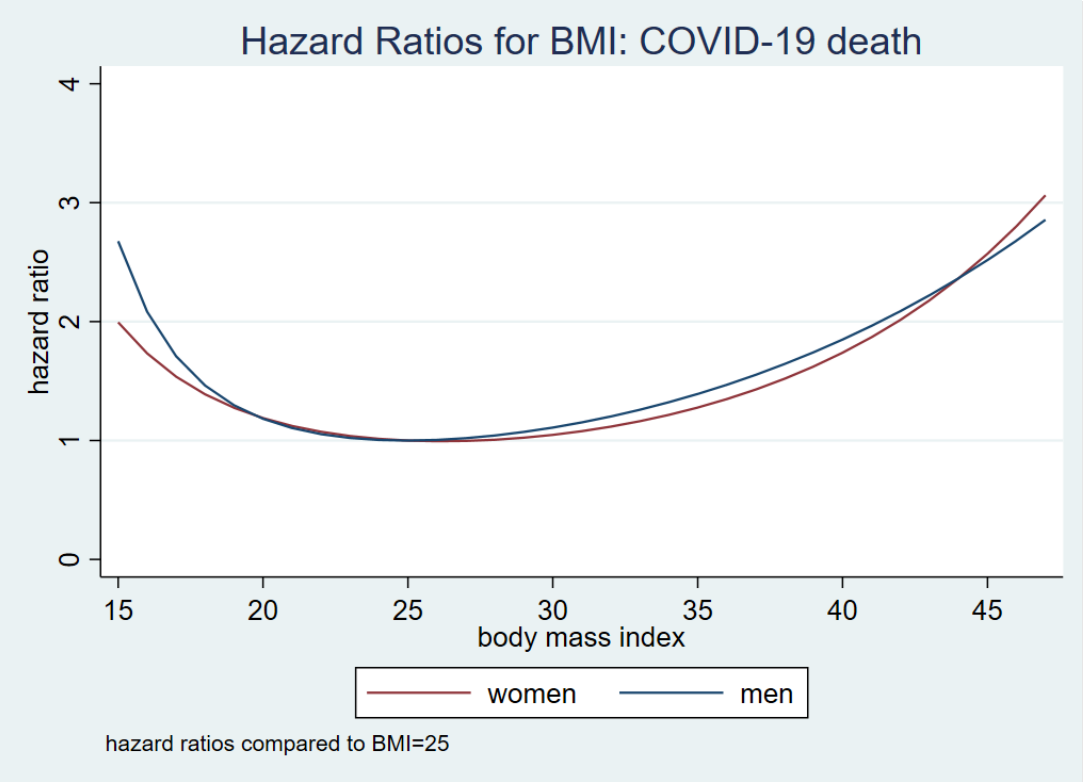

Figure 3. Adjusted hazard ratios for BMI and risk of COVID-19 deaths derived from the living risk prediction algorithm QCOVID[22]

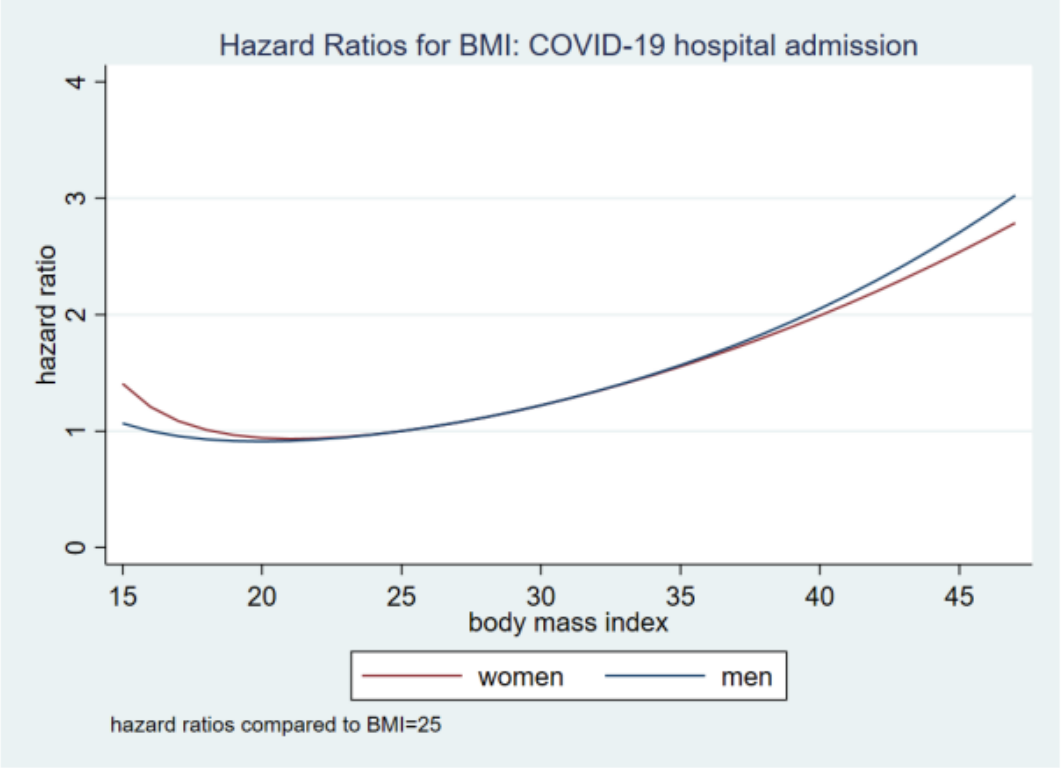

Figure 4. Adjusted hazard ratios for BMI and risk of COVID-19 hospitalisation derived from the living risk prediction algorithm QCOVID[22]

Data from the QCOVID risk prediction tool also demonstrates that being underweight (BMI <18.5) increases risk of hospital admission and mortality in COVID-19 patients (Figure 3 and Figure 4). A recent study used national data, including all laboratory-confirmed COVID-19 test results linked to electronic health record (EHR) data, to analyse trends in the COVID-19 case hospitalisation risk (CHR) and case fatality risk (CFR) in England, during the second wave of the pandemic (i.e., from 1st October 2020 to 30th April 2021). Compared to people of a healthy weight, those underweight had 10% higher odds of admission (95% CI: 1.05–1.14) and 99% higher odds of death (95% CI: 1.87–2.11).[36]

Smoking

Conditions linked to or exacerbated by smoking, such as COPD and lung cancer, are considered risk factors within the appraisal. Additionally, and as noted in the AG response, there is substantial evidence implicating smoking as a risk factor of hospitalisation due to COVID-19.[29,37]

Current smoking was reported as one of the most common prespecified characteristics associated with risk of progression to severe COVID-19 in the EPIC-HR study, where smoking status was recorded in 39% of patients (876 patients) at baseline.[38]

A systematic literature review and meta-analysis investigated mortality risk between ever smoking and never smoking among over 40,000 patients with COVID-19, from 28 observational studies.[32] The reported SRR for death was 1.28 (1.17-1.40), 1.29 (1.03-1.62) and 1.25 (1.11-1.42) for ever, current and former smoking versus never smoking patients, respectively.[32] A further systematic review and meta-analysis reported a similar association, with increased risk of COVID-19-related mortality associated with smoker patients compared to non-smoker patients (pooled OR 1.42, [1.01–1.83]).[21]

Patients receiving treatment for cancer

Several studies including the advisory report from the Department of Health and Social Care and the living risk prediction algorithm QCOVID identify patients receiving chemotherapy or other cancer treatment as one of the most high-risk groups for disease progression and death.[22,39-41] Exact details on which patients with cancer/receiving cancer treatment are considered at high-risk within the PANORAMIC study, and thus within this appraisal, are lacking, and we request clarification on this population.

Patients with splenectomy

In a case-control study of splenectomised patients, splenectomy was associated with increased risk of COVID-19-related hospitalisation or death (adjusted OR for combined endpoint: 1.44 [0.79-2.61]).[42]

Comparison between risk factors included and not included in the eligibility criteria

As used in the AG's report to inform modelling assumptions, data from the QCOVID risk prediction tools[22,39,40] and the ISARIC report[43] are considered to be robust. When comparing data from these studies on the risk of death due to COVID-19 among various at-risk populations, it is clear that risk of death in the above populations is at least comparable to the 'high-risk' populations already considered in this appraisal (Figure 5). It is particularly evident that the risk of death in older patients is elevated substantially, even among patients aged 50-59, which continues to increase among older subgroups. The risk of death in patients aged >50 years is substantially greater that in other populations already considered as 'high-risk' in this appraisal, including patients with diabetes, chronic kidney disease or respiratory disease. In light of this, we believe the evidence base strongly supports the inclusion of age >50 years as an independent 'high-risk' factor in this appraisal. Additionally, it is evident that the risk of COVID-19 death due to obesity is comparable or greater than the inherent risk in the already established risk factors, and that the evidence base strongly supports the inclusion of obesity as an independent risk factor. Not

including these populations within the 'high-risk' group is omitting a large portion of the UK population where treatment should be considered as much of a necessity as the populations already included in this appraisal.

Figure 5 also compares data from the QCOVID3[39] and QCOVID4[40] risk prediction tools. QCOVID3 describes data from patients with between one and two doses of the COVID-19 vaccine between December 2020 and June 2021, whereas QCOVID4 describes data from a more contemporary patient cohort of mixed vaccine status, recruited during the Omicron wave in England. Whilst relative risk of each factor is shown to fluctuate slightly between the two populations, due to the differences in vaccination status and COVID variants, it is apparent that: I) populations that were at an elevated risk due to COVID-19 earlier in the pandemic are still at an elevated risk during the omicron wave, giving assurance that the populations considered in this appraisal are still relevant and representing those who would benefit from treatment. And that II) Older age (>50 years) still poses a substantially greater risk than other factors during the omicron wave. It should be noted that QCOVID4 data is sourced from a pre-print publication, where data may be subject to change.

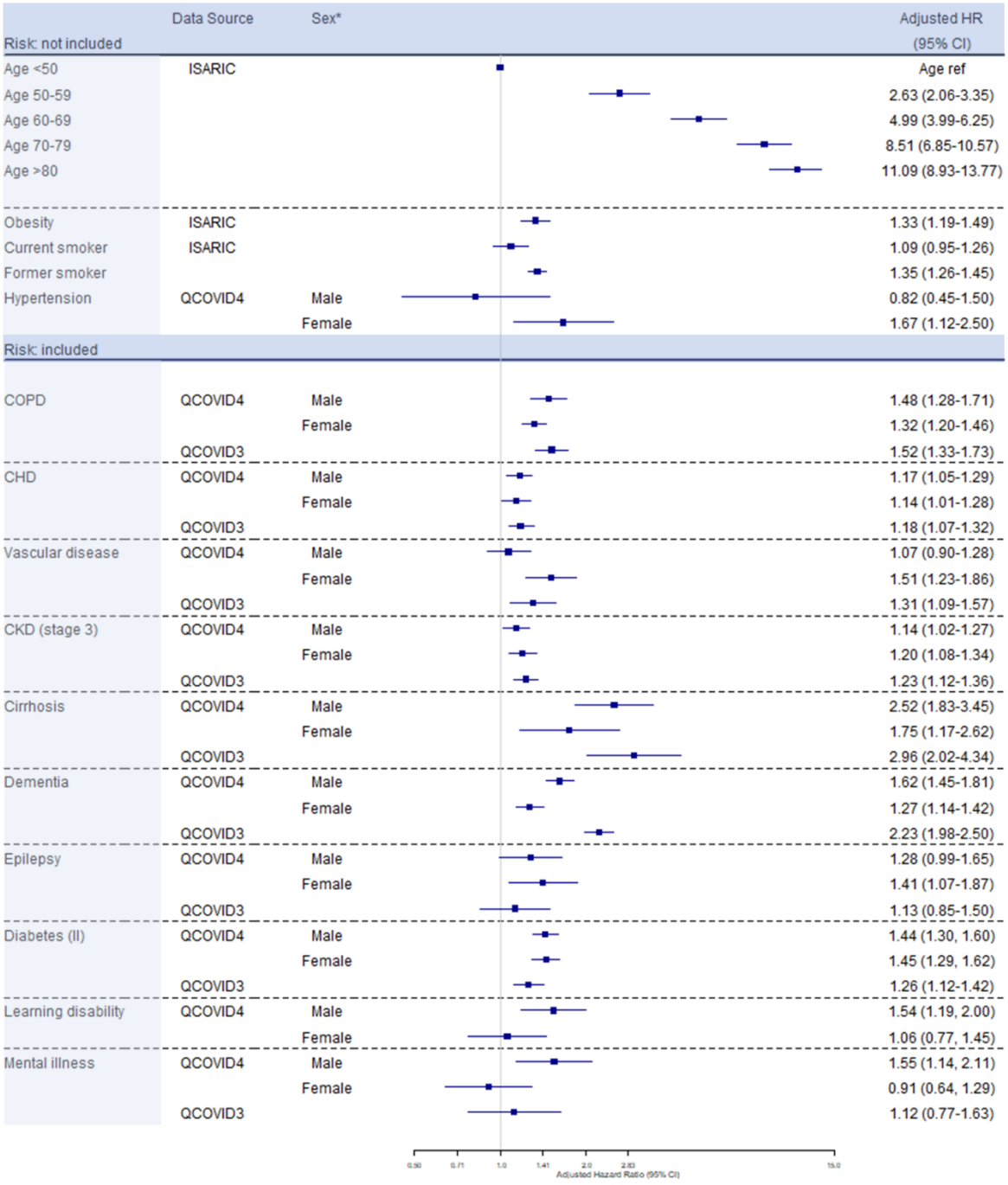

Figure 5 Risk of death due to COVID-19 in at-risk populations (Figure created using data from QCOVID and ISARIC studies).
* Risk data modelled separately for Males and Females in QCOVID4

Additional populations that would benefit from treatment

Evidence is presented to describe the impact and potential benefits of treating COVID-19 in front-line healthcare workers, who are most at risk because of their exposure, and unpaid carers, who play a significant role in supporting the healthcare system.

Healthcare workers

Healthcare workers (HCWs) have been shown to be disproportionately infected with SARS-CoV-2.[44-46] The SIREN study, a multicentre prospective cohort study among NHS staff in the UK indicated that during the second wave of SARS-CoV-2, 12.9% of SIREN participants susceptible to primary infection became infected.[45]

Risk of a HCW getting infected in hospital as a result of contact with an infectious patient/HCW:

An observational cohort study using data from four hospitals in the UK showed that a single day of exposure to an infectious patient with hospital-acquired SARS-CoV-2 or to an infectious HCW were both associated with an additional 0.08% absolute daily risk of transmission to HCWs (95% Credible Interval [CrI] 0.03% to 0.16% and 0.06% to 0.10%, respectively) (Figure 6). Nurses were estimated to be at the highest risk of being infected with SARS-CoV-2 (aOR 1.54, 95% CrI 1.17, 2.04) compared with doctors.[8] The number of infectious HCWs and patients who had hospital-acquired SARS-CoV-2 on the same ward were strongly associated with transmission to HCWs (aOR 1.33, 95% CrI 1.21, 1.45 and aOR 1.45, 95% CrI 1.34, 1.55, respectively).[8]

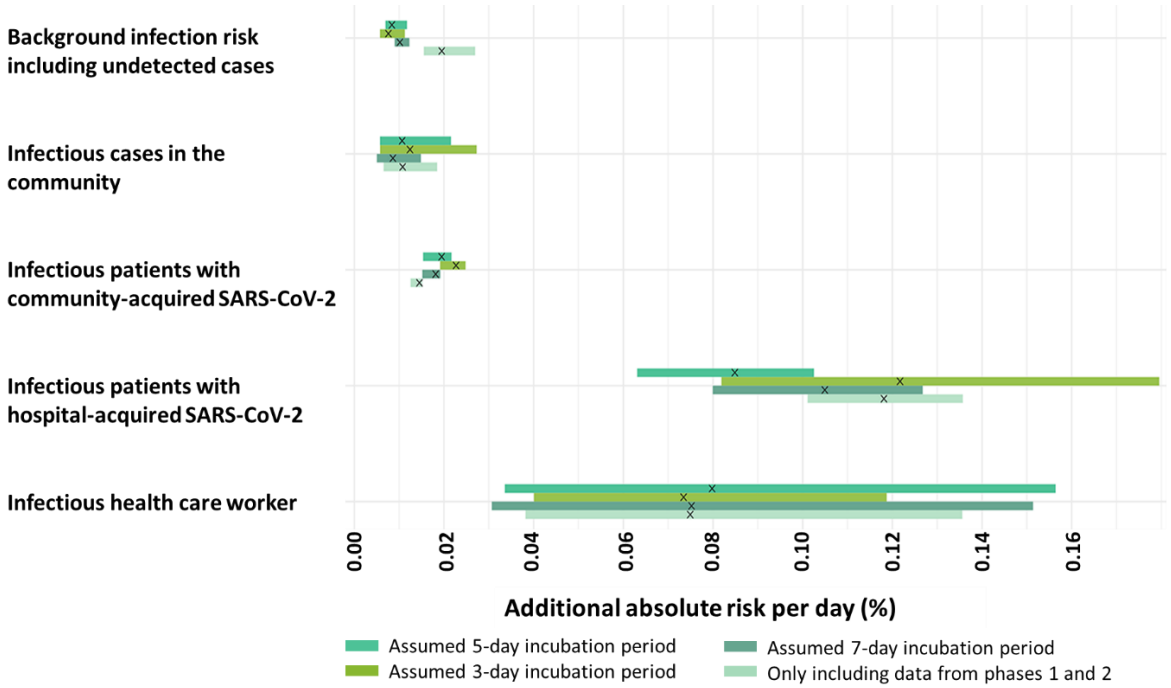

Figure 6. Additional risk of suspected nosocomial acquisition of SARS-CoV-2 experienced by a single susceptible HCW contributed by (i) infectious patients who acquired SARS-CoV-2 in the community (second row); (ii) infectious patients who acquired SARS-CoV-2 in the hospital (third row); and (iii) infectious HCWs (last row).

Each horizontal bar represents the 95% CrI of the estimate. The black crosses in the centre of each bar represent the median of the estimates. CrI, credible interval; HCW, healthcare worker; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

Staff shortages due to COVID-19 have contributed to the already high clinical burden faced by the NHS during the first waves of the pandemic. In December 2020, 362,774 full time equivalent (FTE) days (out of 1,967,352 total FTE) were lost due to COVID-19 related sickness, equating to 18.4% of all absences recorded.[47] Given its impact on the provision of healthcare services, reducing transmission among HCWs will be key in the event of future outbreaks. As noted previously, Paxlovid treatment has been demonstrated to reduce viral load[1] and to accelerate negative RT-PCR respiratory SARS-CoV-2 conversion,[6] which will likely reduce infectiousness and disease transmission. This highlights the potential benefits of ensuring access to Paxlovid treatment for this vulnerable subgroup and ensuring rapid access to treatment is key to reduce COVID-19 related societal burden.

Unpaid Carers

Similar to HCW, unpaid carers are exposed to a higher risk of contracting COVID-19, likely driven by prolonged contact with asymptomatic patients. In a prospective cohort study of 120 075 UK Biobank participants, essential workers (which included medical support staff and sanitary service workers) had a significantly higher risk of developing severe COVID-19, as compared to non-essential workers (RR 1.60, 95% CI 1.05 to 2.45).[48]

Besides being exposed to a higher risk of infection from SARS-CoV-2, unpaid carers may also transmit the infection to people they look after. Informal caregiving is usually delivered by one main caregiver, however, often, additional support is provided by other family members.[49] During the pandemic, these additional family caregivers often reduced their contacts either voluntarily or forcedly to avoid transmission of the virus, negatively impacting the quality and frequency of care delivered to care recipients.[49] Given its impact on the provision of informal care, reducing transmission among unpaid carers, and ensuring rapid access to treatment is key to reduce COVID-19 related societal burden.

Additional evidence to support the efficacy of Paxlovid across different variants and vaccination status

As highlighted in the AG report, there is uncertainty surrounding the relative effectiveness estimates informing the treatment comparison, primarily due to heterogeneity between trials. In particular, it is noted that the standard of care, percentage of people who have had a vaccination, and the dominant SARS-CoV-2 variant could all vary between pivotal studies.

Whilst it is acknowledged that a full assessment of heterogeneity is required to assess the potential for bias, we would like to bring to your attention additional evidence to support the robustness of the effectiveness of Paxlovid for treatment in various settings:

SARS-CoV-2 Variants

Paxlovid retains effectiveness against various SARS-CoV-2 variants including the current omicron variant.[50,51] Current variants of concern can be resistant to treatments that work by binding to the spike protein found on the surface of the SARS-CoV-2 virus. Paxlovid, however, works intracellularly by binding to the highly conserved main protease (Mpro) of the SARS-CoV-2 virus to inhibit viral replication. This mechanism of action has played a key role in Paxlovid's ability to retain activity against the majority of SARS-CoV-2 variants to date a challenge other COVID-19 therapies have faced. [redacted] Takashita et al 2022 went further to demonstrate retained in vitro efficacy of Paxlovid against Omicron BA.1, BA1.1, BA.2, BA.2.12.1, BA.4 and BA.5 variants.[53] Additional laboratory work elsewhere also confirmed that there are no changes in the protease that would affect Paxlovid's ability to be effective against different known variants of SARS-CoV-2 and it has demonstrated potent antiviral in vitro activity against circulating variants of concern, including alpha, beta, gamma, lambda, delta and omicron.[50,51] Further, several real-world studies (RWE) support this in vitro evidence, demonstrating that Paxlovid maintains effectiveness in patients diagnosed with COVID-19 during time periods where the SARS-CoV-2 omicron variant was predominant.[17,54-56]

Vaccination status and the use of Paxlovid during the Omicron variant

In RWE studies Paxlovid has been shown to be effective in both vaccinated and non-vaccinated patients which is consistent with the EPIC-HR clinical trial.[17,54-56] These studies are summarised here.

Pfizer RWE study

We bring to your attention data on file in the form of our manuscript that [redacted]

[redacted] Our manuscript has been submitted for publication and is undergoing peer-review.

Independent RWE studies

An RWE study in the USA looked at the impact of Paxlovid in 1,130 adult individuals who were all vaccinated against SARS-CoV-2.[17] In their primary composite outcome of all-cause emergency or visits, hospitalizations or 30-day mortality, they found an OR of 0.5 (0.39-0.67; p<0.005) consistent with a 45% relative risk reduction between the Paxlovid treated cohort vs non-Paxlovid treated cohort. Furthermore, Paxlovid treatment had a higher event free survival probability HR 0.67 (0.52-0.87; p=0.002).[17] All-cause ER visits and hospitalization were significantly lower in patients who received treatment with ORs of 0.55 (0.41-0.73, p<0.05) and 0.43 (0.2-0.9, p=0.02) respectively. No deaths occurred in the treated cohort compared to 10 deaths in the non-treated cohort.[17]

A RWE study in Israel with 180,351 individuals of which 75.1% where adequately vaccinated against SARS-CoV-2, investigated the impact of Paxlvoid treatment in adults that developed COVID-19.[55] To reduce confounding by indication, inclusion in this study was limited to patients who were potentially candidates for Paxlovid treatment, with at least 1 comorbidity or condition associated with high risk for severe COVID-19, as in the EPIC-HR trial i.e. all over 60 years old and those with specific risk conditions under 60 years of age.[55] The study observed a significant decrease in the rate of severe COVID-19 or mortality with adjusted HRs or 0.54 (0.39-0.75, p<0.01). When analysis was restricted to patients diagnosed with COVID-19 when the omicron variant was the dominant strain, Paxlovid was associated with greater decrease in the composite of severe COVID-19 and mortality HR, 0.43 (0.85-0.64, p<0.001). Subgroup analysis showed that the effectiveness of Paxlovid was unrelated to the COVID-19 vaccination status HR 0.52 (0.32-0.82) for no adequate vaccination vs HR 0.62 (0.39-0.98) for adequately vaccinated individual and an interaction P value of 0.129.[55]

Another Israeli RWE study (n=109,213 eligible participants) aged 40-64 years (n=1,418) and ≥65 years (n=2,484) had previous immunity induced from vaccination, previous infection or both (n=3,520, 90%) or no immunity (n=382, 10%) were treated with Paxlovid (n=3,902, 4%).[54] The rate of hospitalisation due to Covid-19 in Paxlovid treated participants ≥65 years was 14.7 cases per 100,000 person-days as compared with 58.9 cases per 100,000 person-days among untreated patients (adjusted hazard ratio, 0.27; 95% confidence interval [CI], 0.15 to 0.49). The adjusted hazard ratio for death due to Covid-19 was 0.21 (95% CI, 0.05 to 0.82).[54] Among patients 40 to 64 years of age, the rate of hospitalization due to Covid-19 was 15.2 cases per 100,000 person-days among treated patients and 15.8 cases

per 100,000 person-days among untreated patients (adjusted hazard ratio, 0.74; 95% CI, 0.35 to 1.58). The adjusted hazard ratio for death due to Covid-19 was 1.32 (95% CI, 0.16 to 10.75).[54]

In a Hong Kong RWE study [n=407,776 eligible hospitalised participants without supplemental oxygen requirement on admission), matched controlled (n=890) and Paxlovid treated (n=890) participants], a lower risk of all-cause mortality was observed in Paxlovid recipients (10.28 events [7·03–14·51]) versus matched controls (26.47 events [21.34–32.46]; HR 0.34 [0·23–0.50], p<0.0001).[56] Oral Paxlovid recipients also had lower risks of the composite disease progression outcome (HR 0.57 [0.45–0.72], p<0.0001) and need for oxygen therapy (HR 0.73 [0.54–0.97], p=0.032) compared with controls. Time to achieving a low viral burden was significantly shorter among Paxlovid recipients than matched controls (HR 1.38 [1.07–1.79], p=0.013).[56]

Together this data demonstrates the robustness of Paxlovid efficacy data in settings with varying standards of care, proportions of people with COVID-19 vaccinations, and differing SARS-CoV-2 variants. In addition, the risk of COVID-19 future outbreaks and the emergence of new SARS-CoV-2 variants, which may be able to evade vaccine protection or resistant to available treatments, increases the importance of expanding the toolbox of available antivirals to reduce virus transmission and mitigate the impact on the NHS capacity.[59]

3. If you are the manufacturer of one of the interventions, please provide details of your product(s):

- **GB marketing authorisation status/timing**
- **GB marketing authorisation wording**
- **Method of administration and dosage**
- **List price**
- **Any confidential arrangements that would apply in routine commissioning for this product.**

GB marketing authorisation status:

Licensed 31 December 2021[60]

GB marketing authorisation wording:

Paxlovid 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[60]

Method of administration and dosage:

The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days. Paxlovid should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms.[60]

Paxlovid can be taken with or without food. The tablets should be swallowed whole and not chewed, broken or crushed.[60]

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.[60]

If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with Paxlovid, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.[60]

List price

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets. Each pink nirmatrelvir film-coated tablet contains 150 mg of nirmatrelvir. Each white ritonavir film-coated tablet contains 100 mg of ritonavir.[60]

Each pack contains 20 nirmatrelvir tablets (150 mg) and 10 ritonavir tablets (100mg), sufficient for a full five-day treatment course.[61]

Each Paxlovid pack costs £829.[61]

4. Are there any potential equality issues that should be taken into account when considering these treatments?

As noted in our prior response to consultation on the Assessment Report and in section 2 of the present document, the definition of patients at high risk considered in the decision may restrict access to treatment for specific patient populations, raising potential equality issues. These potential equality issues include:

- Elderly populations
- Lower socioeconomic status
- Ethnicity

Evidence is presented to describe why these populations may be impacted by decisions that restrict access to treatments.

Elderly population

The definition of high-risk patients used in the EAG assessment which focuses only on comorbidities, excludes significant groups of patients who are among the most vulnerable population at higher risk of developing severe COVID-19 due to their age.

As outlined in section 2, older age is associated with increased risk of COVID-19-related hospitalisation and death, as reported by a large number of systematic literature reviews and meta-analysis,[20,21,34,62] as well as observational studies[63,64] and the EPIC-HR clinical trial.[1] People with an older age (over 50 years) represent a significant portion of the overall population of UK (38%; based on a 2022 ONS estimate).[65] Therefore, a broader definition should be adopted to ensure these patients have rapid access to treatment, in order to reduce risk of COVID-19-related hospitalisation and mortality and protect the NHS from increasing hospitalisations in this vulnerable group.

Excluding this patient group represents a probable equality issue requiring consideration.

Socioeconomic status

Patients with lower socioeconomic status (SES) have been shown to be at higher risk of contracting COVID-19[66-68], partially due to their working and living conditions, as well as to the higher prevalence in this group of other risk-factors (e.g., obesity).[69] Lower SES patients may also be unable to afford a COVID-19 test kit and thus, have higher likelihood of going undiagnosed or of receiving a late diagnosis, with subsequent late treatment initiation and worse health outcomes.

In a population-based cohort study of the NHIS-COVID-19 database, patients with lower SES were reported to be at greater risk of contracting COVID-19.[66] This may be due to a number of factors. People of low SES are more likely to live in overcrowded accommodation, a factor that has been associated with increased risk of lower respiratory tract infections,[70,71] which will reduce compliance with social distancing and increase community transmission. Additionally, lower income workers are often employed in occupations that do not permit working from home, for example retail and warehouse workers, increasing exposure to the virus.[70,72] In a study investigating social deprivation as a risk factor for COVID-19 mortality among women and men in the UK Biobank, patients in the last fifth of Townsend score* (most deprived) had a significantly higher risk of mortality compared to least

* The Townsend Deprivation Score is an area-based score of social deprivation (accounting for unemployment, overcrowding, non-car ownership and non-home ownership) that was determined immediately prior to the participant joining the Biobank, based on data from the preceding national census

deprived patients (HR†: 2.20 [1.63 to 2.96] for female; 2.62 [2.12 to 3.24] for male). Data from the living risk prediction algorithm QCOVID[22] showed that deprivation (5 unit increase assessed using the Townsend score) was associated with higher mortality and admission risk in both men in both men (mortality HR: 1.46 [1.40 to 1.53];admission HR:1.17 [1.13-1.21]) and women (mortality HR: 1.48 [1.37 to 1.61]; admission HR: 1.52 [1.45 to 1.60]).The QCOVID 4 risk tool[40], a recent update of the QCOVID algorithm which included a cohort of COVID-19 patients with mixed vaccination status during the omicron wave, confirmed this association in both sexes (men: mortality HR: 1.18 [1.09-1.27], admission HR: 1.37[1.31-1.42]; women: mortality HR: 1.18 [1.08-1.28], admission HR:1.17 [1.13-1.21]).

People of low income may be unable to afford a COVID-19 test kit and therefore have a higher likelihood of going undiagnosed or present to healthcare services at a later stage of illness,[72] resulting in poorer health outcomes from COVID-19.[70] A further population-based cohort study reported that patients with low education or low income were less likely to self-report a COVID-19 infection (OR [95% CI]: low education 0.78 [0.71-0.86]; low income 0.86 [0.79-0.93]), or be tested for COVID-19 (OR [95% CI]: low education 0.58 [0.52-0.66]; low income 0.86 [0.78-0.95]) compared with high education or high income groups, respectively.[73]

Furthermore, poverty itself may be a risk-factor of cardiovascular disease, diabetes, obesity and hypertension;[69] conditions that themselves are shown to increase risk of COVID-19-related hospitalisation and death. This suggests that people of low SES may have an increased susceptibility to hospitalisation and death from COVID-19.[70] It is a particularly pertinent consideration, as these factors are partially excluded from the currently applied definition of patients with mild COVID-19 at high risk of progressing to severe COVID-19.

Patients of low SES may therefore represent a vulnerable subgroup that would benefit from Paxlovid treatment in the community. We suggest the definition of high-risk patients used in the EAG assessment be broadened to ensure this patient population is not missed and have rapid access to treatment.

Ethnicity

Ethnicity is strongly linked to COVID-19 outcomes.[74] People of Asian ethnicity have been shown to be at a higher risk of contracting COVID-19 and of developing serious COVID-related complications (e.g., stroke).[75,76] These underlying risks should be considered alongside the established risk factors already included in this appraisal.

Data from the Office for National Statistics collected between 2nd March and 10th April 2020 have shown that patients from Black, Chinese, Indian, and

† HR was adjusted for age, ethnicity, systolic blood pressure, diabetes, smoking, body mass index, total cholesterol, and history of CVD.

Bangladeshi/Pakistani ethnicity have higher risk of death compared with White patients (OR‡ for female and male, respectively: 4.28 [3.81-4.81] and 4.20 [3.81-4.63] for Black; 1.15 [0.72-1.84] and 1.93 [1.41-2.64] for Chinese, 2.67 [2.3-3.1] and 2.39 [2.13-2.69] for Indian; 3.35 [2.80-4.00] and 3.55 [3.13-4.03] for Bangladeshi/Pakistani).[77]

This is supported by a very large systematic review and meta-analysis that explored the relationship between ethnicity and COVID-19-related outcomes using data from over 18 million patients across 50 studies.[75] The study indicated that individuals from Black and Asian ethnicities had a higher risk of COVID-19 infection compared to White individuals (pooled adjusted RR for Black: 2.02 [1.67-2.44]; pooled adjusted RR for Asian: 1.50 [1.24-1.83]). This association was consistent in both the main and sensitivity analyses examining peer-reviewed studies only. Individuals of Asian ethnicity were also reported to be at higher risk of ITU admission (pooled adjusted RR 1.97 [1.34-2.89]) and death (pooled adjusted RR/HR 1.22 [0.99-1.50]).[75] Similarly, a cohort study conducted in the UK in patients admitted to hospital with COVID-19 through the Clinical Characterisation Protocol UK (CCP-UK) between 6th February and 12th October 2020 showed that patients from Black and Asian ethnicities had higher risk of critical care admission (adjusted OR§: 1.58 [1.43-1.75] for Black; 1.37 [1.26-1.50] for Asian) mechanical ventilation (adjusted OR§: 2.03 [1.80-2.28] for Black; 1.49 [1.33-1.68] for Asian:), and in-hospital mortality (adjusted OR§: 1.19 [1.08-1.32] for Black; 1.27 [1.17-1.38] for Asian) compared with White patients.[78] Data from QCOVID[22] showed an increased risk of death from COVID-19 in men from Indian (HR: 1.59 [1.25 to 2.01]), Pakistani (HR: 1.84 [1.39 to 2.44]), Bangladeshi (HR: 2.27 [1.65 to 3.12]) and Other Asian (HR: 12.02 [1.49 to 2.74]) ethnicities. Data from QCOVID4[40] have also recently shown an increased risk of COVID-19 admission among Bangladeshi (HR: 1.26 [1.02-1.55] for men, 1.64 [1.40-1.92] for women) Pakistani (HR: 1.47 [1.24-1.74] for men, 1.69 [1.45-1.96] for women) and Other Asian (HR: 1.19 [1.01-1.42]) and an increased risk of admission for Black African women (HR: 1.27 [1.13-1.42]). Additionally, in a case-control study, patients of Asian ethnicity were more likely to suffer COVID-19-related ischaemic stroke compared to controls (18.8% vs 6.7%, p<0.0002).[76]

In addition, a study (not yet peer reviewed) that used national databases to investigate uptake in community patients across England of Sotrovimab, a neutralising monoclonal antibody (nMAB), currently administrated to treat extremely clinically vulnerable COVID-19 patients, showed that uptake of the treatment was higher amongst Indian (15.0%; 95%CI: 13.8-16.3), Other Asian (13.7%; 95%CI: 11.9-15.8), White (13.4%; 95%CI: 13.3, 13.6), and Bangladeshi (11.4%; 95%CI: 8.8, 14.6).[79] In our RWE study[57],

‡ Data are given as OR [95% CI]. OR is adjusted for age.

§ Data are given as OR [95% CI]. OR is adjusted for age, sex, obesity, diabetes, chronic heart disease, chronic kidney disease, chronic pulmonary disease, and cancer.

[redacted] Together, these data further support the vulnerability of these ethnic groups.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted] - Blood Cancer UK [redacted] - Anthony Nolan [redacted] - Myeloma UK

	[redacted] - Leukaemia Care [redacted] - Lymphoma Action [redacted] - CLL Support
2. Name of organisation	Blood Cancer UK Anthony Nolan Myeloma UK Leukaemia Care Lymphoma Action Chronic Lymphocytic Leukaemia Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Blood Cancer UK** is the UK's leading blood cancer research charity. We fund world-class research and provide information, support, and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma, and myeloma to the rarest blood cancers that affect just a small group of patients. We also provide education and training to healthcare professionals including nurses, caring for people with blood cancer. Blood Cancer UK has around 100 employees and is funded primarily through donations and legacies. **Anthony Nolan** saves the lives of people with blood cancer and other blood disorders. Founded

	in 1974 as the world's first stem cell register, we're motivated by a mother's determination to save her son, Anthony. Now saving three lives every day, our charity is a lifesaving legacy. By growing our register of potential stem cell donors, conducting ground-breaking research into improving transplant outcomes, and providing outstanding support and clinical care for patients and their families, Anthony Nolan cures people's blood cancer and blood disorders. **Myeloma UK** is the only organisation in the UK dealing exclusively with myeloma. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We receive no government funding and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies. We are not a membership organisation. **Leukaemia Care** is the UK's leading leukaemia charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.pdf **Lymphoma Action** is a national charity that provides high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. We have a policy for working with healthcare and pharmaceutical companies –

	those that provide products, drugs or services to patients on a commercial or profit-making basis. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma. **CLL Support** is the only UK CLL specific support charity which was formed in 2005 and is run entirely by volunteers. The charity's remit is to provide support to people affected by CLL and its subtypes by keeping them informed of recent and relevant developments in CLL treatment and research and to provide opportunities for awareness raising and mutual support. This requires the association to support and aid empowerment through education while advocating for improving outcomes and access to better treatments. CLL Support provides support to the UK CLL community and CLLSA membership of 2,000+ association members who live with CLL or are carers and the 15,000+ CLLSA on-line community members on the Health Unlocked CLL Support platform (not all UK based). CLL Support provides up to 6 patient conferences a year including a regular Scottish patient's conference. Since 2020 the meetings have been via Webinars because of COVID19 and have been topical and more frequent. CLL Support supports patients through telephone and email, one to one at meetings, literature in the form of patient information packs, newsletters and the websites: http://www.cllsupport.org.uk and their online presence on Health Unlocked https://healthunlocked.com/cllsupport . The association is supported and generously funded by member's donations, legacies, members' fund raisers and unrestricted educational grants from various pharmaceutical companies.

4b. Has the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	**Blood Cancer UK:** (1) AstraZeneca – £15,000 to fund our COVID-19 policy work and £308 as payment for attending an advisory panel (2) Gilead Sciences – £300,000 to fund research into the effectiveness of COVID-19 vaccines for people with blood cancer (3) GSK – £10,000 to fund a project on the experience of blood cancer in marginalised communities (4) Pfizer – £130,176 to partially fund our support services which were expanded to deal with the increased demand from COVID-19 (5) Roche – £100,000 to fund research into the effectiveness of COVID-19-19 vaccines for people with blood cancer and £25,000 to fund production of our health information **Myeloma UK:** In 2022, we received £7,425 from Gilead Sciences - £5,000 to support our Infoline and Ask The Nurse support services, £2,425 in gift, honoraria and sponsorship. **Leukaemia Care:** (1) AstraZeneca - £650 honorarium (2) Gilead- £10,000 emergency funding (3) Pfizer - £10,000 support services **Anthony Nolan:** (1) Gilead Sciences - £18,200 to fund research into the experiences of patients who have received CAR-T cellular therapy.

	(2) Attendance of Anthony Nolan staff member to Kite CAR-T public affairs advisory board (£420) (3) Attendance of Anthony Nolan staff member to a speaker panel on cancer virtual series webinar 'Living with and Beyond Cancer (£230) **Lymphoma Action:** (1) In 2022 we received £25,000 from Roche – £20,000 to fund our digital events and £5,000 to fund our trials link service. (2) In 2022, we also received £10,000 from Gilead to support our publications and patient support services. **CLL Support** (1) AstraZeneca – £15,000 Core funding of member services (2) Abbvie - £12,000 Core funding of member services (3) Roche – £16,000 Core funding of member services (4) Janssen - £7,500 Core funding of member services
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	Blood Cancer UK: No Anthony Nolan: No Myeloma UK: No Leukaemia Care: No Lymphoma Action: No CLL Support: No

5. How did you gather information about the experiences of patients and carers to include in your submission?	Blood Cancer UK, Anthony Nolan, and Leukaemia Care gathered the information contained in this report through (1) pre-existing case studies and direct quotes from patients in contact with our support and advocacy service advisors, (2) contact with our network of healthcare professionals, and (3) a survey created by Leukaemia Care and disseminated to our patient communities. The survey had 568 responses from different blood cancer patients who had previously contracted COVID-19. It was distributed via each organisations' social networks, and included questions on the experience of contracting COVID-19 and subsequent questions on treatment pathway. Respondents were self-selecting and therefore likely to be biased towards our existing networks. Their views, therefore, are less likely to reflect the views of groups who are underrepresented in our networks, some of whom may be marginalised due to e.g., ethnicity. For these groups, the impacts that we discuss below may be heightened. Myeloma UK gathered the information included in this submission from the myeloma patients and carers we engage with through our research and services programmes. This includes via the aforementioned survey, and via a multi-criteria decision analysis study of 560 myeloma patients. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen, explored patient preferences for different benefit and risk outcomes in myeloma treatment. It has also been informed by analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays and posts to our online Discussion Forum.
Living with COVID-19	
6. Please tell us what is it like for patients you support who have tested positive for COVID-19?	For this submission, we spoke to anyone with a blood cancer diagnosis. This includes leukaemia, lymphoma, myeloma and other rarer blood cancers. Every point we make applies to all types unless otherwise stated. While there is heterogeneity within the blood cancer cohort, we treat it as a single group here in accordance with the definition of 'high risk' employed by the NHS and NICE (in question 17 below).

	Our survey conducted for the purpose of this submission revealed that 72.1% of all blood cancer patients surveyed (534 respondents) felt anxious after testing positive for COVID-19. 41% also felt scared, and 9.2% felt depressed. Patients with blood cancer who have tested positive for COVID-19 describe the experience as "worrying", "scary", and "a battle". Many of them explain that the attitudes, behaviours, and practices of the general public towards COVID-19 are "very difficult to deal with" and "frustrating". Many feel isolated, and that due to their immunosuppressive condition and high risk from COVID-19 they can rely only on "me, myself, and I; walk in my shoes and tell me [COVID-19] is over". One survey respondent said: "[I] was so ill I lost my job. The headache lasted over two weeks and was horrific. I don't think I'll ever be the same." Another explained, "I had the worry that if I deteriorated I would be on my own to live or die. Horrible." Such feelings of extreme fear are echoed by others, one of whom stated, "I believed that I would die." This fear of high risk of death is well-founded, as evidenced by ICNARC's analysis of data on intensive care admissions, which shows that people with haematological malignancies (blood cancer) accounted for 4.6% of intensive care admissions for Covid in the first half of 2022. This is despite them making up around 0.4% of the population in England. People with blood cancer who test positive for COVID-19 report being given conflicting information by their secondary care teams, primary care teams, and other healthcare professionals, with some telling the same patient that they are no longer at high risk, and others in their team warning them of severe danger to their health when they test positive. For reasons outlined in further detail below, while the risk of adverse COVID-19 outcomes is significantly reduced for many people with blood cancer as a result of post-exposure COVID-19 treatments, many others are unable to access these treatments despite their eligibility.
7. What do carers experience when caring for someone with COVID-19?	There is a distinction between people with blood cancer caring for someone with COVID-19, and for people caring for someone with blood cancer who has COVID-19. For people with blood cancer caring for a loved one with COVID-19, the experience is harrowing and highly disruptive. One blood cancer patient's daughter contracted COVID-19, so they were forced to stay with a

	relative for two weeks until their daughter tested negative. These blood cancer patients often describe such experiences as “terrifying” and that they feel “completely at the mercy of others” who do not understand “the devastation COVID-19 can cause to someone with blood cancer and their family”. For those caring for someone with blood cancer who has COVID-19, their experience is often deeply traumatic. Dozens of people who lost loved ones to COVID-19 have contacted charity support lines for bereavement support. One person said the following: “My Dad died of COVID-19 and had blood cancer. Got through 2 and a half years of lockdowns, isolation, all of that. A diagnosis of blood cancer, 6 sessions of chemotherapy, to then be in hospital and catch COVID-19 from someone, and die in 12 hours.” Another told us, “I’ve been struggling a lot since we lost my Dad. In particular, I’m angry a lot of the time, mostly with anything surrounding COVID-19, and the lack of precautions the majority of people now take.” Some of these bereaved family members told us that their loved ones who eventually passed away from COVID-19 were told by healthcare professionals at the COVID-19 Medicines Delivery Units that they were ineligible for treatment, usually “due to them managing their symptoms okay”. Upon questioning from our team of Nurse Advisors, it became clear that these patients were indeed eligible according to the criteria. People with blood cancer often begin a COVID-19 infection with seemingly mild symptoms, but they progress quickly into severe illness and can swiftly lead to death.
Interaction with underlying conditions	“Living with COVID-19” can cause significant disruption to the normal treatment pathway for people with blood cancer.In our survey, we focused on the impact on treatment for blood cancer, but the impact can extend beyond treatment into appointments, routines and holistic care support. **Impact on treatment:** For 42% of patients hospitalised for their blood cancer, their treatment for blood cancer was affected by testing positive for COVID-19 and receiving treatment in hospital. 29% of patients

8. For people with underlying conditions (for example cancers, autoimmune disorders): ● If applicable, how has living with COVID-19 affected their condition? ● If applicable, how has the normal treatment pathway for their condition been affected? (For example, cancer treatment options, regularity of assessments, accessibility issues related to treatments)	told us that their treatment for blood cancer was delayed for a period of time due to COVID-19. One patient told us that they had a different cancer treatment than planned and two patients said they received their cancer treatment in a different location. Two patients also told us that they stopped receiving cancer treatment altogether as a result of COVID-19. 52.7% of patients receiving treatment for COVID-19 in the community, and on treatment for their blood cancer, said there was no change to their blood cancer treatment as a result of testing positive. This is significantly fewer people than those who are hospitalised. Although 35.4% said their treatment was delayed for a period of time, only 3.6% said they had to stop receiving treatment altogether. Clinical decisions would have determined the best interests for the patient in these instances where treatment was affected, and it's possible that the risk to the patient's health of not receiving COVID-19 antivirals could have been higher than the risk of stopping cancer treatment for a limited period of time. The treatment pathway for stem cell transplantation and CAR-T cellular therapy has also been significantly impacted by the COVID-19. In early stages of the pandemic initial advice was to delay the transplant due to the risk of catching COVID-19 for highly immunocompromised populations, except in the most urgent cases. Catching COVID-19 was also a significant concern for stem cell donors, with transplants regularly delayed by 4-6 weeks due to COVID-19 infection. This often posed a significant and potentially life-threatening risk to the patient. 2020 saw some transplant centres deliver up to 30% fewer transplants as a result of service change caused by the pandemic. For highly immunocompromised CAR-T cell therapy and stem cell transplant recipients, post-treatment isolation and regular monitoring, normally as essential part of treatment and care, have been significantly disrupted. Those who need to regularly make hospital visits have been under enormous stress and anxiety, particularly now that COVID-19 -green and -red sites have been removed and mask wearing is no longer mandatory in hospital settings. **<u>Other impacts on cancer care:</u>**

	Anecdotal evidence suggests a particular impact on the regularity and quality of assessment for their cancer. A considerable number of patients have not seen their specialist team/haematologist in person since the start of the pandemic. Many cite fears that they "have been abandoned" and that they are not adequately assessed at virtual, remote clinics. Some find it "challenging" to discuss issues arising from their condition over the phone. One patient reported that, after a bone marrow test, it took 5 weeks for his consultant to tell him, over the phone, that he had relapsed and his leukaemia had returned. It then took another month before he was invited to a face-to-face appointment. Another patient's consultant has not been working for 5 months, due to contracting Long COVID-19. Others describe considerable delays in securing crucial appointments due to staff such as GPs and GP receptionists being ill from COVID-19. Further, COVID-19 care (vaccines and antivirals provision) has been separated from the secondary care setting. This has led to patients feeling that consultants "distance themselves" from giving COVID-19 advice or information, despite its impact on and interaction with blood cancer and cancer treatments.
Short term versus long term 9. For the people you represent who have tested positive for COVID-19, on average, how long did their symptoms last for?	Blood cancer patients and stem cell transplant recipients consulted through our survey reported a variation in the duration of symptoms and the length of time they tested positive for the virus. Some reported mild infection and tested positive for 1-2 weeks, while others reported extremely worrying symptoms including difficulty breathing and extreme fatigue. Some patient groups test positive for longer; stem cell transplant recipients (who are highly immunocompromised), reported testing positive for over 14 weeks and it is reported that chronic lymphocytic leukaemia (CLL) patients also stay positive for an extended period of time. Of survey respondents who did not receive treatment for COVID-19, 48% reported experiencing long term effects from COVID-19. These patients indicated that a range of symptoms persisted. Particularly, 35% of respondents reported experiencing extreme tiredness and fatigue. Other commonly reported long-term symptoms included dizziness, a sore throat, a cough, headaches, joint pain and nausea. Brain fog/memory loss was experienced by around 18% of respondents,

a) Did anyone have any long-term effects from COVID-19? Approximately what proportion does this represent? b) If yes, ● What were they? (for example physical and mental impacts, impact on ability to work) ● On average, how long did the effects last for? ● What treatments did they need for the long-term effects of COVID-19?	with roughly 9% reporting long-term tightness in the chest or shortness of breath. Some patients also reported long-term mental health impacts, including feeling depressed and anxious. Of these respondents (who did not receive treatment for COVID-19), 50% had symptoms that lasted over 1 month, with 36% experiencing symptoms for between 1 and 3 months and 15% for 3-6 months. For those who didn't receive treatment, 45% required physical support from close family and friends when they had COVID-19.
Current treatment for COVID-19 in the NHS	
10. What do patients or carers think of current treatments and care available in the NHS?	Blood cancer patients who tested positive for COVID-19 and were able to access the post-exposure treatments almost universally agree that the treatments are beneficial. Patients claim that they "felt better almost immediately", they "helped immensely", and "probably saved [them] from more difficulties". Initial findings from an unpublished study conducted by Dr Helen Parry show that no blood cancer patients who received COVID-19 treatment in the community

- for preventing severe COVID-19 in people with high risk of hospitalisation - for treating people in hospital with severe COVID-19	setting were later hospitalised. Most patients also say that having the treatments "eased a lot of anxiety" for them, and that despite the lack of a prophylactic treatment option, the post-exposure treatments are "reassuring" as mechanisms of protection from severe illness and death from COVID-19. In the survey conducted for the purpose of this submission, the majority (51.3%) of blood cancer patients surveyed said that the December 2021 announcement that antiviral treatments were available to the immunocompromised made them feel less concerned about catching it.
11. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?	Paxlovid is contraindicated by the following treatments: - Commonly used to treat blood cancer (for those with Multiple Myeloma, acute lymphoblastic leukaemia, and chronic lymphocytic leukaemia): afatinib, abemaciclib, apalutamide, ceritinib, dasatinib, nilotinib, vincristine, vinblastine, encorafenib, fostamatinib, ibrutinib, and ivosidenib - Anticoagulants (relevant for MPN patients): warfarin, apixaban, dabigatran, rivaroxaban, and vorapaxar. - Antifungals (often used for haematology patients post-chemotherapy or those with chronic leukaemia): ketoconazole, itraconazole, and voriconazole. - Immunosuppressive treatments (used commonly post-stem cell transplant to manage GVHD): cyclosporine, tacrolimus, and everolimus - Steroids including corticosteroids used to treat inflammation (for those with acute lymphoblastic leukaemia on chemotherapy treatments): budesonide, dexamethasone, fluticasone propionate, prednisolone and triamcinolone. We have received reports that some CMDU (COVID-19 Medicines Delivery Unit) staff have advised patients to stop taking Ruxolitinib (a cancer growth blocker) in order to take Paxlovid. As

	one haematology consultant put it, this is “frankly dangerous, especially with active infection”. There are also potential interactions between Paxlovid, remdesivir, and molnupiravir and small-molecule inhibitors (e.g., BTK inhibitors). While small-molecule inhibitors would normally be interrupted in patients requiring hospitalisation for infection, this limits the number of COVID-19 treatment options in community settings for this patient group before they progress to severe disease. Finally, nirmatrelvir and ritonavir have been highlighted as having significant drug interactions with a range of medication regularly taken during stem cell transplantation treatment and care. However, none of these interactions should be considered barriers to access. It would be difficult to subgroup people based on the treatment they are on, as many can be on multiple and this to change over time; it should be a balance between interactions and risk of severe COVID-19 infection. Clinicians should be able to judge the treatment best suited to those in front of them.
12. What impact does having these drugs available in the NHS have on your community?	Post-exposure COVID-19 treatments are a vital cornerstone of the protection programme for those who remain at very high risk from COVID-19. For those who are less likely to mount an adequate immune response from COVID-19 vaccines – such as those with blood cancer – post-exposure treatments are one of the only effective protection mechanisms in place. It is essential that these drugs continue to be part of the clinician’s toolkit to provide patients with the highest possible level of protection from COVID-19 infection.
13. Is there an unmet need for patients with this condition in relation to therapies for treating COVID-19? Are there any key subgroups of patients we should consider?	The most pressing unmet need for blood cancer patients around post-exposure COVID-19 treatments concerns barriers to access. This will be elaborated upon below in response to question 15. As was mentioned above, COVID-19 infections in blood cancer patients often progress quickly into severe illness. One haematology consultant told us that patients are sometimes encouraged to decline COVID-19 treatment if their symptoms are minimal early on, or if they seem to be recovering from COVID-19. She advises that this is dangerous as “patients can often deteriorate markedly”. Being refused COVID-19 treatment has contributed to death in some cases, as is outlined in response to question 7 above.

	Further, the eligibility list for treatment excludes patients with T-cell cancers who are not currently undergoing treatment. While they may mount an antibody response to vaccines, their lack of T-cell response places them at very high risk of developing severe disease and of death. Post-stem cell transplantation patients are also at particularly high risk of contracting the virus, as stated in Q16. For those surveyed who did not receive treatment for COVID-19, 49% respondents indicated that the availability of antiviral treatments helped their anxiety around catching COVID-19. However, 33% of people felt that the availability of antiviral treatment options did not make them feel any differently about COVID-19. While numerous factors likely contribute to this, many of those surveyed faced challenges when trying to access treatments for COVID-19. 16% (33/204) of respondents could not get access to treatments or did not know how. One patient described feeling that the medical staff did not listen to them or take their concerns seriously, despite feeling extremely unwell, meaning they were unable to address appropriate antiviral treatments. A further 37% (76/204) either were never contacted after testing positive for COVID-19 or delays meant that they were unable to receive treatment.
Hospital and community treatment settings 14. For those people that you represent who were <u>hospitalised</u> due to COVID-19 ● At what point after being diagnosed with COVID-19 did	<u>Hospital treatment setting</u> From our survey, 8% (39/497) of blood cancer patients who tested positive for COVID-19 were hospitalised and received treatment. There was variation in the time that patients went into hospital after testing positive for COVID-19. 28% (11/39) of patients went to hospital straight away and 41%(16/39) went within 48 hours. In hospital, over half (56%) of patients received an antiviral treatment like nirmatrelvir/ritonavir (Paxlovid) or remdesivir. Nearly a quarter (24%) received monoclonal antibodies like sotrovimab. 15% of those treated in hospital were given antibiotics, 18% were given a steroid like dexamethasone and 12% were given oxygen. Despite receiving treatment, having COVID-19 is still a scary time for patients. One patient who completed our survey said his experience of being

they receive any form of treatment? ● What did their treatment pathway look like? ● How long did they spend in hospital? If they had an underlying condition how did this impact the condition? 15. For the people you represent that had treatments for COVID-19 in <u>community settings</u>: ● At what point after being diagnosed with COVID-19 did they receive any form of treatment from the NHS?	treated for COVID-19 in hospital was *"terrifying. I had antivirals for 10 days & oxygen. The hospital forgot to give me one dose. I thought I would die."* Over half of blood cancer patients (52%, 20/38) that were treated for COVID-19 in hospital spent 1-2 days in hospital. Nearly a quarter (24%, 9/38) spent 1-2 weeks in hospital but there were a few who spent up to 6 months+ in hospital. Therefore, preventing patients from developing disease severe enough to go into hospital would be beneficial, due to the significant resources used. <u>Community Settings:</u> From the most recent survey conducted for the purpose of this submission, we asked patients who received COVID-19 treatments in community settings how long it took them to get treatment after they tested positive. The largest groups were those who said it took 1-2 days (52.2%), and those who said it took 3-4 days (34.3%), indicating that the majority of patients got their community treatment within the appropriate time frames (i.e. within 5 to 7 days of testing positive). When asked how ill COVID-19 made them feel on a 5 point scale (1 being asymptomatic and 5 being very ill) the largest number of respondents selected option 4 out of 5. However, 82.6% of blood cancer patients said that the treatment they received in a community setting made them feel better quickly (in a matter of days). 50.5% of patients who received treatment in a community setting said that after testing positive for COVID-19 they needed support from friends and family. This included physical help as well as support with daily activities like cooking. It can be inferred that needing physical help would likely extend to requiring support from friends and family when travelling to clinics for COVID-19 treatments. When we asked patients what kind of challenges, if any, they faced in accessing community antiviral treatments the most common challenges reported were not receiving a call from the NHS within 24 hours of registering a positive test and not knowing what to do, e.g. who to call to

● What did their treatment pathway look like? ● Was there a preference for receiving tablets versus treatment with other administration methods (for example intravenously) ● Can you tell us a bit about their experience of accessing these treatments? (for example travelling to clinics/outpatient settings while testing positive for COVID-19) ● Were there any issues with accessing these treatments?	get antiviral treatment. One leukaemia patient recalls *"the NHS sadly did not call within 24 hrs. I did feel a little abandoned".* This patient tried to contact 119, their GP and haematology team but had *"no joy"* in accessing antivirals or knowing where to go, so instead they phoned Leukaemia Care. These issues of not receiving calls from the NHS and not knowing what to do next were experienced by 20.1% of the total respondents who went on to receive community treatment. In this instance the charity intervened and the patient consequently received a call from the CMDU, after which she says *"I felt relieved that someone has made an assessment and I have the right medication at hand if the symptoms continue to get worse."* Qualitative data from Blood Cancer UK also reveals that many eligible patients who register their positive COVID-19 test are either never contacted for assessment or are contacted several days after the onset of symptoms and the registration of a positive test. This issue is greatly exacerbated when patients register their positive test on a Friday, as many CMDUs tell patients that they cease operations on Saturdays and Sundays. Patients, like the patient above, are forced to advocate for themselves with 111 call handlers, their primary care team, their secondary care team, and by calling the charity helplines or advocacy services for support and advice. Yet they are conducting these activities while ill from COVID-19, and afraid of potentially taking a turn for the worse at any point. Some describe this process as *"hours and hours of being pushed from pillar to post*". It's likely that some of these people who don't receive a call from the NHS and don't know who to contact end up never receiving treatment. So while the majority of respondents to our survey said they had no issues accessing antivirals, the problems for those who do struggle are significant with potentially severe health consequences. When we asked patients how satisfied they were overall with their experience of getting and taking antiviral treatments on a scale of 1 to 5 (1 being very unsatisfied, 5 being very satisfied), the most common response was option 5, very satisfied (37.3%). However, those patients who were unsatisfied experienced significant challenges to accessing community antiviral treatments, as outlined above. Because this system relies upon patient self-advocacy, this leads to unequal access to treatment for those who are unable to do so either due to a lack of health literacy, not speaking English as a first language, or other issues that contribute to socioeconomic and racial disparity in treatment access. For those who are sent in circles to different groups in an attempt to access the

	treatments for which they are eligible, some say that “the system failed us” and “getting to the point of treatment was a nightmare”. Other eligible patients “didn’t sound ill enough” on the phone during assessment, as one survey respondent says. In a considerable number of instances, patients in this situation passed the treatment window of 5 to 7 days and were unable to access treatment. This has led to some patients being hospitalised, as one survey respondent says: “I called numerous times to arrange treatment and was repeatedly told they'd get back to me, but [I] didn’t get treatment and ended up in hospital.” In addition, there are serious concerns about a lack of education among CMDU staff on the eligibility list including blood cancer conditions and treatments. Many patients are refused despite their eligibility, only to be accepted after an interjection by their haematology teams or by charity staff, who clarify the guidance for CMDU staff. Further, CMDU staff sometimes incorrectly tell eligible patients that they should not receive COVID-19 treatment because they are up to date on their COVID-19 vaccinations – despite, of course, these treatments being available precisely because some patient groups remain at very high risk from COVID-19 despite vaccination. One woman called us to tell us that her father, who had blood cancer and caught COVID-19, was refused treatment for this reason, and that he soon passed away as a result. Lastly, patients who live in rural areas or otherwise live several hours or more from the nearest available site for intravenous infusion prefer to take treatments in tablet form. Many are unable to organise transport - especially while ill from COVID-19 - to hospital sites.
Patient population	
16. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	In considering which patient subgroups may benefit more or less from COVID-19 treatments, the effects on both COVID-19 and cancer outcomes must be considered. Patients at severe risk of adverse COVID-19 outcomes, including hospitalisation and death, include those with little to no immunity from COVID-19 as a result of their condition and/or its treatment, as well as those with additional COVID-19 risk factors (both clinical and non-clinical). For example, some of the most at risk from COVID-19 due to biology of disease are those with chronic B cell conditions such as

	chronic lymphocytic leukaemia; they can also have their risk level increased by use of BTK inhibitors like ibrutinib. Patients at severe risk of adverse cancer outcomes include those with aggressive and/or potentially curable conditions – such as high-grade Non-Hodgkin Lymphoma or acute leukaemia – and who contract COVID-19 during or immediately before their cancer treatment, causing significant disruption to their cancer treatment schedule. Additionally, post-stem cell transplantation, patients will have no immunity against COVID-19 and are required to be fully revaccinated, putting them at a particularly high risk of contracting the virus. All patients with blood cancers should be included as eligible, leaving it to clinicians to determine their risk from severe illness and thus determining access. This would likely simplify both treatment delivery and communications to patients.
17. For the people you represent, what do they think about the definition of 'high risk' used to determine access to treatments for preventing severe COVID-19. ● Does the definition exclude any key 'high risk' patient groups?	The definition of 'high risk' is an appropriate way to refer to patients who should have access to treatments for preventing severe COVID-19. Further, patient eligibility should be followed as per the COVID-19 enhanced protection programme's Independent Advisory Group's recommendations for identifying people who are at the highest risk of developing severe complications from COVID-19. It should be noted that people with T-cell blood cancers who are not undergoing B-cell depleting treatment are unduly excluded from this list. While B-cell antibodies are measurable through serology testing and are correlated with risk from COVID-19, T-cells also play a crucial part in protecting from adverse COVID-19 outcomes. Also, T cell cancers tend to be rarer than B cell cancers (e.g. T cell acute lymphoblastic leukaemia), and so fewer studies have been conducted on these patients' response to vaccination/their risk of COVID-19. We urge that these patients be included in the spirit of the precautionary principle. Further, the following statement in the eligibility list should be amended. It currently reads: "*People with secondary immunodeficiency receiving, or eligible for immunoglobulin replacement therapy*". Some patients at high risk are unduly excluded by this statement, which defines risk by whether or not a patient can access or are known to be eligible for certain treatments, many of which are increasingly difficult to obtain. This should be rectified by amending this statement to the following: "*People with secondary immunodeficiency receiving, or eligible for, immunoglobulin*

	replacement therapy, or who are experiencing recurrent infections as a consequence of their immunodeficiency". This would include those with significant immunodeficiency who cannot access this replacement therapy, and for whom this therapy is not effective.
Equality	
18. Are there any potential equality issues that should be taken into account when considering COVID-19 and the available therapies?	
Other issues	

19. Are there any other issues that you would like the committee to consider?	While there are some blood cancer patients and stem cell transplant recipients who receive post-exposure COVID-19 treatment quickly and easily, there are a significant number of eligible patients who are unable to access treatment. OpenSafely data shows that only 27% of patients with haematological disease who test positive for COVID-19 and are referred for treatment at CMDUs eventually receive treatment . Further, patients living in the most deprived areas, and patients from minority ethnic backgrounds are least likely to receive post-exposure COVID-19 treatment. The deployment of post-exposure COVID-19 treatments may therefore exacerbate pre-existing health inequalities. It is vital that these treatments be deployed in such a way as to enable equitable access to all those eligible. Further, patients see the need for a clear protective strategy that includes both pre- and post-exposure treatment. It would be sensible to consider the delivery of these two treatment types together, as the cohort considered here includes patients who would benefit from prophylaxis.

Key messages

20. In up to 5 bullet points, please summarise the key messages of your submission:

- Half of surveyed blood cancer patients who did not receive treatment for COVID-19 experienced long-term effects from COVID-19, and nearly half required physical support from close family and friends as a result. Initial findings from a study conducted by Dr Helen Parry show that those who did receive treatment in the community universally recovered without the need for hospitalisation.
- Our surveys show that patients consider treatments to have been effective and rarely impact on their cancer treatment. Community treatments made them feel better within a matter of a few days. However, hospital treatments are still vital, in light of access issues with community treatment and the fact they are unlikely to be 100% effective for all.
- Even among all blood cancer patients, there are many factors that can contribute to risk of severe COVID-19, such as which cancer type they have, the treatment they are on, age and co-morbidities. The committee should keep its recommendation broad so no-one

slips through the net, adapting existing lists of those at risk, addressing concerns with these and ensuring suitably expert clinicians can give access to any patient they feel is at risk.

- Post-exposure treatments are one of the only effective protective measures for blood cancer patients who are less likely to mount an adequate immune response from COVID-19 vaccines. Addressing any barriers to access is a priority to ensure protection for these patients, with one patient noting that medical staff did not listen to them or take their concerns seriously.
- While the availability of these treatments are a significant priority for patients, it is vital that they are made available in an equitable manner with significant consideration given to overcoming ongoing access concerns.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Down's Syndrome Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Down's Syndrome Association is a national charity focusing on all aspects of living with Down's syndrome. Established in 1970, we have around 20,000 members. The Association is in contact with over 130 affiliated local support groups and a range of professionals from different agencies. We have an annual income around £3M and raise funds from a variety of sources, including events fundraising, individual donors, corporate and trust applications and some small-scale statutory funding (mainly from the Governments in Wales and Northern Ireland to deliver specific projects e.g. an employment project). We generate some income from the provision of training. We are the lead provider of information, advocacy, support and training to anyone with an interest in Down's syndrome. We are a membership-led organisation, with our membership comprising primarily the family-carers of children and adults with Down's syndrome and a growing membership of adults with Down's syndrome aged 18+. We are well placed to reflect the needs and views of people we seek to serve. We have a commitment to inclusive participation and work closely with a diverse group of individuals who have Down's syndrome called "Our Voice", who come together regularly to help shape and inform our work. Down's syndrome is a genetic condition, caused by the presence of an extra chromosome 21 in the body's cells. Everyone with the condition will have some degree of learning disability. In addition, there are a number of associated medical conditions, which affect some, but not all, people who have Down's syndrome, meaning the services that they access from the NHS (and social care settings) are of paramount importance to their wellbeing. The number of people in England and Wales with the condition was estimated as 37,090* in 2013.

	Some people who have Down's syndrome lead semi-independent lives in a supported environment and others, with more complex needs, will always require a high level of support. Generally needs increase with age. With appropriate healthcare, many people who have Down's syndrome are now living to the age of 60 and beyond. * Wu J, Morris JK The population prevalence of Down's syndrome in England and Wales in 2011 Eur J Hum Genet 2013 Sep; 21(9):1016-9. doi: 10.1038/ejhg.2012.294. Epub 2013
4b. Has the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	None
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	We provide a helpline which receives 10,000 calls and emails a year. During the beginning stages of the pandemic we set up a weekly webinar for families to brief them on everything connected to COVID-19 and gain feedback on their experiences of accessing services – these attracted up to 650 people at a time and were shared via our YouTube Channel. Over the last 2 years we have been contacted by families who have experienced the death of a loved one who had Down's syndrome and died following a COVID infection, some of these have resulted in an Inquest. We are members of the Advisory board for the LeDeR programme (Learning from Life and Death Reviews) https://leder.nhs.uk/ which record the premature or avoidable deaths of people who have a learning disability in the UK. We have also assisted researchers focused on the experiences of people who have learning disability during the Covid pandemic e.g. https://www.ndti.org.uk/projects/coronavirus-and-people-with-learning-disabilities-a-study-of-the-lives-of-people-with-learning-disabilities We have collaborated with an international research team looking at the impact of COVID19 on children and adults who have Down's syndrome https://www.t21rs.org/covid-19/covid-19-initiatives/ and through our work in hosting The Down's Syndrome Medical Interest Group in UK and Ireland, we have gained a good picture of the experiences here in the UK https://www.dsmig.org.uk/
Living with COVID-19	
6. Please tell us what is it like for patients you support who have tested positive for COVID-19?	Individuals who have Down's syndrome were identified as being Clinically Extremely Vulnerable to COVID-19, following the publication (in the BMJ) of the *Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study* in October 2020.This study showed that adults who have Down's syndrome were up to 13 times more likely to die from COVID-19 than individuals, of a similar age, without Down's syndrome. People who have Down's syndrome aged 16 and over were prioritised for COVID-19 vaccination at priority group 4 in the initial vaccine roll-out and younger children were prioritised for early access to COVID-19 ahead of the general population of children.

	A minority of individuals who have Down's syndrome and have an additional health condition (e.g. a blood cancer) or are receiving a treatment, such as steroid medicine, biological therapy, chemotherapy or have had an organ or bone marrow transplant means they meet the criteria to be classed as immunosuppressed, have been offered a 4th (spring) booster dose. All individuals who have Down's syndrome aged 5 and over will be eligible for an autumn booster from September 2022. The experience of the COVID-19 vaccination programme has generally been extremely positive for people who have Down's syndrome. Uptake has been high and the performance of the vaccine (amongst those who are not immunosuppressed) appears to have been good. However, anxiety levels remain high, the fear of becoming unwell, should an individual who has Down's syndrome be infected with COVID-19 is ever present. Access to COVID-19 therapeutics have, therefore, been fundamental in the confidence of people who have Down's syndrome to begin to resume normal patterns of living. From the autumn of 2021, anyone who has Down's syndrome aged 12 and over been eligible for a COVID-19 therapeutics assessment and this has been a crucial additional mechanism in the protection being afforded to this patient-group.
7. What do carers experience when caring for someone with COVID-19?	It has been stressful. Often Covid-19 infection has affected an entire household and some carers are managing their own symptoms / illness at the same time as trying to coordinate care and access to therapeutics for their loved-one who has Down's syndrome. There have been high degrees of anxiety, many families have been extremely cautious in resuming anything approaching normal patterns of living. The dropping of asymptomatic community testing and the fact the majority of the public do not wear face masks has added to these anxieties. The majority of family-carers work and they have had to juggle these pressures with work commitments and some have found this particularly challenging. The experience of accessing therapeutics have been extremely cumbersome and has failed many– see additional comments in this response.

Interaction with underlying conditions 8. For people with underlying conditions (for example cancers, autoimmune disorders): • If applicable, how has living with COVID-19 affected their condition? • If applicable, how has the normal treatment pathway for their condition been affected? (For example, cancer treatment options, regularity of assessments, accessibility issues related to treatments)	A minority of individuals who have Down's syndrome and have an additional health condition (e.g. a blood cancer) or are receiving a treatment, such as steroid medicine, biological therapy, chemotherapy or have had an organ or bone marrow transplant means they meet the criteria to be classed as immunosuppressed. This has caused a significant amount of confusion amongst families, as it applies to only a small proportion of people who have Down's syndrome. Many families have expressed concern that they haven't been offered a spring booster, when someone else who has Down's syndrome has been offered one. It has taken a significant amount of our Information Team time to explain why this is. Everyone who has Down's syndrome is entitled to an annual health check with their GP and many of these has been paused, meaning they have missed out on these important opportunities to monitor general health.
Short term versus long term	The experience of the virus has been quite typical of the general population. Since vaccine roll-out, people who have been double jabbed and had a booster have often experienced mild

9. For the people you represent who have tested positive for COVID-19, on average, how long did their symptoms last for? a) Did anyone have any long-term effects from COVID-19? Approximately what proportion does this represent? b) If yes, • What were they? (for example physical and mental impacts, impact on ability to work) • On average, how long did the effects last for? • What treatments did they need for the long-term effects of COVID-19?	symptoms and recovered within 2 weeks. A proportion of people who have Down's syndrome have become more unwell and some have needed to be hospitalised. There is very limited knowledge of people who have Down's syndrome and have had a COVID infection getting Long Covid. This is definitely an area that requires further research, especially since people with a learning disability may find it harder to describe their ongoing symptoms – this may be occurring under the radar of health professionals managing their care. As with many groups of patients, we are seeing far higher levels of emotional distress amongst people who have Down's syndrome – for some this relates to the traumatic experience of being very unwell (and hospital admission and for some a stay in critical care) because of a COVID19 infection and for others, who may not have experienced a COVID 19 infection, the effects of lockdowns on their mental health and have been significant.

Current treatment for COVID-19 in the NHS	
10. What do patients or carers think of current treatments and care available in the NHS? - for preventing severe COVID-19 in people with high risk of hospitalisation - for treating people in hospital with severe COVID-19	
11. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?	
12. What impact does having these drugs available in the NHS have on your community?	

13. Is there an unmet need for patients with this condition in relation to therapies for treating COVID-19? Are there any key subgroups of patients we should consider?	
Hospital and community treatment settings 14. For those people that you represent who were hospitalised due to COVID-19 • At what point after being diagnosed with COVID-19 did they receive any form of treatment? • What did their treatment pathway look like? • How long did they spend in hospital?	

If they had an underlying condition how did this impact the condition? 15. For the people you represent that had treatments for COVID-19 in <u>community settings</u>: • At what point after being diagnosed with COVID-19 did they receive any form of treatment from the NHS? • What did their treatment pathway look like? • Was there a preference for receiving tablets versus treatment with other administration methods (for example intravenously) • Can you tell us a bit about their experience of accessing these treatments? (for example	Since the autumn of 2021, our helpline has received very many calls from families telling us the process, outlined in the letters sent to them about being eligible for COVID-19 treatments, is not being followed. Typically, individuals are on day 4 or day 5 following a positive test and have failed to receive a call back to facilitate contact with a COVID19 Medicine Delivery Unit. The particular failures are: 1. NHS111 staff being unaware of their role in the system. They do not seem to have any information relating to the agreed pathway for referral to a CMDU. 2. Once more than 48 hours from a positive test has elapsed, families who follow the advice given in the NHS letters they had last year about COVID19 therapeutics, call their GP and are often met with opposition. Primary care staff invariably tell families to call 119 (which is not the agreed protocol). Other GPs refer families back to NHS111 and there is frequently a stand-off that can last several days. 3. The majority of eligible patients in these scenarios get “timed out” and find themselves on day 6 or 7 following a positive COVID-19 test, meaning they are too late for the treatments to be effective 4. Additionally, there are a series of difficulties for families of *children* who have Down’s syndrome being able to access a CMDU with the capacity to prescribe for anyone under the age of 18. Many ICBs have not commissioned a paediatric CMDU facility. For example, a family in Hull (who were on day 5 of waiting for a CMDU assessment) eventually discovered that their nearest paediatric facility was in Leeds – an hour and half away.

travelling to clinics/outpatient settings while testing positive for COVID-19) • Were there any issues with accessing these treatments?	These issues are not localised to a particular area or isolated in their occurrence and have occurred in the North, South, East and West regions of England (and are replicated in their frequency across Wales, too). We have fed-back these operational issues to relevant policy leads at NHS England and Wales and to the DHSC and Welsh Government, but make these comments here, as we feel these significantly impact on the potential benefits being experienced by patients. In initial discussions with DHSC, it was noted that there were plans to increase the range of clinicians able to prescribe the COVID-19 therapeutics. We would be supportive of that and if possible, would suggest that primary care teams are given a more direct role in this pathway. We would highlight that, for a significant proportion of individuals who have Down's syndrome, a venous route for a medication can be more problematic, due to the willingness of the individual to submit to this process. These issues can frequently be overcome with the right approach, but the skill level of clinicians working in settings differs greatly, as does the availability of specialist learning disability nurses, who can provide additional supports and advice on strategies to assist compliance and minimise distress. For this reason, there seems to be an inherent advantage to those therapeutics that can be administered orally and ideally in the community, removing the need for an individual to attend a clinical setting.
Patient population	
16. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	

17. For the people you represent, what do they think about the definition of 'high risk' used to determine access to treatments for preventing severe COVID-19. • Does the definition exclude any key 'high risk' patient groups?	
Equality	
18. Are there any potential equality issues that should be taken into account when considering COVID-19 and the available therapies?	
Other issues	
19. Are there any other issues that you would like the committee to consider?	In assessing the benefits of COVID-19 therapeutics, we would emphasise: 1. Individuals who were originally designated Clinically Extremely Vulnerable felt the effects of the pandemic earlier than the general population (as they began to 'shield' as a way of mitigating their risk of being infected and to deal with anxieties) even before this became established advice.

	2. Even though formal shielding advice and the CEV patients list was wound-up many months ago, many individuals previously designated CEV still experience very high levels of anxiety and some people are still 'shielding'. Ensuring there is ready access to COVID-19 therapeutics, is one way of providing reassurance to affected individuals, especially during periods when community transmission remains so high. 3. The value to individuals who have Down's syndrome to be able to return to paid work, education and reengage socially is hard to overestimate – it is of paramount importance, as these freedoms have been very hard won. 4. The detrimental emotional and psychological impact of hospitalisation must be noted. For individuals who have a learning disability, being in a hospital setting, especially a critical care setting, can be very stressful. Difficulties in staff being able to make reasonable adjustments (especially around investing time in finding appropriate ways to communicate with a patient) can make these experiences very traumatic. The value of preventing a hospital admission for someone who has a learning disability should therefore be given greater weight in these cost / benefits calculations. 5. The cost to family-carers of a hospital stay for a child or adult who has Down's syndrome (both emotional and monetary e.g. a parent missing work) should also be noted. Any therapeutic which prevents a hospital stay has a value that extends beyond just the patient, but impacts on their family, as a whole.

Key messages

20. In up to 5 bullet points, please summarise the key messages of your submission:

- Quickly improve the mechanism for accessing COVID-19 therapeutics in the community, with a particular emphasis on training for NHS111 personnel
- Maintain free testing for people who were previously designated as CEV

- Expand the number of professionals able to prescribe COVID19 therapeutics, with a greater involvement of primary care professionals
- Keep public communications high on the agenda and work with relevant partners in the charity sector to share these messages
-

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Therapeutics for people with COVID-19 [ID4038]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Immunodeficiency UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Immunodeficiency UK (previously known as PID UK) supports people affected by primary and secondary immunodeficiency (PID and SID). We help give advice on managing their condition, their treatment; promote awareness and understanding of PID and SID within the general public and medical profession to promote better understanding of these conditions and their impact. We provide a helpline service, events and practical help and advice and advocate for improved healthcare. Our funding comes from public donations, events, legacies, pharmaceutical companies and trusts and foundations (Immunodeficiency UK - Sponsors). We currently have over 1000 members.

4b.	No funding has been received from any of the companies listed.
4c tobacco funding?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Immunodeficiency UK carried out a survey of its members with questions addressing the issues of this consultation. The survey was a mixture of quantitative and qualitative (free text) questions. Access to the survey was via a link sent by a membership mailing. We received 516 responses: 254 from people directly affected by PID; 194 affected by SID and 68 responses from carers of those affected. Responses were collected from 11 - 27 August 2022. **Numbers of people testing positive:** Of 254 PID respondees 101 (39.76%) had tested positive for COVID. For 194 SID patients 62 (32%) had tested positive for COVID.
Living with COVID-19	
6. Please tell us what is it like for patients you support who have tested positive for COVID-19?	It is important to understand the context of the situation of people with PID and SID living with COVID for the MTA. Published data, of which NICE will be aware, has shown that there are subgroups of patients with PID and SID that have poor COVID-19 vaccination responses. Consequently, there remains considerable fear, distress about the consequences of having a COVID-19 infection and profound fear within the community of contracting the virus, as shown by the survey data below of the number of people who are still shielding, with the subsequent severe impact on mental health and quality of life. This remains the case even for a large proportion of people who have benefitted from the safety net of accessing COVID therapies. **Overall confidence in living with COVID:** Of 439 respondents in our survey affected with either SID or PID, 30% were not going out at all, 43% had little confidence in going out; 16% (71) were moderately confident; 6% were mostly confident and 5% very confident. There was no statistical difference when analysing the results for the PID and SID groups separately. **These results indicate that a significantly high proportion of our community are effectively continuing to shield so there are lots of individuals who have yet to be exposed to COVID for the first time.** **Confidence of living with COVID who have tested positive and had accessed therapy:** Of 105 respondents (affected by PID or SID) 20% were not going out at all, 38% had little confidence in going out; 21% were moderately confident; 13% were mostly confident and 8% very confident. Indicating that even having had the experience of a 'safety-net' there remains considerable concern about getting COVID again. Average confidence in accessing healthcare in a hospital setting was 50 (scale 0 - 100; no confidence to full confidence. **Quality of life (QoL) survey data** reporting on a scale of 1 -100 (poor to excellent). Average ratings are quoted. **All PID patients:** pre-pandemic QoL rating 78 (248 responses). QoL now rated as 28 (246 responses). **PID patients testing positive:** pre-pandemic QoL rating 76 (100 responses). QoL now rated as 42 (100 responses).

	All SID patients: pre-pandemic QoL rating 76 (191 responses). QoL now rated as 27 (189 responses). **SID patients testing positive:** QoL rating 77 (60 responses). QoL now 37 (60 responses). These findings underline the significant impact of the threat of COVID has on the lives of people affected by PID and SID. The impact on health of having a COVID-19 infection was variable and person specific ranging from mild illness to serious illness, including the need for hospitalisation – 4 patients said they needed admittance to ICU. Those who were badly affected described the experience as frightening, terrifying, scary, distressing. Some people described the quick deterioration of their health and the anxiety of accessing COVID medicines. **Experiences:** 'I thought I was going to die, I was alone and terrified. It was incredibly difficult to access treatment and help. How I drove myself to be tested and eventually to receive sotrovimab I'll never know, I'm surprised I didn't crash the car and of course no-one wanted to take me. I have never been that sick and I never want to feel like that again'. 'Horrific and the most frightening time of my life'. 'Very, very frightening. I don't want to go through it again'. 'Fairly mild in comparison to what I was told would happen'; 'Like a bad cold but it cleared in a few days. I was scared that I would become very unwell though.' **Data from CO-VAD study (antibody deficient patients)** indicates that inpatient mortality has remained high (19% for PID, 42.8% for SID) suggesting if you are sick enough to end up in hospital then that is a poor prognostic sign. CO-VAD (patients with antibody deficiency) data is available on 155 individuals with SARS-CoV-2 infection since the deployment of vaccination (January 2021). This comes from a mix of CO-VAD and UKPIN data. Hospitalisation rate with Omicron was 9.9% vs 2.2% for the general population and mortality was 2.7% vs 0.2% for the general population. As of August 2022 (publication under review), the cumulative incidence of infection in the longitudinal cohort is 28.6% which is much, much lower than the ONS cumulative incidence of infection in the general population which was 70% back in February 2022. The COVAD patients were infected later in the pandemic, mainly during the latest Omicron wave. Survey data results concerning experiences in access, attitude to accessing healthcare are given below.
7. What do carers experience when caring for someone with COVID-19?	Carers experience stress, anxiety, feeling inadequate, worry and anger and frustration about the access to medicines process and access to good information, the lack of knowledge about the conditions that their loved ones have when accessing COVID medications and having to educate the CMDU and other medical professionals about their needs. It is important to state that many carers are still shielding and leading very restrictive lives, in order to protect their relatives. We received 68 free text experiences from carers – here are some response:

	'It was really scary. There was significant breathlessness and she had to go into hospital alone for treatment. She was breathless for weeks and we were significantly worried she might die. This is continuing as she is extremely worried about getting it again.' 'Scary, long hours on the phone trying to get antivirals. Very worried about how it would effect condition and coping alone. Monitoring breathing, fluids and blood pressure without support.' 'Very scary particularly the way their breathing was affected. They still have a terrible cough and tire easily. I used vaporizers and lots of pillows to help them to breathe. Fortunately they were never so ill as to require hospitalisation. They were unable to have the vaccines due to allergies. I sat up every night cupping my bands and massaging to bring up the mucus when they had Covid.' 'Terrifying at first!!!! But my son's COVID infection turned out to be no worse than other viral infections he has had in the past.' 'My daughter was extremely sick at home. Terrible opinion from 111, she should at least she been assessed by paramedics. I'm a doctor and I was worried about her. She now has many health problems as a result, (Long Covid is such a benign sounding term for how ill she is). She is mostly bed bound and has PTSD from being in fear for her life at the beginning.' 'My dad had CLL, when he tested positive for covid he was declined anti virals as he felt OK. He died of covid several months later'. 'Awful, worrying and unknown. We dread him getting it again.' 'Which way would it go....frustrating as they thought I was over anxious. Anger as they not only had not come across di George before but then failed to actually look it up.' 'Despite all of our best efforts, our immunosuppressed daughter contracted Covid because she had to go into work one day, and despite her wearing high quality masks, because there are no longer any mitigations in place, she was infected. It was absolutely terrifying, our worst nightmare. Fortunately her specialist team accessed Sotrovimab for her really quickly, but it didn't seem to neutralise anything. She was very poorly, dropping SATs which we constantly monitored, isolated her at home and double masking in the house. She tested positive for 15 days, had to come off all of her other disease modifying medications to give her immune system a chance to recover, and has now had to go on a high dose of steroids to help get her back on track before resuming her usual treatments. All because of the position this government is taking that despite all of the real world wide data there is regarding effectiveness, it will not procure Evusheld. She leads a virtually non-existent life, she is a young woman whose life has shrunk to nothing. I have seen her change form a strong person who dealt with her underlying condition (Lupus) as best she could and led as full a life as possible to a shadow of her former self, frightened of contact with people and who I now not only fear for physically, but mentally as well. She used to have a life, she used to socialise, travel, do normal things all of which meant putting money into the economy. She doesn't do any of that now so if we dispassionately take out the physical and mental effects of not being able to live with Covid, the economical impact is significant. Because this doesn't only affect her, it affects us as her carers as well. Our lives have shrunk too, we are in our 60s and cannot enjoy a full life because we have to weigh up everything in the context of what risk might we bring home to her. We only socialise now in a limited way, we have only travelled once and I am reluctant to do so again. So we too aren't putting money into the economy.'
Interaction with underlying conditions	The survey results showed that COVID-19 has adversely affected confidence in accessing healthcare in a hospital setting. 169 of 437 respondents (38%) were < 20% confident; only 86 of 437 respondents (20%) had > 60% confidence. Some responses indicated that

8. For people with underlying conditions (for example cancers, autoimmune disorders): • If applicable, how has living with COVID-19 affected their condition? • If applicable, how has the normal treatment pathway for their condition been affected? (For example, cancer treatment options, regularity of assessments, accessibility issues related to treatments)	people were willing not to access any healthcare in hospital due to the risk of getting Covid, especially as restrictions have been lifted. The regularity of appointments and face-to-face appointments has decreased for people with PID and SID. 56% reported a decrease in appointments with 6% reporting an increase. 87% of respondents reported a decrease in face-to-face appointments with 5% reporting an increase. These findings have important consequences as there is a need for regular monitoring. PID and SID are chronic conditions affecting multi-organ systems. Routine care should involve regular blood tests, scans, lung function tests etc. Many people reported a complete lack of confidence in attending in hospital appointments, having dental, eye, breast screening checks, smear tests, etc due to the fear of mixing with other people who were not wearing masks. Some people welcomed the shift from face to face to phone or video consultations to mitigate the risk of getting COVID through travel and in hospital settings but recognised the need that physical examination and hospital-based tests are required to fully assess their health. Patient quotes: 'Since freedom day in 2021 I have not been able to safely visit NHS sites. Worried about catching covid whilst travelling to the appointment or in the NHS venue'. Attending hospital environment is so traumatic and stressful'. 'Many safeguards have been removed that would help protect me.' 'Scans and checks missed so many areas I have got far worse. Was meant to have a bone density scan but this was missed for 18 months and it dropped 25%!' 'Haven't had any maintenance x-rays, Ct-scans etc for over 2yrs now'. 'I have not had my usual yearly scan for 3 years.' 'Since the advent of COVID-19 I have had more regular clinic appointments but no scans or tests since 2019 to assess the health of my organs and my body overall.' 'As an insulin-dependent diabetic I no longer get diabetic reviews, either in the community or at hospital.' 'Supply of my medicine [immunoglobulin] has been affected'. 'I did not get my treatment with Rituximab for 16 months and this led to a flare up.' 'I was referred to a cardiologist, had one appointment and my 2nd appt is nearly 2.5years later! I am terrified to go to face to face appointments'. 'Failure to have face to face examination has led to an undiagnosed incisional hernia as a result of the transplant'.
Short term versus long term 9. For the people you represent who have tested positive for COVID-19, on average, how long did their symptoms last for? a) Did anyone have any long-term effects from COVID-19? Approximately what	**Short term.** Symptoms were reported to last for a few days to many weeks and were person specific. 32/157 (20%) respondents reported symptoms lasting < 10 days, with 63/157 (40%) respondents reported symptoms lasting several weeks. It is noteworthy that 37% of respondents reported that receiving COVID-19 medications did not clear their infection, resulting in COVID rebound, recurrence of symptoms and in some cases, people required 2nd courses of treatment. This inability to clear infection resulted in time off from work and in some cases long periods of illness and hospitalisation. 'It [Paxlovid] definitely improved my condition and I believe I would have ended up in hospital very poorly without it. However I was still positive on day 18, ended up in A&E on day 20, was very poorly for weeks to come and still suffering after effects now'; 'tested positive for ten weeks after taking paxlovid'; 'I continued to develop different symptoms and remained very unwell signed off work for 3 weeks. I tested positive continually for 17 days'; 'I was still testing positive at 21 days but had to return to work on day 19 whilst still feeling terrible.'; 'Admitted to hospital with a very high viral load 10 days after finishing outpatient treatment'. 'Molnupiravir did not clear the infection needed to have Sotromivab as a follow-up treatment'. 'The first course of Paxlovid failed to

proportion does this represent? b) If yes, • What were they? (for example physical and mental impacts, impact on ability to work) • On average, how long did the effects last for? • What treatments did they need for the long-term effects of COVID-19?	clear the virus and so I got COVID rebound, recurrence of symptoms and I needed a 2nd course of Paxlovid before I was consistently COVID-free.' **Long term effects.** 59% (93/157) of PID + SID respondents who had tested positive for COVID reported long-term effects of having had COVID. 70% (64 of 92 respondents) reported effects lasting several months. **Physical impacts reported included**: reduced breathing capacity for several months, lung pain, constant coughing, exacerbation of previous health problems, increased susceptibility to infection, mobility issues, fatigue and exhaustion, anosmia, gastrointestinal problems; joint pain, cognitive difficulties with memory/attention /concentration/word finding difficulties (brain fog), dizziness, fainting, headaches & migraines, post exertion symptom exacerbation (PESE/PEM), diarrhoea, neurological symptoms such as vertigo, spells of deafness in one or both ears, spells of agonising headaches, vision problems, heart problems. **The mental health impact,** in this group, was mentioned in 21% (20/93) of responses. Anxiety, worry, fear, depression, isolation, panic attacks, PTSD, frustration at losing previous relatively fit lifestyles were reported. **Impact on ability to work** was mentioned in 13% (12/93) responses and included loss of employment, bedbound/unable to work – on disability benefits, need to take several months off work, taking reduced hours/ inability to work full-time, phased returns to work, occupational health support and reasonable adjustments at work, need to take early retirement and expectation to lose jobs due to continuing health problems. These problems have led to people losing income with resulting financial instability. There was also mention of the on-going need to depend on other people for care and support. **Treatments offered:** Montelukast, Stemetil, Amantadine (recommended by consultant neurologist/access refused by GP), home oxygen, inhalers, steroids, carbocisteine, ivabradine, antibiotics, pain medications. Other treatments included breathing exercises, physiotherapy, CBT referral, referral to other specialities. 5 people reported being referred to long-COVID clinics but reported long waits for referral and triage. Many people still waiting for referrals. 33 people reported no interventions have been offered.
Current treatment for COVID-19 in the NHS	
10. What do patients or carers think of current treatments and care available in the NHS? - for preventing severe COVID-19 in people with high risk of hospitalisation	We had 430 survey responses to this question and received a mixed response. Here are some examples of responses: 'The vaccine roll out was chaotic. The treatment - infusion of antibodies was very efficient'. 'Excellent'. 'Prevention would be better than treatment'; 'Completely inadequate and patchy.'; 'Helpful to me if I test positive for covid in time and get access quickly enough to care required, but I don't feel safe 'in between' with all preventions lifted'; 'To date, I've have been very happy with treatments offered.' 'It's slowly got better with the introduction of new treatments such as antivirals'; 'It is comforting that there are treatments available, but the path to accessing them seems quite complicated.'; 'Appreciate access to antivirals which made a difference to recovery after Covid although process could have been speedier, not available at weekend.'; 'I feel abandoned'; 'There are good drugs available for covid for people already on treatment. But these are post infection and not preventative.' 'There are very good options but they are challenging to access'; 'In a word, mystifying. I am baffled by the UK's approach to protecting the clinically vulnerable. The rest of the developed world has adopted a multi-pronged strategy for the vulnerable, but for some

- for treating people in hospital with severe COVID-19	unknown reason, the UK government seems to be stubbornly sticking to a narrow plan of Paxlovid only. At least that was my experience when contracting COVID last month – Paxlovid was Plan A, Plan B and Plan C. In no way was the therapy tailored to my immune deficiency. Anti-virals suppress the virus, not kill or clear it. My whole life I have struggled to clear infections – a simple cold turns into something that could put me in hospital or even kill me. Surviving my infancy was a miracle that I owe to the NHS. But my clinicians have strategies for such "breakthrough" infections. My concern is that my clinicians' hands are tied. They were not consulted about the best treatment options for me when I got COVID. And that was because there really was only one treatment option – 5 days of Paxlovid. They weren't even allowed to modify the length of the course of Paxlovid. Previously the approach was a combination therapy of anti-virals (to suppress the virus) and mAbs (to help clear it). But this was not an option available to me.' 'I think having the antivirals available for the immunocompromised is fantastic. They helped me enormously when I tested positive in June 2022. 'I do not currently feel safe with the treatments available in the UK. At the moment, if we contract Covid we are given post-exposure therapies. This then relies on us taking the risk of becoming infected and then seeking help. This feels incredibly risky and, as a result, we are still shielding with incredibly limited lives'. 'The two treatments available to people previously designated as CEV appear to be sotrovimab and Paxlovid. Sotrovimab has been withdrawn by the FDA as ineffective against Omicron variants. Paxlovid has problems with breakthroughs, and is also unsuitable for many people who take medications'. 'When I had Covid I was given monoclonal antibodies within 2 days of testing positive. These seemed to make a difference to me. I think it is brilliant that these treatments are available otherwise I could have been much more unwell.' **Further examination of views and unmet need are given in other sections.**
11. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?	Yes, there are significant drug interactions with other antivirals and medications that are used to treat primary and secondary immunodeficiency that limit the options available to treat COVID-19. This restricts treatment options and further adds to the stress patients feel once they have tested positive. High spike antibody levels from prior vaccination for monoclonals (and this may apply also to spike antibody from immunoglobulin replacement soon). There is concern about the misinterpretation of antibody levels in primary and secondary immunodeficiency patients. People in our community have been rejected for monoclonal antibody therapy on the basis they've made an antibody response, but antibody binding capacity doesn't mean the antibodies work - this has been proven in patients affected by CVID.
12. What impact does having these drugs available in the	COVID-19 treatments offer a vital safety net for those people with PID and SID who are eligible for treatment and test positive and can access the therapies in the prescribing therapeutic window. They have proved life-saving for some patients and have significantly reduced patient mortality since the start of the pandemic. They are welcomed and valued. However, there are issues concerning the ease of accessibility to the therapies, the ability to meet demand for those requiring treatment, with more transparency needed for patients about the decision-making process, and a requirement for better communication of the availability of these therapies, the need for widening of eligibility and better training of GPs, 111 and 119 services to ensure smooth access

NHS have on your community?	pathways. Most importantly, our survey shows there is a huge unmet patient need (survey data below) for the availability of prophylactic preventative therapies to improve the quality of life, mental health of people, to increase the participation of immunodeficient patients in society, including economic benefits, not withstanding significantly reduced clinical risk and less hospital bed use.
13. Is there an unmet need for patients with this condition in relation to therapies for treating COVID-19? Are there any key subgroups of patients we should consider?	COVID continues to pose a significant risk to patients with PID and SID and there remains an unmet need to understand the correlates of protection against severe disease and optimise mitigation, prophylactic and therapeutic strategies to minimise the ongoing burden of the pandemic to these vulnerable groups. Key groups that require prioritisation are given in section 16. It is noteworthy that the APPG on Vulnerable Groups to Pandemics has produced a 'National Clinical Expert Consensus Statement 'Coronavirus monoclonal antibodies as a prophylactic therapy against COVID-19 for immunocompromised groups'. This was produced and endorsed by over 120 clinicians indicating that the medical profession is also of the opinion that there is an unmet need. https://bit.ly/3bpE6oO . **Survey data on unmet need:** 79.67% (341/428 responses) from people affected by SID or PID indicated an unmet need. Of those responses 40% (139/341) specifically mentioned the need for Evusheld and 12% (41/341) stated the need for prophylaxis/prevent infection therapies, indicating that people recognise 'fall-back' treatments are available but desperately want a protective strategy. Only 3.5% (15/428) of respondents said there was no unmet need; 4.4% (19/428) stated they didn't know. 'I do not generate memory antibodies – so DoH banging on repeatedly about the success of the vaccine program is very frustrating. Vaccines might be good enough for some vulnerable patients, but vaccination alone is not enough for my needs.' Other responses concerning the question of unmet need included communication and access issues - confusion about who is eligible, access - especially for people who live alone and are feeling ill and don't know how to chase for access; concerns about who makes the decisions on access with many responses indicating that access should be under the control of speciality consultants; eligibility too tight; concerns about demand not being met; concerns about no access to CMDU at weekends; the need for longer doses of anti-virals to clear COVID-19 infections; delays in access; the anxiety of not knowing if you will get access to the medicines on offer (people are very frightened and this is causing mental health issues and distress); need for a clearer strategy/message given so people know what is available and the criteria needed; concerns about the over dependence on one anti-viral – Paxlovid and underuse of Sotrovimab; the need for combination therapies; unmet need in relation to antibody testing to see if a protective response has been made by vaccination.. 'I am very concerned about the lack of transparency about who is eligible for covid treatments (antibody or anti-virals). I have not been contacted and when I spoke to my GP they could not say with certainly that I would receive them, only that it would be

	evaluated based on the rules and criteria at the time I caught covid. If I knew for certain I could receive them that would make a difference in my assessment of my risk from Covid.' 'Yes, there is prophylactic options available such as Evusheld which is being used in other countries. This has not been made available so consequently life is still anything but normal for me and I am having to be incredibly careful still. If I keep contracting covid and needing months off work then I will lose my job. I still cannot go to the shops or a restaurant or meet friends and family in their homes because I do not want to experience the terrifying experience I have already had once with covid. I think much, much more needs to be done to support the immune compromised in getting back to normal life and being able to function in society and prophylactic medicines would facilitate us being able to take steps to do this.' 'Yes, absolutely. There are many thousands of primary and secondary immune deficient people still living their lives under shielding conditions - removed from society and from 'normal' life, unable to go into public contact situations without fear - people with children, jobs, family, dependents, etc - who still cannot participate in everyday activities because of the lack of protection available. There is an enormous unmet need. None of the therapeutic options currently on offer give any protection for these vulnerable people, and Evusheld is the only option available for these people to be able to return to some kind of 'normal' life.'
Hospital and community treatment settings 14. For those people that you represent who were <u>hospitalised</u> due to COVID-19 • At what point after being diagnosed with COVID-19 did they receive any form of treatment? • What did their treatment pathway look like?	**Hospital setting -**These are hard questions to answer comprehensively because the treatment pathways keep changing. There are the known knowns and unknowns. CO-VAD study data (under review for publication; Shields et al.,) indicates that 63.2% (n=98/155) of individuals in this cohort received specific treatment for COVID-19 (73 treated as outpatient, 25 as inpatient). **<u>Access in community settings survey data</u>** – we received 154 responses who had tested positive for COVID -19. Results on the timing on access to COVID medicines results showed that: 30.46% (46) of these patients were not offered any form of treatment – see comments below; 4.64% (7) received treatment on day 1; 17.22% (26) received treatment on day 2; 19.87% (30) received treatment on day 3; 9.27% (14) received treatment on day 4; 14.57% (22) received treatment on day 5; 1.99% (3) received treatment on day 6; 0.66% (1) received treatment on day 7 and 1.32% (2) received treatment after 7 days. **Treatments were offered to 105 patients in our survey. Breakdown**: Paxlovid 39%; Remdesivir 5.71%; Molnupivir 6.67%; Sotrovimab 37.14%. 11.4% of respondents couldn't remember the medication given. **COVAD data** - Since the deployment of CMDUs, 61.4% (n=70/114) of treatment eligible patients actually got treatment from a CMDU. We found significantly lower rates of hospitalisation (4.3% vs 15.9%, p=0.03) amongst individuals treated by CMDU but overall mortality was not affected (2.8% vs 4.5%, p=0.63).

• How long did they spend in hospital? If they had an underlying condition how did this impact the condition? 15. For the people you represent that had treatments for COVID-19 in <u>community settings</u>: • At what point after being diagnosed with COVID-19 did they receive any form of treatment from the NHS? • What did their treatment pathway look like? • Was there a preference for receiving tablets versus treatment with other administration methods (for example intravenously) • Can you tell us a bit about their experience of	**Reasons given for not being offered medication were** refusal without giving an explanation was a common occurrence; not ill enough; too young (person aged 44 years of age); no capacity to provide the medication needed 'told there was high demand and I wasn't considered a priority'; on the eligibility list but when needed people told they weren't eligible. Not on the 'NHS list' - 'No consideration was given whatsoever to the fact that I have a long-standing diagnosis of immunodeficiency with chronically low T cell levels. My condition was effectively not recognised by the wider NHS and my NHS immunologist did not by their own admission have power within the system to ensure that their patients were added to the list to people with rapid timely access to anti-viral medication'. Data from this report <u>https://reports.opensafely.org/reports/antivirals-and-nmabs-for-non-hospitalised-covid-19-patients-coverage-report/</u> indicates that only a small proportion of eligible people are actually getting access to COVID medicines. Regional variability in prescribing is evident from government statistics: <u>Statistics » COVID-19 Therapeutics (antivirals, neutralising monoclonal antibodies and interleukin 6 inhibitors) (england.nhs.uk)</u> **Difficulties reported were** with access helplines – unanswered calls leading to people being outside the treatment window, lack of knowledge of helpline personnel, no contact by the CMDU sometimes in spite of chasing by GP; doctors; medicines promised were not delivered. Many people reported the need to chase constantly ('fight for access') the system to get treatment. In many cases specialist health teams had to get involved to gain access either by direct contact with CMDU or via providing patients with consultant letters. **Preference:** of 120 respondents, 56.67% (68) stated they were not given an option on treatment. 35.83% (43) were happy to receive the recommended treatment and 7.50% (9) stated a preference for receiving tablets. **Access:** 63 people (37%) out of 142 respondents reported having to travel to outpatient settings while positive for COVID. Of 27 respondents who stated transport used: 7 people were offered ambulance/hospital transport; 6 had to drive themselves to centre whilst feeling unwell; 10 people had to rely on family members to take them as so ill; 1 person reported having infusion at home delivered by a nurse; 1 person reported delivery of tablets (Paxlovid) at home; 1 person reported walking to the centre. 1 person stated being offered a sotrovimab infusion but elected to receive tablets as they didn't want in infect as didn't want to infect anyone else. **Overall experience of access was variable**: Of those people who accessed COVID treatments, and rated their experience, the average rating of patient experience on access (103 responses) was 3.4 on a rating of 1 to 5, where 1 = very poor and 5 = excellent. Breakdown of rating was (%; no of respondents): Very poor/Poor – 23.53 % (24); Average – 25.49% (26); Good – 26.47% (27); Excellent 24.51% (26).

accessing these treatments? (for example travelling to clinics/outpatient settings while testing positive for COVID-19) • Were there any issues with accessing these treatments?	**Comments of people who had accessed therapies:** 'They are absolute life savers for us! Being on anti CD-20 therapy for three plus years has meant that I mounted an absolute ZERO antibody response to the four covid vaccines I was given which has left me with terrible covid anxiety which is having a major impact on my life! Having caught covid for the first time in July just gone being able to have the Sotrovimab infusion helped me massively.' 'It was awful, I was hospitalised within 24 hours of testing positive it was then a fight and a battle to get the antibody treatment as everyone agreed I was eligible but couldn't have them due to being in hospital. I only got them in the end because we got my MP involved. I got them with 1 hour to spare!' 'I struggled for 5 days to get antivirals. One person was going to ring me later that day when I tested positive, she said someone else would ring me day after and they didn't. Day 3 I had to ring again said Dr would ring me he said pharmacist would ring me on day 4, he didn't, I had to contact CMDU again. Day 5 someone rang from pharmacy and said couldn't deliver till day after as it was almost 4pm I had to resort to ringing round to see if someone could pick up antivirals for me before 5 otherwise it would of been day 6 and would of been too late.' 'My experience was excellent. I have had 5 jabs. I had a call in less than 24hrs when I tested positive, and was offered Paxlovid straight away the following day. Within a few days I felt much better. Paxlovid definitely worked for me.' 'I had to wait 19 hours on hospital trolley (including one night) to get Sotravimab and had to insist. It was a real struggle.' 'Excellent! Both me and my daughter were contacted promptly when we tested positive for Covid and both received Sotrovimab within 24-48 hours (one in London, one in South West).' **Impact of contraindications on therapy offered:** Of 102 people that received COVID medicines in community settings 21.57% (22) of people had a contraindication which meant they couldn't be given a certain therapy. These included blood thinners, chemotherapy/immunosuppression treatments, liver function problems, underlying nature of medical condition. Several people reported having to stop their routine medicines to be given COVID medicines, which caused health problems down the line.
Patient population	
16. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	Yes. Anyone who has not made a good antibody response to vaccination. It is essential for those patients with primary antibody failure who will not recover B cell function and for those patients who have had B-cell depleting agents. Possibly even more important for those who are older/have co-morbidities e.g. poor lung function. There are also PID patients that can make antibodies but who may be susceptible for different reasons and are not on the list. Low grade lymphomas are over-represented in SID clinics, suggesting a more profound immune system problem. Recent rituximab, CD19 CAR-T, BTK inhibitors treatment patients. Based on current epidemiology data: older patients, more lymphopenic patients and patients with more comorbidities are more likely to end up in hospital.

17. For the people you represent, what do they think about the definition of 'high risk' used to determine access to treatments for preventing severe COVID-19. Does the definition exclude any key 'high risk' patient groups?	Exclusions from the eligibility high risk list include: • Combined immunodeficiencies which aren't explicitly stated • Monogenic phenocopies of CVID which aren't explicitly stated • 22q11 should be covered under the chromosomal abnormalities affecting immune function Immune mediated inflammatory disease patients e.g. individuals with stable rheumatoid arthritis, but have terrible lungs with poor pulmonary function, have been turned away because their underlying disease isn't active. This needs addressing as they are at high risk. **Equality issues concerning access**: these are highlighted in the report Antivirals and nMABs for non-hospitalised COVID-19 patients: coverage report | OpenSAFELY: Reports; section: Key demographic and clinical characteristics of treated patients.

Key messages

20. In up to 5 bullet points, please summarise the key messages of your submission:

- COVID-19 is still having a high impact on PID and SID community with a large proportion of people still shielding and reporting poor quality of life and mental health issues. There remains a lack of confidence in accessing healthcare in a hospital setting with the regularity of appointments, treatment pathways and routine testing adversely affected.
- Having COVID-19 medications available is highly valued but there are problems with gaining access and patchy availability. A significant proportion of people reported COVID 're-bound' after receiving therapy and concerns about the limited number of options available given contraindications of some therapies. In those people who have had experience of access and benefitted from anti-COVID therapies there remains the fear of being re-infected, with many still living very restrictive lives. High-risk groups are missing from the eligibility list.
- A significant proportion of people who had tested positive for COVID reported long term health problems lasting several months with severe impacts on physical health, mental health and ability to work.
- Despite the availability of current COVID medications as a 'safety net', our community overwhelmingly reported an unmet need - the need for access to prophylaxis/prevent infection therapies.
- COVID continues to pose a significant risk to PID and SID patients and there is a need to improve, speed up access pathways to the therapies available. There is a need to optimise mitigation, prophylactic and therapeutic strategies to minimise the on-going burden of COVID on PID and SID patients.

Thank you for your time.

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Kidney Care UK

3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Care UK is the UK's leading kidney patient support charity providing advice, support and financial assistance to thousands every year. It is not a membership organisation, but it is in touch with thousands of kidney patients through its direct patient services (e.g. advocacy, counselling, Facebook support group, patient grants), social media channels, telephone helpline, newsletters, magazines and website. As an example our Coronavirus website www.kidneycareuk.org/coronavirus had nearly 1 million page views (774,000 of them unique views) with an average read time of just over 5 minutes during the Covid pandemic. The organisation is primarily funded by voluntary donations and through interest on or drawing down from our investments.
4b. Has the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	May 2022, GlaxoSmithKline - £25,000 in support of patient information for Anaemia of CKD. Astra Zeneca £20,000 towards web development on kidney disease awareness Dec 21 £657.20 attendance & travel at Chronic Kidney disease attending a CKD roundtable Dec 21 £250 per meeting - ACT on CKD international board online attendance quarterly (so Sept 21, Dec 21, April 22) £300 Attendance at impact of COVID-19 on immunocompromised patients: advisory board (no drug discussion permitted) Dec 21
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	The information and views represented in this submission has been gathered through a range of sources: Kidney Care UK patient support and advocacy officers, counselling services, phone answering team, Facebook support group, other social media including Twitter and Instagram private and public messages, responses to our newsletters and magazines, the views of Kidney Care staff who are kidney patients, our Patient Advisory Group. We have also run regular surveys and Question Time webinars throughout the Covid pandemic to capture the experience and challenges faced by people with kidney disease during the pandemic. Our series of 10 Covid Question Time webinars has also provided a significant insight into people's experiences and concerns. Throughout the pandemic people with kidney disease have turned to the charity for advice, information and guidance and to share their experiences. This has provided a very deep and broad understanding of the experience of this group. During Covid, we ran 3 surveys on patient experience. They highlighted the mental health, employment, carer and employment effects of the disease on people with kidney disease and their families. They are: **Worried Sick** https://www.kidneycareuk.org/news-and-campaigns/news/fears-kidney-patients-government-coronavirus-advice-leaves-thousands-dark/ **Out of Sight, Out of Mind** https://www.kidneycareuk.org/news-and-campaigns/news/thousands-kidney-patients-need-more-support/ **Lifting Lockdown** https://www.kidneycareuk.org/news-and-campaigns/news/lifting-lockdown/
Living with COVID-19	
6. Please tell us what is it like for patients you support who have tested positive for COVID-19?	It is important to acknowledge that Covid has been unlike any other disease in living memory, particularly for people at highest risk, given its impact on nearly every aspect of life and the anxiety and fear experienced by those most at risk of severe illness and death. While these impacts may have reduced for many in the general population, the high risk group are still living with the knowledge that cases remain high and they remain vulnerable. This is the context in which these treatments are embedded. Even before a person tests positive for Covid, the virus may be impacting on their mental health and physical health as well as their day to day activities

	(The latest ONS data (May 2022) showed 13% of people previously considered CEV reported continuing to follow previous shielding advice and 69% were no longer shielding but were taking extra precautions.) Patients that we support who have tested positive have had extremely high rates of severe illness and mortality. OpenSafely data highlights the increased risk of death from Covid among people with kidney disease (ref 1), and their most recent paper (still in preprint) highlights that while rates of death from Covid fell in all groups between Wave 1 and Wave 3, the amount by which they fell was less in those with kidney disease, blood cancers and other immunosuppressed conditions. The importance of these results is that they highlight groups who remain at relatively higher risk of worse outcomes from COVID-19 compared with the rest of the population and whose needs must be carefully considered. The relative risk of death among people with a kidney transplant increased from 7 times higher compared to people without a kidney transplant in wave 1, to 26 times in wave 3. (ref 2) Earlier in the pandemic, the UK Renal Registry produced a great deal of data on mortality for kidney patients. The collection is housed here https://ukkidney.org/audit-research/publications-presentations/report/covid-19-surveillance-reports Key papers are this on the second wave https://ukkidney.org/sites/renal.org/files/ALL_REGIONS_CENTRES_covid_report_030322_FINAL.pdf And this on the first wave https://ukkidney.org/sites/renal.org/files/covid_report_first_wave_FINAL_041220.pdf It is estimated that up to 6% of kidney patients on dialysis or with transplants died from Covid. The mental health impact of this cannot be underestimated which is why supported, targeted communications have been vital all along, and continue to be essential now. This has not always been forthcoming and a number of patients feel forgotten by the system, and left behind. Refs: 1. Williamson, E.J., Walker, A.J., Bhaskaran, K. et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. Nature (2020). **https://doi.org/10.1038/s41586-020-2521-4** 2. Changes in COVID-19-related mortality across key demographic and clinical subgroups: an observational cohort study using the OpenSAFELY platform on 18 million adults in England The OpenSAFELY Collaborative, Linda Nab,

	Edward P K Parker, Colm D Andrews, William J Hulme, Louis Fisher, Jessica Morley, Amir Mehrkar, Brian MacKenna, Peter Inglesby, Caroline E Morton, Sebastian CJ Bacon, George Hickman, David Evans, Tom Ward, Rebecca M Smith, Simon Davy, Iain Dillingham, Steven Maude, Ben FC Butler-Cole, Thomas O'Dwyer, Catherine L Stables, Lucy Bridges, Christopher Bates, Jonathan Cockburn, John Parry, Frank Hester, Sam Harper, Bang Zheng, Elizabeth J Williamson, Rosalind M Eggo, Stephen JW Evans, Ben Goldacre, Laurie A Tomlinson, Alex J Walker medRxiv 2022.07.30.22278161; doi: **https://doi.org/10.1101/2022.07.30.22278161 and published here https://www.opensafely.org/research/2022/covid-mortality-changes-over-time/**
7. What do carers experience when caring for someone with COVID-19?	Throughout the pandemic carers have reported their great concerns at inadvertently being a source of infection for their loved ones who are at risk. This anxiety is compounded when they are not able to distance from them because of their caring responsibilities. We have heard from carers who have given up their employment (particularly public facing roles) in order to protect their family members. Availability of effective treatment can reduce some of this impact. A positive Covid test in someone who is at highest risk generally creates significant anxiety, given the clear messages about risk levels that people have been subject to since the beginning of the pandemic. Carers often put their own health at risk in providing care for family members with Covid. In addition, because of the sometimes complex routes to securing treatments advocating for a vulnerable family can be time consuming and cause all sorts of stress for the carer. There is no clear path to support for a carer to take an infected loved one to hospital. We heard from carers through our Covid experience surveys about their anxieties and how some gave up their jobs or moved out to protect their vulnerable family members.
Interaction with underlying conditions 8. For people with underlying conditions (for example cancers, autoimmune disorders): • If applicable, how has living with COVID-19 affected their condition?	Kidney Care UK does not have data on how living with Covid-19 has affected the kidney health of the people we support, although we have received advice from clinicians that among people who are already close to needing dialysis, it might be that being sufficiently ill with Covid-19 to need a hospital admission means that they have to start dialysis sooner than they otherwise would have. People receiving in centre dialysis who test positive for Covid have had to receive dialysis in isolation to avoid passing the virus to staff and fellow patients. This has impacted the resources of dialysis units and also been a challenge for patients. This is particularly the case for patients who have had to travel to a different dialysis unit because their usual unit does not have the capacity to provide dialysis in isolation. This has normally meant longer travel times are added to an already onerous schedule of dialysis, which is generally three days a week for an

• If applicable, how has the normal treatment pathway for their condition been affected? (For example, cancer treatment options, regularity of assessments, accessibility issues related to treatments)	average of four hours at a time even without travel time. They also have to go on separate patient transport which can introduce further delays.
Short term versus long term 9. For the people you represent who have tested positive for COVID-19, on average, how long did their symptoms last for? a) Did anyone have any long-term effects from COVID-19? Approximately what proportion does this represent? b) If yes, • What were they? (for example physical and mental impacts, impact on ability to work)	We do not have any robust data on the length of symptoms. We have received numerous reports from people with kidney disease who have experienced symptoms over a long period of time, including tiredness, confusion, problems with smell and taste and breathlessness.

• On average, how long did the effects last for? • What treatments did they need for the long-term effects of COVID-19?	
Current treatment for COVID-19 in the NHS	
10. What do patients or carers think of current treatments and care available in the NHS? - for preventing severe COVID-19 in people with high risk of hospitalisation - for treating people in hospital with severe COVID-19	Given the high risk posed by Covid to people with kidney disease, availability of effective treatments has been extremely important to the people we support. This is particularly the case for the treatments that can be given in the community which can prevent progression to severe Covid. Having lived through many months of anxiety brought on by the risk of severe illness and death, the availability of these treatments has provided some reassurance. We have heard from a number of patients who have used the treatments and found their Covid symptoms have resolved quite quickly. We have not heard reports of significant side effects. There has been concern about being able to access the treatments within the optimum timeframe, given the method of access is fairly complex. We discuss this elsewhere. There is certainly a strong feeling expressed by patients that people do not not to contract Covid in the first place and the majority of people with kidney disease would prefer access to preventative treatments as a first option, to reduce the likelihood of having to rely on the current treatments and care, of kidney damage and of long Covid. Further data from the Open Safely database points to the fact that if we look at transplant recipients/people with kidney disease we can see that only 29% of them received treatments. As these are very likely to be eligible people (in particular those with transplants who are all immunosuppressed) we would like to understand more about what the problem is. It can also be seen that the proportion of people in care homes (just 6%) and of people of Black (10%) or Asian ethnicity (15%) receiving these treatments is also lower than for those of White ethnicity (18% overall). So far, this variation is unexplained. https://reports.opensafely.org/reports/antivirals-and-nmabs-for-non-hospitalised-covid-19-patients-coverage-report/

11. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?	A number of the drugs cannot be used by people with kidney disease or transplants, because their kidney function is too low or they interact with commonly prescribed drugs. Particularly given the evidence that people with kidney disease and those who are immunosuppressed are among those at highest risk, it is important that they can access the treatments that they *are* able to take. Remdesivir cannot be used in patients with an eGFR <30mls/min not on haemodialysis. Paxlovid is not recommended for those with CKD stage 4 and 5 or those on dialysis due to lack of information on dosing; and contra-indicated in those with solid organ transplants due to drug interactions. Baricitinib is not recommended for those with an eGFR <30mls/min
12. What impact does having these drugs available in the NHS have on your community?	See section 10 comments on the availability of these drugs going some way to reducing anxiety, particularly amongst those for whom the vaccines are less effective. Although the anxiety about the risks of Covid have not gone away, having systems in place which can provide access to these drugs provides some reassurance for people. However we have heard regularly from people who are extremely worried that they cannot get their treatments within the first 5 days of the infection and that this happens particularly at weekends. The level of knowledge of Covid treatments is extremely variable in healthcare professionals and communications are frequently poor. **Uptake of Sotrovimab for prevention of severe COVID-19 and its safety in the community in England** https://www.medrxiv.org/content/10.1101/2022.08.17.22278893v1 This study shows (again) the variability of access to the Covid treatments, in this case, Sotrovimab. **QCovid 4 - Predicting risk of death or hospitalisation from COVID-19 in adults testing positive for SARS-CoV-2 infection during the Omicron wave in England** https://www.medrxiv.org/content/10.1101/2022.08.13.22278733v1

	And this QCovid4 study highlights the greater risk for, among others, kidney transplant recipients at the highest rates of mortality. Its conclusion states "The algorithm is modelled from data during the UK's Omicron wave now includes vaccination dose and prior SARS-CoV-2 infection and predicts COVID-19 mortality among people with a positive test. It has excellent performance and could be used for targeting COVID-19 vaccination and therapeutics."
13. Is there an unmet need for patients with this condition in relation to therapies for treating COVID-19? Are there any key subgroups of patients we should consider?	A clear unmet need is access to preventative treatment amongst people who are less likely to gain strong protection from vaccines. In terms of the therapies for treating Covid, some people with kidney disease have found accessing the treatments challenging. OpenSafely data shows of those kidney patients eligible for treatment just 29% received it. This is observational data so we cannot be sure what explains this low proportion. However, coupled with the reports we receive from patients about challenges in accessing the treatments in time we believe it is important to investigate. Barriers to access may be particularly acute for some subgroups. The proportion of people in care homes (just 6%) and of people of Black (10%) or Asian ethnicity (15%) receiving these treatments is also lower than for those of White ethnicity (18% overall). https://reports.opensafely.org/reports/antivirals-and-nmabs-for-non-hospitalised-covid-19-patients-coverage-report/ This is unexplained and is echoed in other papers e.g. from the QCovid team
Hospital and community treatment settings 14. For those people that you represent who were hospitalised due to COVID-19	We do not have data to answer question 14. 15. The experience of people receiving treatment in the community has varied, with some being contacted and provided with medication in just a couple of days. Other people have had to make multiple phone calls and wait. Challenges have been lack of knowledge of how to access the treatments among GPs, 119 or renal units. Some people have experienced delays which have taken them outside the short treatment window. Some concern about how to travel to hospital, particularly with cost of living concerns.

• At what point after being diagnosed with COVID-19 did they receive any form of treatment? • What did their treatment pathway look like? • How long did they spend in hospital? If they had an underlying condition how did this impact the condition? 15. For the people you represent that had treatments for COVID-19 in <u>community settings</u>: • At what point after being diagnosed with COVID-19 did they receive any form of treatment from the NHS? • What did their treatment pathway look like?	Initially some people expressed a preference for receiving tablets but and there has been concern about how to travel to hospital, particularly given their illness and also cost of living concerns. However, optimum efficacy of treatment is clearly important and kidney doctors have advised us they recommend Sotrovimab in light of reports of low effectiveness for Molnupiravir and contra-indications for Paxlovid. We have also heard from many patients that they would rather receive better preventative treatment such as Evusheld.

• Was there a preference for receiving tablets versus treatment with other administration methods (for example intravenously) • Can you tell us a bit about their experience of accessing these treatments? (for example travelling to clinics/outpatient settings while testing positive for COVID-19) • Were there any issues with accessing these treatments?	
Patient population	
16. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	The people in this group, as already defined by the NHS here https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report/defining-the-highest-risk-clinical-subgroups-upon-community-infection-with-sars-cov-2-when-considering-the-use-of-neutralising-monoclonal-antibodies

17. For the people you represent, what do they think about the definition of 'high risk' used to determine access to treatments for preventing severe COVID-19. • Does the definition exclude any key 'high risk' patient groups?	No comment
Equality	
18. Are there any potential equality issues that should be taken into account when considering COVID-19 and the available therapies?	Challenges with accessing treatment may create equality issues. It is not a straightforward process of contacting a GP to report illness and access a prescription. Some patients have found they have had to make multiple phone calls in order to access treatment and have had to be quite determined. People who are less able to advocate for themselves may find it more difficult to get the treatment they need. There was a serious problem for patients trying to access their 3rd Covid vaccination and some trust in the system was lost as a consequence – see our short survey results https://www.kidneycareuk.org/news-and-campaigns/news/continued-confusion-leaves-inexcusable-exposure-risk-thousands-kidney-patients/
Other issues	
19. Are there any other issues that you would like the committee to consider?	

Key messages
20. In up to 5 bullet points, please summarise the key messages of your submission: • The Covid pandemic has had a huge impact on people living with kidney disease, who have been among those most at risk of severe illness and dying. OpenSafely data shows this risk has reduced far less among with kidney disease than those without. • While the rest of population are being encouraged to live with Covid, many people with kidney disease continue to feel extremely anxious and restrict their day-to-day activities to reduce their risk from the virus. • People with kidney disease have welcomed access to treatments to reduce the risk of severe disease and death. • There have been challenges in accessing treatments for some, who have found it difficult to find information and have had to be quite determined in order to get the treatment within the short window that they are recommended. • There is unexplained variation in access to the Covid treatments, with it being lower in certain groups, such as those in care homes and those in black and mixed communities. • Many people with kidney disease feel strongly about access to a preventative treatment • Many of the current Covid therapeutics drugs are not suitable for people with kidney disease and kidney transplants. It is important that this groups of high-risk patients can access the most effective treatments that are suitable for them.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Long Covid Kids
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Charity supporting children and parents of children with Long Covid/Post COVID-19 syndrome, and raising awareness, based in the UK. Approximately 10,000 members,
4b. Has the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	no
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

5. How did you gather information about the experiences of patients and carers to include in your submission?	From personal experiences shared in the Long Covid Kids support groups and collected over the last year from conversations and support meetings with families and children, and our own personal experiences of COVID-19 infection in ourselves and children.
Living with COVID-19	
6. Please tell us what is it like for patients you support who have tested positive for COVID-19?	The severity of covid-19 infection varies between children, we have a spectrum from children who have ended up in intensive care with PIMS to those who had only a mild cough initially but have been left with life changing post COVID-19 symptoms, fatigue, POTS (postural orthostatic tachycardia syndrome) alteration to cognitive function, mental state/behaviour and pain to name the most common. Children are affected in all the same ways has adults but with the added risks of PIMS and PANS and difficulty in expressing how they feel. Children as young as 2yrs old are complaining of sore legs, fatigue, headache, and parents are noticing significant personality and behaviours changes after a COVID-19 infection. Children are struggling to attend school, from those who sleep 20 hrs a day, and struggle to even get out of bed, to those who manage to attend school a couple of hours a day but spend the rest of the time exhausted, sleeping, in bed, finding it difficult to speak or communicate because of fatigue and cognitive impairment. To those who are getting back to previous function but still struggle with symptoms. This is a dramatic change in the childrens' lives, stories are frequently shared of children who were competitive swimmers, dancers, always active, being kids, running around, and who now struggle to stand because they get pain, fatigue and their hearts race. These children are facing a significant change in their ability to be kids, to play with friends, to learn, to be independent. Young people are worried and concerned that subsequent infections will worsen symptoms, set back any improvements and cause further damage/Post COVID-19 symptoms. For the reason that repeated infections seem to have potential for further damage and symptom worsening.
7. What do carers experience when caring for someone with COVID-19?	The overwhelming experience is of frustration and fear, of trying to seek help for their child but finding people do not believe that Covid-19 can be serious for children. It causes physical body and brain issues, similar to encephalitis, affecting children's focus, cognition and personality. They face a medical system which at times can be supportive, listen to the concerns and understand and accept that the child has changed physically/mentally during or after COVIID-19 infection. But unfortunately at the other side frequently symptoms are dismissed, and concerns are put down to anxiety, instead of the physical changes that a parent can see in their child, which understandably makes them seek help for their child.

	They have to take time off work to care for the young person, it can affect their personal life, careers and finances significantly. For those with Post COVID-19 syndrome a subsequent infection can be worrying and cause worsening of symptoms. For example a child who initially was left with dizziness following the first infection and had worked out how to manage and be at school with that, developed vomiting and headaches following the second infection. Carers are worried and concerned that subsequent infections will worsen symptoms, set back any improvements in their children and cause further damage.
Interaction with underlying conditions 8. For people with underlying conditions (for example cancers, autoimmune disorders): ● If applicable, how has living with COVID-19 affected their condition? ● If applicable, how has the normal treatment pathway for their condition been affected? (For example, cancer treatment options, regularity of assessments, accessibility issues related to treatments)	Relevant to this appraisal is for children who have Long Covid is the risk that their symptoms will worsen with a subsequent COVID-19 infection. They should they be considered as having an underlying conditions and therefore get antivirals. There is an increasing body of published evidence demonstrating a maladaptive immune response to SARS-Cov-2 infection in those with Long Covid and this includes aberrant innate immune response, non-classical monocytes and T-cell (CD4 and CD8 effector cell) exhaustion as well as high levels of proinflammatory cytokines . So in summary - Covid 19 infection triggers maladaptive immune response which triggers inflammation which triggers endothelitis (vascular inflammation everywhere in the body but probably worse in the capillary vascular beds) which triggers platelets activation and activation of the coagulation cascade which triggers fibrin amyloid microclots which are difficult to break down, which get trapped in capillary vascular beds, which causes 1) multi organ hypoperfusion and contributes to the symptoms of long Covid and 2) May increase local microvascular inflammation which compromises capillary endothelial protective barrier and allows inflammation of the brain and other organs. This is shown in the cases of children and young people as well as adults who are developing severe problems as described previously, which are appearing to worsen in subsequent infections for significant numbers. The only way to prevent Long Covid is to not catch COVID-19, those who already have POST COVID-19 syndrome are therefore immunocompromised. All of this above is important because it explains why: 1) Both children and adults with Long Covid are immunocompromised (maladaptive immune response and T cell exhaustion) and therefore should be treated as high risk, medically vulnerable and offered antivirals as soon as they test positive for repeat Covid infection
Short term versus long term	On average at least a year, with significant number still ongoing at 2 years since their first infection.

9. For the people you represent who have tested positive for COVID-19, on average, how long did their symptoms last for? a) Did anyone have any long-term effects from COVID-19? Approximately what proportion does this represent? b) If yes, ● What were they? (for example physical and mental impacts, impact on ability to work) ● On average, how long did the effects last for? ● What treatments did they need for the long-term effects of COVID-19?	Currently the data shows over 31,000 children 2-16 with symptoms at least 12 months and 149,000 with symptoms lasting over 4 weeks in 2-16 year olds. Approximately 100% of people in the Long Covid Kids support group have suffered with long-term affects following covid-19 infection. The effects of Long covid are Affecting ability to attend school/nursery, take exams, meeting with friends, work, to be a child and play and socialise, not being able to attend clubs etc Physical – Pots Fatigue, Rashes, MCAS, new allergies, autoimmune conditions (ie Diabetes mellitus) Pain, fatigue, insomnia, hypersomnolence, GI- bloating, diarrhoea, abdominal pain, vomiting, Brain- headache, vertigo, nausea, lightheaded, change in vision, change in smell, loss of sensation, loss of proprioception, reduced cognitive function, personality changes, tiredness Nervous system- POTs, feeling anxious due to symptoms, flight or fight mode “stuck on”, loss of sensation to pain/heat/proprioception. Muscle- weakness, pain, fatigue following activity in an abnormal way – 24-48hrs later, more than would be expected, or struggling to do activities used to due to fatigue. This is all acute in onset and not due to deconditioning. Significant numbers have symptoms lasting over a year, majority at least 6 months. Treatments – currently few treatments are available, some have managed to get medication to treat: MCAS- antihistamines – H1 and H2 being most effective combinations, some Medication for POTs- b-blockers, fluids, salt, PIMS have received treatment in ICU etc and then rehab and support after. The majority of children we support were never in hospital with their COVID-19 infection and, those between the ages 16-18 have struggled to get any support as they fall between children and adult services. Poor treatment offers have included CBT and graded exercise which goes against the NICE guidance on post viral fatigue, (CFS). And has not helped.

	Pacing and support from the paediatric team/school where the young person is listened to, and supported with reduced hours/walking/rest places available, use of wheelchairs/aids has been the most effective. Antivirals have not been tried in this group, although with emerging evidence that there might be persistence of COVID-19 in the gut, could the drugs being considered here be used for those who continue to have symptoms and continue to potentially have therefore COVID-19 infection, meaning they may fall under the scope of this guidance?
Current treatment for COVID-19 in the NHS	
10. What do patients or carers think of current treatments and care available in the NHS? - for preventing severe COVID-19 in people with high risk of hospitalisation - for treating people in hospital with severe COVID-19	It is variable, there is a “postcode lottery” as to whether there are services available and the approach of those services. Children, young people and adults are all missing out on antivirals and treatment for subsequent infections as they are currently not considered high risk,
11. How do the COVID-19 treatments being offered interact with your community’s disease area? Are there any contra-indications?	Currently the community of those with Long covid/post covid syndrome is excluded from the treatment groups for acute Covid-19 symptoms. Given those with Post Covid Syndrome have high morbidity and Covid-19 infection has already caused a significant effect on quality of life and future quality of life due to disruption of education and normal childhood development in the LC community they should be included in the group at significant risk of harm from a further COVID-19 infection. Also we the emerging evidence that Covid-19 virus is still replicating in the gut of people with Post covid syndrome, they would therefore be considered as still being infected and should be included in an evaluation of the benefits of antivirals and the other treatments in this appraisal.

12.What impact does having these drugs available in the NHS have on your community?	
13. Is there an unmet need for patients with this condition in relation to therapies for treating COVID-19? Are there any key subgroups of patients we should consider?	Yes, there is a lack of treatments for COVID-19 in children and those who have developed Post COVID-19 Syndrome. Currently they are not treated when they contract a second COVID-19 infection even though the first has caused significant morbidity, putting them at risk in further infections and for all the reasons explained above. Patients with Post COVID-19 Syndrome should be considered for a trial of antivirals and other treatment options if persistence of virus in those with Post Covid Syndrome is possible.
Hospital and community treatment settings 14. For those people that you represent who were <u>hospitalised</u> due to COVID-19 ● At what point after being diagnosed with COVID-19 did they receive any form of treatment? ● treatment with other administration methods (for example intravenously	For a majority if was supportive care, they did not receive antivirals or antibodies and PIMS diagnosis was retrospective. Some received corticosteroids. Most who were hospitalised it happened 2-6 weeks after the start of the infection with COVID=19. Some with respiratory symptoms but a significant number with PIMS. For example a 7 year old who had mild symptoms and seemed to recover well, then four weeks later developed a sudden high fever with a rash, cracked lips, headache an nausea, she was difficult to wake and unable to walk to the bathroom. Her family called 111 who advised multiple times she did not need to be seen in the hospital despite her being desperately unwell. On day 8 the fever broke and she began to recover slowly. She has been given a backdated clinical diagnosis of PIMS, Although those symptoms have improved she was left with overwhelming fatigue, severe sleep disturbance, swollen glands, abdominal pains, headaches and peeling skin, tics, rash which

What did their treatment pathway look like? ● How long did they spend in hospital? If they had an underlying condition how did this impact the condition? 15. For the people you represent that had treatments for COVID-19 in <u>community settings</u>: ● At what point after being diagnosed with COVID-19 did they receive any form of treatment from the NHS? ● What did their treatment pathway look like? ● Was there a preference for receiving tablets versus) ● Can you tell us a bit about their experience of accessing these treatments? (for example travelling to clinics/outpatient settings while testing positive for COVID-19) ● Were there any issues with accessing these treatments?	continued, sensitivity to light, noise. She was diagnosed with PANS (Paediatric, acute onset neuropsychiatric syndrome). She was unable to return to school, In July 2021 she had a second Covid-19 infection and was unwell with fever and malaise, one recover from that her Long Covid symptoms were worse and so severe that she struggled to walk at all and has been using a wheelchair. Her first infection with PIMS should have been enough for her to be marked as high risk from COVID-19 infection, if she had had treatment for her second acute COVID-19 infection she may not have ended up in a wheelchair. For most of the people we represent their COVID-19 treatment was for Post COVID-19 syndrome. Some are nearly 2 years since first suspected infection and still awaiting to be seen. The pathways have varied in different areas but there is currently no specific treatment for Post COVID-19 syndrome, which is why preventing infection/repeated infection is so important for the population and our LC Kids population. Of our Long Covid Kids population very few have received antivirals and they have received them due to another previous condition. The majority were fit and well prior to the COVID-19 infection which cause their Post COVID-19 Syndrome.

Patient population	
16. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	Those with Post COVID-19 Syndrome currently are proven to come to harm with COVID-19 infection, therefore these treatments to reduce their risk of harm from subsequent infections are vital (prevention, with filters, masks etc would reduce risk significantly). Those with Post COVID-19 syndrome are increasingly likely to still have virus in their bodies, and a trial of these technologies to reduce carriage and infection burden could prove to be a treatment for this debilitating condition. For example, there is a feline coronavirus infection called FIP that causes a necrotising thrombotic vasculitis in cats which is treated and cured with a three month course of antivirals, most of those with Long Covid would be keen for a trial of treatment.
17. For the people you represent, what do they think about the definition of 'high risk' used to determine access to treatments for preventing severe COVID-19. ● Does the definition exclude any key 'high risk' patient groups?	High risk should include those with Post COVID-19 Syndrome because they have been shown to be at high risk of life changing affects, and harm, especially in children where education and important childhood development is impacted. Also those who are unable to have the vaccine due to reactions to the vaccines, especially those with Post COVID-19 Syndrome and post vaccine Syndrome.
Equality	
18. Are there any potential equality issues that should be taken into account when considering COVID-19 and the available therapies?	

Other issues	
19. Are there any other issues that you would like the committee to consider?	Does any of the evidence show that any of these treatments were given to those with Long Covid? Did it improve their symptoms? Was it given for long enough? Please can NICE recommend investing in prevention (such as air filtration in schools) as well as treatment? Children would be protected better and in turn would better protect vulnerable household members from catching Covid from them

Key messages

20. In up to 5 bullet points, please summarise the key messages of your submission:

- **Those with Post COVID-19 syndrome should be considered high risk.** Long Covid has a significant debilitating effect on children and young people, it affects their immune system and they have proven harm from COVID-19 if they have Post COVID-19 Syndrome. Therefore, those with Long Covid/Post COVID-19 Syndrome should be considered high risk of harm from a future COVID-19 infection and be offered treatment options as soon as a positive test or suspected infection.
- New evidence shows COVID-19 infection persisting in the guts of people with Post COVID-19 Syndrome and therefore they should receive a trial of treatment antiviral/antibodies to clear their persisting acute infection.
- There is currently a highly variable service across the country in the treatments, assessment of children with acute COVID-19 causing atypical presentations- specifically brain and nervous system, there should be a high suspicion of COVID-19 infection and rapid treatment.
- There is a problem with the 'list' of people who are eligible for antivirals, the mechanism for adding people who have e.g. damage from a previous infection (Long Covid) needs to be clear and to be publicised. This needs to be done to avoid the difficulty and frustration of ill people trying to get antivirals and receiving a refusal.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Long Covid SOS
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Long Covid SOS is a Charity registered in England and Wales. We are a small body with 4 Trustees and 5 volunteers. We are not a membership organisation, instead we interact with our community through social media platforms, including Twitter and Instagram, and through our website to which people can subscribe and also contact us for further information.
4b. Has the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	Through interactions with those with Long Covid through our social media channels, direct messages to us through our website and through our links with the Body Politic Slack support group. Due to the time and resources constraints, we did not contact a qualitative survey to further inform our submission.
Living with COVID-19	
6. Please tell us what is it like for patients you support who have tested positive for COVID-19?	Testing positive for Covid-19 can be a worrying thing within the Long Covid community that we serve. Being in the part of the population who were left with long-lasting symptoms from a previous infection, this can be a complicated process for people. They can have concerns about whether they will go back to their previous baseline or not. Whether there will be a further deterioration in their health. Also, as they aren't within the group judged to be ''at severe risk of hospitalisation', they are not eligible to receive antivirals (unless they have a previous condition that falls within this criteria). There are many in the community that question the reasoning for this, as in some ways Long Covid could be seen to be a maladaptive response to a previous Covid infection. As one of the theories for the cause of Long Covid is viral persistence within the body, this does not make sense to our community. They are impatient to have medications that will help them return to a higher quality of life. Unfortunately, we seem to be in a situation where research on the effects of antivirals for the prevention (in the form of long term follow up studies) and treatment of Long Covid is not being performed. This leads to an evidence gap. There is also evidence that Covid-19 may have a cumulative health impact. This potentially means that those with Long Covid are at increased risk compared to others within the population.

7. What do carers experience when caring for someone with COVID-19?	We do not hear often from carers of those with Long Covid. Those carers who do appear tend to be those where the Long Covid sufferer sadly took their own life due to the impact on their health and lack of support or treatments to improve their situation. Some carers try to get information and find ways to care/ support the Long Covid sufferer, especially in the case of reinfection. Sometimes it appears in the lack of biomarkers, healthcare professionals can be dismissive of the very real symptoms presented by people. This can lead to feelings of powerlessness.
Interaction with underlying conditions 8. For people with underlying conditions (for example cancers, autoimmune disorders): ● If applicable, how has living with COVID-19 affected their condition? ● If applicable, how has the normal treatment pathway for their condition been affected? (For example, cancer treatment options, regularity of assessments, accessibility issues related to treatments)	N/A
Short term versus long term	We represent people who are already experiencing long term symptoms from a previous Covid-19 infection. There are still significant numbers still reporting symptoms 2.5 years later, originally having their first Covid-19 infection before the vaccines were available or pre vaccination rollout

9. For the people you represent who have tested positive for COVID-19, on average, how long did their symptoms last for? a) Did anyone have any long-term effects from COVID-19? Approximately what proportion does this represent? b) If yes, ● What were they? (for example physical and mental impacts, impact on ability to work) ● On average, how long did the effects last for? ● What treatments did they need for the long-term effects of COVID-19?	to their age group. Some people do recover or at least to an extent to drop out of the communities. The potential to determine recovery trajectory would be of interest to our community. Long Covid has been reported in all adult age groups with the highest proportion being in those in the younger age groups. This is a different profile to those that are hospitalised, yet a lot of extrapolations are being made on the basis of research in those that have been hospitalised and/ or died. 100% of our community have experienced long term effects from Covid-19. Long Covid has been demonstrated to have both physical and mental impacts as well as impacts on the ability to work. Symptoms have been demonstrated in the cardiovascular systems (vascular inflammation, abnormal blood clotting and POTs), neurological (cognitive , proprioception, temperature regulation issues), fatigue, pain, loss of taste and smell, breathing difficulties, sexual dysfunction and effects on periods, hair loss, gastrointestinal, muscle weakness sometimes leading to diagnosis of Ehlers-Danlos syndromes, autoimmune effects such as rashes and diagnosis of conditions such as diabetes, as well as anxiety and depression. The relapsing and remitting nature of Long Covid means that people can experience difficulties participating in day to day life and being able to work (people are being released from the workforce on the grounds of ill-health and their employers not being able to accommodate reasonable adjustments). The length of the effects is hard to determine due to the relapsing and remitting nature Rehabilitation and self-management techniques for breathing difficulties, pain and pacing. Some patients are being referred to existing pain and ME/CFS clinics.

	Some treatments have been used to manage individual symptoms such as anti-histamines for the autoimmune effects, beta blockers for elevated heart rates, ivabradine (off label POTs), Low dose Naltrexone (LDN) to boost immunity, vitamin B2 injections, vitamin D. Members of the community are also travelling/paying for treatments that do not have an evidence base such as Heparin induced extracorporeal LDL precipitation or HELP apheresis and InceIDX molecular diagnostics panels with accompanying treatment regime. This is of serious concern as these treatments are not without risk. There is also the issue of health inequalities as not everyone can pay for treatments. CBT and referrals to IAPT is the most consistently offered treatment.
Current treatment for COVID-19 in the NHS	
10. What do patients or carers think of current treatments and care available in the NHS? - for preventing severe COVID-19 in people with high risk of hospitalisation - for treating people in hospital with severe COVID-19	There is a sense of anger and frustration at the current lack of treatments on offer through the NHS, for those who have developed Long Covid through a previous infection. As well as the fact that they are not seen as being at enhanced risk of deleterious effects from subsequent infections.
11. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?	Covid-19 treatments are not currently being offered to our community unless they qualify for treatment through a comorbidity.

12. What impact does having these drugs available in the NHS have on your community?	N/A
13. Is there an unmet need for patients with this condition in relation to therapies for treating COVID-19? Are there any key subgroups of patients we should consider?	Yes. Research needs to be conducted with the current antivirals and other treatments for Covid-19 to determine if they can improve the situation for those with Long Covid. Even if it is discovered that it is only a subpopulation within those living with Long Covid that can be treated this way, the theory of viral persistence needs to be researched and a treatment discovered to recover their lost health. Enough evidence exists from other conditions from previous infections such as Lyme disease, Helicobacter pylori and others that are not adequately cleared from some people can be treated through medicines targeting the infectious agent. Research has shown that Long Covid may be an insufficient or maladapted immune response to a Covid-19 infection, so there may be a way to determine the best Long Covid group to research this within.
Hospital and community treatment settings 14. For those people that you represent who were hospitalised due to COVID-19 ● At what point after being diagnosed with COVID-19 did they receive any form of treatment? ● What did their treatment pathway look like?	Treatments are not offered routinely for the community we represent. Access to the Long Covid clinics differs depending on the waiting lists in the region the person resides in and treatments offered also seem to have a postcode lottery depending on the way that they are set up

● How long did they spend in hospital? If they had an underlying condition how did this impact the condition? 15. For the people you represent that had treatments for COVID-19 in <u>community settings</u>: ● At what point after being diagnosed with COVID-19 did they receive any form of treatment from the NHS? ● What did their treatment pathway look like? ● Was there a preference for receiving tablets versus treatment with other administration methods (for example intravenously) ● Can you tell us a bit about their experience of accessing these treatments? (for example travelling to clinics/outpatient settings while testing positive for COVID-19)	

• Were there any issues with accessing these treatments?	
Patient population	
16. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	N/A
17. For the people you represent, what do they think about the definition of 'high risk' used to determine access to treatments for preventing severe COVID-19. • Does the definition exclude any key 'high risk' patient groups?	We would make the case for those with Long Covid to be deemed as a high risk population to have severe effects from Covid-19. We are aware that the current definition is the risk of severe covid-19 infection leading to hospitalisation and death. There is the scenario that this may not adequately capture the long term healthcare needs and cost to the wider economy Subsequent reinfections may have an accumulative risk within this group and this will not be understood until there is research into this.

Equality	
18. Are there any potential equality issues that should be taken into account when considering COVID-19 and the available therapies?	The proportional representation from ethnic minorities within the Long Covid clinics seems to be lower than that reported in the literature.
Other issues	
19. Are there any other issues that you would like the committee to consider?	
Key messages	

20. In up to 5 bullet points, please summarise the key messages of your submission:

- No research has been conducted on the possible effects of Covid-19 treatments on treating Long Covid. This evidence gap should be addressed as assumptions are being made on the basis of the hospitalised population which may have a different profile. Long term ill health in people and costs to healthcare systems/ people retiring/ reducing hours through ill-health may be higher over subsequent years in those in the community.
- Members of the Long Covid community feel at higher risk of subsequent Covid-19 infections and it should be determined if they do have an increased risk from further Covid-19 infections
- There is a pressing need to look at viral persistence within those with Long Covid and whether this can be treated with the acute Covid-19 medicines.
- Consideration that those with Long Covid should be treated as an at risk population

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Therapeutics for people with COVID-19 [ID4038]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	LUPUS UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	LUPUS UK is the only national registered charity supporting people affected by lupus. The charity produces high-quality information for patients, carers, employers and clinicians. Through volunteer-led regional groups the charity provides support group meetings and raises awareness of the disease within local communities. LUPUS UK also funds medical research and Specialist Lupus Nurses in UK hospitals. LUPUS UK receives most of its income from public donations, fundraising events, and legacies. Additional funds are secured as grants from charitable trusts and foundations, with a small amount from companies. The charity has approximately 4,000 subscribed members, however, we are here for all people affected by lupus and therefore engage with many more people with the disease in the UK.
4b. Has the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	LUPUS UK has received the following funding from pharmaceutical companies in the past 12 months: • £5,000 of restricted funding from Janssen Pharmaceuticals in January 2022. This funding was to assist LUPUS UK in the development of an initiative to engage more patients in research, particularly covering the costs of a new CRM database and staff time.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• LUPUS UK conducted an online survey which was shared with members and supporters of the charity from 16/08/2022 to 23/08/2022. The survey questions were based on those found within this submission template to help guide our organisation's contribution. The survey received a total of 204 responses. • RAIRDA conducted an online survey between 23/03/2022 and 07/04/2022 about access to COVID-19 vaccines and treatments. The survey received a total of 526 responses. We have used the summary of findings in preparing our submission. https://rairda.org/2022/06/21/survey-shows-poor-communication-around-covid-19-vaccine-and-treatments-for-people-with-rheumatic-conditions/ • The RECORDER Project studied COVID-19 infection, hospital admission and death amongst people with rare autoimmune rheumatic diseases in England from 01/03/2020 to 31/07/2020. We referred to their findings in preparing our submission. https://www.medrxiv.org/content/10.1101/2021.08.17.21260846v3 The final draft of the submission was circulated to LUPUS UK's Board of Trustees and a small selection of Expert Patients to review and provide additional comments.
Living with COVID-19	
6. Please tell us what is it like for patients you support who have tested positive for COVID-19?	A review of cases included in the COVID-19 Global Rheumatology Alliance registry from March 2020 to June 2021 (**HERE**) found that most individuals (69.9%) with systemic lupus erythematosus (SLE) were not hospitalised. The significant factors contributing to risk of hospitalisation included older age, male sex, chronic renal insufficiency or end-stage renal disease, hypertension/cardiovascular disease, and the number of other comorbidities. In addition, those who were not being treated for their SLE, or had moderate or high SLE disease activity, also experienced more severe outcomes. According to a RECORDER analysis of 168,680 people living in England with a rare autoimmune rheumatic disease (such as lupus), of whom 1874 (1.11%) had a positive COVID-19 PCR test between 01/03/2020 and 31/07/2020, 713 (0.42%) people died with COVID-19 on their death certificate and the age-sex-standardised mortality rate for

	COVID-19-related death was 2.41 (2.30 – 2.53) times higher than in the general population. There was no evidence of an increase in deaths from other causes in this population at the time. (**HERE**) A review of literature about COVID-19 in people with SLE (**HERE**) identified various reports suggesting COVID-19 may worsen SLE symptoms. This is challenging to ascertain without long-term studies ruling out other important factors such as lack of medical care, difficulty continuing SLE medications and additional psychosocial stressors of the pandemic. However, this finding was supported by patient reports of flaring lupus symptoms in our online survey. LUPUS UK surveyed people with lupus about their experiences of having COVID-19. Of the 204 respondents, 91 reported that they had ever had COVID-19. The most commonly reported symptoms were fatigue, sore throat and flu-like symptoms. A small selection of reported experiences are below: • *"Started with extreme fatigue, then very high temperature, sickness, nausea and chills for two days, then slow recovery. I'd been very lucky, according to my consultant, as I had received my booster two weeks earlier."* • *"I've had COVID twice in 2022. First time was awful; didn't get out of bed for nine days – felt like bad flu. Still having breathing issues; took about 12 weeks to fully recover. Second time I just had one really bad day but the tiredness is still there."* • *"Very poorly with it. Joint and muscle pain so severe, could not move. Was given morphine to help me mobilise and manage pain. Headache for days, runny nose, constantly sleepy, not functioning, very low energy levels, unable to do daily tasks at all. Going from bed to sofa and vice versa. COVID flared lupus, and lost muscle strength. Took ages to recover (weeks!)"* • *"Severe sore throat. Intense prolonged headache. Generally unwell, aches and fatigue. Loss of taste and smell."* • *"Hospitalised with double pneumonia and COVID lung changes. Required at home O_2 for two months post discharge as I failed to maintain O_2 levels."* • *"I was very poorly and tested positive over 15 days. First 5 days were the most unwell I have ever felt. I had fluctuating low oxygen levels, pain that no medication helped to ease. It was also a period of high stress trying to access antivirals and determine when to reach out to see if additional treatment was needed. I experienced severe dizziness and loss of taste. For the first 5 days I couldn't rest or sleep because I was in such pain."*
7. What do carers experience when caring for someone with COVID-19?	Many people who care for someone with lupus at high risk from COVID-19 have made significant adjustments to their lifestyle to help protect their loved-one and reduce the chances of them contracting the virus. It can be very scary and stressful if the person they care for contracts COVID-19. In some cases, the carer may also belong to a high risk group and need to balance the needs of the person they care for against their own. Some carers express

	feelings of guilt (if they suspect they could have brought the virus into the home) and anger (often towards the Government for not sufficiently supporting people who remain at high risk from coronavirus). Unfortunately, our online survey only received three responses from people caring for someone else with COVID-19. One of the respondents reported that the person they cared for had symptoms akin to a cold. One respondent wrote about their daughter with lupus who caught COVID-19: • "*Despite all of our best efforts, our immunosuppressed daughter contracted COVID because she had to go into work one day, and despite her wearing high quality masks, because there are no longer any mitigations in place, she was infected. It was absolutely terrifying, our worst nightmare. Fortunately her specialist team accessed sotrovimab for her really quickly, but it didn't seem to neutralise anything. She was very poorly, dropping SATs which we constantly monitored, isolated her at home and double masking in the house. She tested positive for 15 days, had to come off all of her other disease modifying medications to give her immune system a chance to recover, and has now had to go on a high dose of steroids to help get her back on track before resuming her usual treatments."*
Interaction with underlying conditions 8. For people with underlying conditions (for example cancers, autoimmune disorders): • If applicable, how has living with COVID-19 affected their condition? • If applicable, how has the normal treatment pathway for their condition been affected? (For	In our online survey, 96 respondents reported having COVID-19. Of these, approximately 44% said that COVID-19 had affected their lupus with a further 34% saying they were unsure whether the virus had impacted their lupus. Many reported worsened symptoms or flares of their lupus and this frequently required additional treatment, such as increased corticosteroids. • *"I have been left with more painful joints and extremely tired."* • *"COVID put me into a flare that lasted for four months; limiting the amount I could do and leading to severe fatigue and constant pain in my joints."* • *"COVID triggered my lupus & polymyositis - joint/muscle pain and inability to move due to excruciating joint pain. I was then put on steroids."* • *"I had to stop immunosuppressants for 3 weeks which meant a flare of some of my lupus symptoms."* Of those who responded, approximately 43% indicated that having COVID-19 had disrupted their normal treatment. Some people reported that they were instructed to pause their lupus medications until recovered from COVID-19 and this risked flares of their disease. • *"I had to come off drugs. It caused a lupus flare."* • *"I was unable to restart medication due to having COVID and not being able to repeat bloods or be on immunosuppressant due to infection, which resulted in joint pain and swelling."* • *"Had to stop medication and felt like I was in a flare for circa 2 months despite restarting medication."*

example, cancer treatment options, regularity of assessments, accessibility issues related to treatments)	• *"I was taken off immunosuppressants during antibody treatment. I had a small flare after but it was nothing compared to COVID."* Having COVID-19 also affected other important aspects of people's care, including cancelled routine check-ups, blood monitoring tests and initiation of planned treatments; • *"I had to postpone some medical tests and treatments relating to lupus because I was taking a long time to recover. I was too unwell/fatigued and in pain to attend the appointments."* • *"Cancelled in-hospital consultant appointment due to having COVID-19."* • *"Prevented regular blood monitoring - had to cancel due to COVID."* • *"I had to delay both a Venofer (iron) IV treatment and Zolodronic Acid IV treatment, also dental work."*
Short term versus long term 9. For the people you represent who have tested positive for COVID-19, on average, how long did their symptoms last for? a) Did anyone have any long-term effects from COVID-19? Approximately what proportion does this represent? b) If yes,	Of the 96 survey respondents who had COVID-19, approximately 50% experienced symptoms for 1 to 11 days. Approximately 33% experienced symptoms for 12 to 30 days. The rest of the respondents reported symptoms lasting between one to 12 months, with only one respondent reporting symptoms lasting longer than 12 months. • *"Six weeks later I am still extremely tired; too tired to do anything except essentials and reading."* • *"Multiple rounds of antibiotics, follow-ups for lung damage and 2+ months of at-home oxygen."* • *"Still suffering symptoms. Have been absent from work for 60 days suffering from extreme fatigue and breathlessness. Also affecting sleep."* • *"The acute symptoms of headache, sore throat and POTs flare lasted about 6 days but I have ongoing joint and severe muscle pain which is worse than my usual pain from lupus. Brain fog, memory and cognitive abilities are worse since getting COVID. I have weakness in my legs. I was struggling with lupus MSK symptoms before but was managing. After having COVID, all MSK pain has worsened. Fatigue has also worsened. This has had a detrimental effect on my life as I am less able to do things. I live alone and it has made being independent harder and I do not have as much energy to do things. The energy I had prior to COVID was already limited because of lupus. Basically, COVID made everything more painful and more tiring."* • *"It was mainly the breathing issue that lasted and I just had to take it easy and do shorter walks than usual and build up. No treatment prescribed"*

• What were they? (for example physical and mental impacts, impact on ability to work) • On average, how long did the effects last for? • What treatments did they need for the long-term effects of COVID-19?	
Current treatment for COVID-19 in the NHS	
10. What do patients or carers think of current treatments and care available in the NHS? - for preventing severe COVID-19 in people with high risk of hospitalisation - for treating people in hospital with severe COVID-19	We received some comments expressing frustration and disappointment that the prophylactic preventative treatment Evusheld is not available on the NHS, especially to help prevent severe COVID-19 infection in people who are unlikely to have adequate protection from vaccines: • *"As an immunosuppressed person, I am very disappointed that Evusheld was not made available. As a result I am continuing to 'shield'. From experience, I am not confident I would be able to access treatment in a timely fashion. Although there is a process in place, NHS provision in my area is unreliable."* A significant proportion of people who have accessed treatment for COVID-19 in the community reported satisfaction with the service and believed it helped prevent progression to severe disease: • "*It is efficient and provided fast treatment which was reassuring and probably prevented severe impact on my existing conditions."* • *"Brilliant. My experience was very positive. The last time I had COVID-19 as soon as I reported a positive LFT I was contacted straight away and treated the next day with antibody infusion."*

- *"I felt severely unwell for three days (chesty cough, pain on breathing, temperature, sore throat, swollen glands, fatigue, loss of appetite, muscle aches). I received anti-viral medication (big pink capsules) and within 24 hours my symptoms lessened to more like a heavy cold; much more manageable."*

A common theme in dissatisfied comments was related to delays in being assessed for COVID-19 treatment by the COVID-19 Medicines Delivery Units (CMDU):

- *"It is hit and miss whether you are offered them and can obtain them at the right time."*
- *"I feel there should be an easier way to get the treatment if immune suppressed than having to call then wait up to 48 hours for someone to phone and say yes. I definitely feel the GP should be able to help with COVID treatment and all dispensing pharmacies allowed to make-up prescriptions."*

Another theme from dissatisfied comments was related to poor awareness and understanding of the COVID-19 treatment pathways amongst healthcare professionals. This caused frustration and distress for people trying to navigate their own access to the treatments:

- *"Please consider the impact this virus has had on people who already were at higher risk on infections. We were drip fed fear for two years and told how awful it would be for us to catch it, that we should stay in, that we should get vaccinated, that we shouldn't hug our loved ones, that we are entitled to anti-virals if we get it as it's dangerous and, in the words of the first point of contact when I got COVID, it will stop me from dying! Only then to be told I don't qualify for the anti-virals; I was TERRIFIED my family were TERRIFIED for me! It's unforgivable to do this to people, to put fear into them so much. The guidelines need to be clearer, so the doctors actually understand thoroughly who is eligible across the board. You get passed around like a hot potato at a time when you feel poorly and very frightened for your own life, because you've been told it's something really bad for you because you already have autoimmune disease. Please make it clearer!"*
- *"Ignorance and a lack of understanding from medical professionals/staff is not acceptable at this stage of the pandemic. It is clear we will all have to 'live ' with COVID for the foreseeable future and changes do need to be made. Those of us who need and are entitled to treatments and additional vaccines should not be made to feel difficult, punished or guilty because we have underlying chronic health conditions."*
- *"The most concerning thing is the complete lack of knowledge and understanding of autoimmune conditions and being immunosuppressed - despite showing them/quoting the letter I received. At one stage I was told it was inconsiderate of me to be ill at the weekend and for being a hassle to them because I am eligible for treatment. Even when I was finally having the treatment, the nurse just laughed and said she knew nothing about it - apart from it being expensive and did I really need it."*

One respondent reported significant problems in accessing the treatments when admitted to hospital:

- *"The rule about not giving anti-virals to inpatients needs to be urgently reviewed. I was given a 10% survival chance after getting multiple different pneumonias from COVID (COVID pneumonitis joined by bacterial and fungal then*

	multiple organ involvement). The spinal fluid leak from the coughing caused a lot of brain inflammation and subdural haematomas and structural brain damage. It gave me seizures which has meant a year's driving ban. Almost six months very unwell and some permanent damage, when I am almost certain if they had given me the anti-virals it would haven't have progressed so dangerously and damagingly. Even after having COVID three times and four vaccines, my latest tests showed I'd made no antibodies (I take high dose steroids, rituximab and others). There needs to be an easier pathway and possibly the most vulnerable to have a supply of anti-virals ready so they don't miss the deadline for treatment due to NHS inefficiencies or bank holidays!"
11. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?	Due to the variety of treatments used for lupus and associated comorbidities there is a risk of contra-indications and interactions. As such, a variety of COVID-19 treatments are needed to increase the likelihood of having a suitable option for as many people as possible. A UK population-based study of more than one million people eligible for treatment with sotrovimab in England found that, when slitting the 28-days risk period for hospitalisation into narrower periods, there was an increased risk of hospital admission for systematic lupus erythematosus (IRR 5.15, 95% CI 1.60, 16.60) in the 2-3 days following the treatment (**HERE**).
12. What impact does having these drugs available in the NHS have on your community?	The availability of these treatments in the NHS provides important reassurance to people from our community. As measures to limit the spread of SARS-CoV-2 are lifted, the risk of contracting the virus has increased for many people with lupus. Knowing that treatments are available to help reduce the risk of severe illness from COVID-19 has enabled some people to live a better quality of life and be less isolated than that otherwise might have been. Due to the widespread use of immunosuppressants, corticosteroids and biologic treatments in the management of lupus, many people in our community do not have as much reassurance of protection from the vaccines. As such, the availability of post-exposure treatments is essential. • *"I am grateful for the treatment I received. I had remained shielding and concerned for 28 months until I caught COVID-19 from my son, but knowing I can access treatment and recover if I get it again has made me a bit less concerned and I am shielding less (but still not socialising in crowded indoor settings/other's homes)."* • *"As clinically vulnerable and immunosuppressed, knowing that I will be given priority for treatments should I get COVID has allowed me to stop shielding and return to the office but I still do avoid busy places."* • *"The availability of treatments greatly puts my mind at ease. I feel less scared about contracting COVID knowing that treatments are now available. This means I'm happier going out and about in my daily life."* • *"Knowing that the antiviral medication would be available to me, should I contract COVID again, means that I have become more confident to leave the house and start living my life, carefully again."*

13. Is there an unmet need for patients with this condition in relation to therapies for treating COVID-19? Are there any key subgroups of patients we should consider?	Unfortunately, many people with rare autoimmune rheumatic diseases (including lupus) have been missed when the NHS has been identifying individuals who may be eligible for the COVID-19 therapies. From 23/03/22 to 07/04/22, RAIRDA found that approximately 40% of respondents to their online survey who identified as meeting eligibility criteria had received no correspondence from the NHS to notify them of their eligibility, give instructions on accessing treatments, or provide COVID-19 tests. Of these people, 50% who had contracted COVID-19 reported the process to get referred to a COVID-19 Medicines Delivery Unit (CMDU) to be 'very difficult' (**HERE**). • *"I recently tested positive for COVID and having been classed as CEV I have been very anxious about catching it but have felt reassured knowing that there are antiviral treatments available. So far (I am now on day five) accessing those antivirals is proving almost impossible. I keep being told by the COVID-19 Medicines Delivery Unit that I am on the list for a doctor assessment but it is a very long list and I am not yet near the top."* • *"I was very unwell with COVID-19. I registered my test result in order to access anti-viral treatment but did not receive it due to a late response from the NHS. I developed a chest infection and sinusitis."* Incomplete identification of higher risk individuals has been a recurring problem throughout the COVID-19 pandemic. Some people experienced significant delays in receiving shielding letters and support during the first national lockdown. Later, some people with lupus were denied priority access to COVID-19 vaccinations and most people treated with immunosuppressants had problems accessing a third primary dose of COVID-19 vaccine in autumn 2021. More accurate digital coding is needed for the identification of people with rare autoimmune rheumatic diseases accompanied by enhanced education about eligibility within rare disease cohorts, particularly for primary care services. • *"I think it's a postcode lottery. I was refused the antivirals even though I was sent a letter saying I was to have them. This made me feel extremely frightened & anxious & I do believe I should have been given them, as a relative was given them even though on no medication!"* • *"My GP records were wrong so when I tried to access treatment I was told it wasn't needed. It wasn't until I recovered slightly that I was issued with an apology and told it that I should have received treatment."* • *"I wasn't put on list for treatment until about six weeks after contracting COVID."* A further unmet need is having timely access to the COVID-19 therapeutics following a positive lateral-flow test (LFT). All the treatments have a window of up to 5-7 days following the onset of symptoms to be effective. Unfortunately, due to capacity issues with CMDUs, these treatment windows are not always met. • *"I was very unwell with COVID. I registered my test result in order to access anti-viral treatment but did not receive it due to late response from the NHS. I developed a chest infection and sinusitis."* Lastly, there is a significant unmet need for immunosuppressed/immunocompromised people who are unlikely to have adequate protection from COVID-19 vaccines. The treatments being assessed in this appraisal can be effective in preventing serious COVID-19 infection for many people, but we are aware of some interactions and

	contra-indications which could prevent people from having them. Preventative prophylactic treatments such as tixagevimab–cilgavimab (Evusheld) are needed to address this unmet need. • *"I think we are falling dreadfully behind the support offered in other countries. Not only are treatments like bebtelovimab and Evusheld not yet available, the treatments we do have aren't provided to everyone who needs them quickly enough."*

Hospital and community treatment settings 14. For those people that you represent who were hospitalised due to COVID-19 • At what point after being diagnosed with COVID-19 did they receive any form of treatment? • What did their treatment pathway look like? • How long did they spend in hospital? If they had an underlying condition how did this impact the condition?	Of the 96 respondents in our online survey who had COVID-19, eight were hospitalised. A common theme in their responses was that they were hospitalised to be treated for secondary infections such as pneumonia; • *"I was given dexamethasone and treatment for adrenal crisis, bacterial and fungal pneumonias and meningitis after about 2-3 weeks (later than it should have been given as the hospital was very short staffed on COVID ward)."* • *"7 days after diagnosis antibiotics were prescribed."* The time from onset of symptoms to hospitalisation and treatment ranged between eight hours and seven days. A few respondents provided more detail about their treatment pathway; • *"It was very difficult to get any treatment. I was very poorly could hardly talk as COVID affected my throat and I had to keep calling doctors to get any help."* • *"I was given oral antivirals at home. I then received both infusions and oral medication in hospital together with oxygen."* 50% of respondents who were hospitalised spent between one to seven nights in hospital. 25% of the respondents reported spending more than three weeks in the hospital.

15. For the people you represent that had treatments for COVID-19 in <u>community settings</u>: • At what point after being diagnosed with COVID-19 did they receive any form of treatment from the NHS? • What did their treatment pathway look like? • Was there a preference for receiving tablets versus treatment with other administration methods (for example intravenously) • Can you tell us a bit about their experience of accessing these treatments? (for example travelling to clinics/outpatient	Of the 88 respondents to our survey who had COVID-19 and were not hospitalised, approximately 35% received COVID-19 treatment in the community setting. • 30% received treatment within one day • Approximately 37% received treatment within two to three days • Approximately 27% received treatment within four to six days • Approximately 3% received treatment within seven days and the rest took longer. Many respondents shared details of their treatment pathway, with most expressing no difficulties: • *"I phoned the NHS helpline, then received a call to say I would have a prescription at a chemist seven miles from where I live for COVID treatment."* • *"I was given an anti-viral drug at hospital intravenously. It helped manage COVID very quickly and effectively. I was so thankful after being so poorly with it the first time. The treatment was highly effective and I am grateful to have received it. I did not become totally immobile or debilitated by pain this time round, thanks to the treatment."* • *"I tested positive at 8am. I called 111 at 9am, as advised by my specialist nurse and was called back by a doctor at 10am followed by the CDMU doctor at 12 (all very efficient)! I started the infusion in hospital at 4pm. I was advised that I could not take antivirals as these were contraindicated with some of my regular medicine - so sotrovimab was the only option."* • *"I tested positive on Tuesday evening. I had medication sent to my home late on Wednesday afternoon."* • *"On day 1 I notified the GP at 10am. At 11am the GP said she would refer me for anti-viral treatment. At 1.30pm the consultant called and recommended Paxlovid meds which were delivered 11.30pm that night! I started Paxlovid next morning and started to feel difference within 24 hrs."* Unfortunately, some respondents did report some issues with the treatment pathway, typically relating to delays in getting assessed by the CMDU and needing to be persistent despite feeling unwell: • *"I received notification of a positive PCR test on Friday and was advised I would get a call from a doctor about treatment within 24 hours. That didn't happen. I called 111 as advised on Saturday PM. I was promised a call back and again, it didn't happen. I eventually received a call from a 111 doctor on Sunday evening after I had called 111 again as my symptoms worsening; they gave general advice. Later I received a call from CMDU doctor to confirm eligibility for treatment and was advised that I should hear from someone either the next day (Monday) or Tuesday. I received another call from the CMDU on Monday AM to confirm I'd be offered infusion treatment at local hospital and likely to be that day at short notice. I received IV treatment that lunchtime."* • *"I tested Sunday, and reported to 119, but my records were incorrectly coded despite my efforts to resolve prior to this. I had to have an appointment with the GP by phone on Monday for a referral to get the drugs."*

settings while testing positive for COVID-19) Were there any issues with accessing these treatments?	There was a mixture of responses about ease of access to the treatments. Some reported an excellent service which suited their needs: • *"Prescription was delivered to my home by hospital pharmacy as I could not travel."* • *"Treatment easily accessible at a unit set up on the grounds of a local hospital."* • *"No issues. Private free taxi dropped my medication to my door."* Whilst others reported a range of issues: • *"I had to get my partner to drive 7 miles there and back to collect my prescription as none of my local chemists could dispense COVID meds."* • *"I travelled to hospital by car. Arrived at hospital but was not segregated. They were not well set up for the infusion. It took place on a normal ward in a separate room. I was masked at all times."* • *"I had to go 20+ miles for treatment. My partner doesn't drive, I couldn't ask elderly parents to take me as didn't want to give them COVID. I didn't know whether I would react to intravenous meds so didn't want to drive so far down a motorway. They sent hospital transport for me in the end. Was an ambulance with two personnel, seemed such a waste of their time."* Approximately 66% of respondents indicated that they have no preference for the method of treatment administration, with the rest of the respondents evenly split between preferring tablets or intravenous infusions.

Patient population	
16. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	People who are immunosuppressed/immunocompromised due to their health condition or treatment are more likely to benefit from post-exposure COVID-19 therapies because they frequently do not have the same level of protection from the COVID-19 vaccines. The OCTAVE study showed that a significant proportion within this group have a low or undetectable immune response after two doses of the vaccines (**HERE**). Additionally, patients who were unable to complete their course of COVID-19 vaccine doses would also benefit more from access to these treatments. Some people could not complete their COVID-19 vaccination doses due to history of anaphylaxis or a significant adverse reaction to an early dose.
17. For the people you represent, what do they think about the definition of 'high risk' used to determine access to treatments for preventing severe COVID-19. • Does the definition exclude any key 'high risk' patient groups?	The current definition of 'high risk' does not include people with systemic lupus erythematosus (SLE) who are treated with only hydroxychloroquine and/or sulfasalazine or are receiving no treatment. The current definition only includes those who are receiving a treatment associated with greater risk of severe COVID-19 outcomes. However, a review of cases included in the COVID-19 Global Rheumatology Alliance registry from March 2020 to June 2021 (**HERE**) suggests that SLE patients with no DMARD treatment are the highest risk for requiring ventilation and/or death. The poor outcomes seen in this group may be multifactorial, and it is plausible that social risk factors play a role, such as lack of access to SLE care or treatment. We would, however, request a review of the 'high risk' criteria, taking this data into consideration. The criteria should not only consider the risk of severe COVID-19 infection, but also the risk of COVID-19 triggering other issues with a person's health. A large proportion of people with lupus reported that COVID-19 affected their disease, with many reporting flares and needing additional treatment such as corticosteroids. People with lupus are also at a higher risk of secondary infections such as pneumonia. The results from our online survey suggested that the majority of people who were admitted to hospital required antibiotic treatment rather than anti-virals for COVID-19. • *"Review eligibility criteria to include all people with SLE and consider risk of COVID-19 triggering flares requiring additional treatment."* The current definition of 'high risk' on the NHS website (**HERE**) is too vague. It does not specify systemic lupus erythematosus (SLE) which results in some healthcare professionals and NHS staff interpreting the risk of this patient group differently. • *"…the specialists monitoring my conditions did not think I met the criteria but I disagreed and on contacting the CMDU they felt I did meet the criteria and gave me sotrovimab."* • *"Lack of understanding of the term in the medical community."*

Equality	
18. Are there any potential equality issues that should be taken into account when considering COVID-19 and the available therapies?	Sotrovimab and Ronapreve are administered by intravenous infusion in a hospital setting. This may present a barrier to access when compared to the orally administered treatments because of the costs associated with attending hospital. A significant number of eligible people with rare diseases have not been notified by the NHS. If they have not obtained information for themselves from another source (such as a patient support group/charity) they may be unaware of their eligibility and not access the treatment. Some people who are eligible and haven't been identified by the NHS have experienced significant difficulty getting referred to a CMDU to be assessed for treatment. Those who have more support or are less unwell may be more able to advocate for their own access to treatment. Uptake of sotrovimab in eligible patients has been shown to differ across ethnic groups with the higher uptake in White, Indian, Bangladeshi and Other Asian groups and lower in Black Caribbean and Black African groups. This indicates some inequalities in uptake but does not identify significant factors causing this (**HERE**).
Other issues	
19. Are there any other issues that you would like the committee to consider?	There needs to be more investment in education and awareness campaigns about COVID-19 treatments, eligibility and pathways for access. Communications to high risk people with rare diseases have been incredibly inconsistent and unreliable throughout the pandemic. As a result, a significant number of people are unsure of their eligibility for treatment. • *"I'm unaware of them [COVID-19 treatments] and I wasn't informed of them."* • *"I'm not sure whether I will get the treatment that I need if I catch COVID, so I'm still shielding."* • *"From discussions with friends I don't know how or whether to report it, if I should get it."*
Key messages	
20. In up to 5 bullet points, please summarise the key messages of your submission:	

- COVID-19 treatments have helped reduce the risk of severe disease and hospitalisation for people with lupus. In addition, they provide vital reassurance for those who may contract COVID-19, sometimes enabling a better quality of life and reduced social isolation.
- Many people with lupus and other rare autoimmune rheumatic diseases who are eligible for COVID-19 treatments are not reliably and accurately identified with existing NHS digital coding.
- Many people report delays in being assessed by COVID-19 Medicines Delivery Units (CMDUs) despite a short window to start the treatments.
- The eligibility criteria should be reviewed to include all people with systemic lupus erythematous (SLE) regardless of treatment. The impact of pausing treatment and or triggering lupus flares should be considered as well as the risk of severe COVID-19.
- Improved awareness and education is needed to ensure all people with lupus know about the treatments, their eligibility and pathways for access.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	MS Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Society is a charitable company limited by guarantee. The legal responsibilities for our charitable company rest with our Board of Trustees and National Council Chairs. Each national council usually has 12 members (15 in England). They're ultimately accountable to our 12 Board of Trustees. The majority of our funding comes from a combination of donations, legacies, charitable activities, other trading activities and investments.
4b. Has the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	In 2021, MS Society received a financial contribution from Roche Products Ltd of £50,000.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Our submission is based on a combination of existing MS Society surveys and research carried out with our supporters and wider MS community, a review of relevant queries to our Helpline, consultation with our medical advisors, and a brief review of academic research.
Living with COVID-19	
6. Please tell us what is it like for patients you support who have tested positive for COVID-19?	Multiple sclerosis (MS) is one of the most common neurological conditions in the UK. In England, there are over 100,000 people living with MS. It's a progressive condition and people commonly experience their first symptoms in their 20s and 30s. No two people with MS experience the condition the same way. Symptoms vary greatly between individuals, many are invisible, and they often fluctuate. The most common symptoms of MS include vision problems, numbness and limb weakness, fatigue, bladder and bowel problems, and pain. As many as 55,000 people with MS in England could need care and support for daily activities at any one time. People with MS are eligible for Covid therapeutics due to the associated health risks Covid can pose for this group. Some treatments for MS might increase vulnerability to infection, or make recovery more difficult. Vaccine effectiveness may be lower in people with MS on certain treatments, but are still thought to provide some protection.

	Evidence suggests that Covid infection can worsen existing MS symptoms and/or see the development of new symptoms. Covid infection may also be linked to MS relapses in some cases[1],[2], though further research is needed into this. Research prior to vaccine roll-out indicated that symptoms of long Covid were more likely in people with MS than the general population. Evidence prior to vaccine roll-out also found that people with MS who reported testing positive for Covid reported greater anxiety and depression symptoms than those without Covid.[3] The Association for British Neurologists (ABN) outline the strongest evidence for severe Covid disease in people with MS is with any of the following risk factors: higher disability (EDSS>6.0 and/or significant swallowing or breathing difficulties), progressive disease with longer disease duration, older age (usually above the age of 65), obesity, male sex and presence of significant co-morbidities such as diabetes and cardiorespiratory disease.[4]
7. What do carers experience when caring for someone with COVID-19?	Carers continue to experience disruption to services as a result of the pandemic. These range from care, health and local services for the person they care for, as well as support and respite services for carers themselves. As outlined below for Q. 15, reports from our Helpline point to frustration and confusion among some carers while trying to support someone with MS to access Covid treatments. Several queries and reports to our Helpline indicated a lack of understanding and information around eligibility and access to treatments, particularly within primary care. Carers reported that their GP would signpost them to one place to access treatments, only for the carer to be signposted back to GP. More broadly, 2021 research by Carers UK found that barriers to carers for accessing support services included not knowing about services available in their local area (38% of UK carers), concerns relating to Covid transmission (30%), the high cost (or perceived cost) of support services (24%), and lack of transport availability for the person requiring support services

	(12%).[5] We believe it is likely that many of these barriers remain in place for carers of people with MS, and that these have knock-on impacts on carer health and wellbeing.
Interaction with underlying conditions 8. For people with underlying conditions (for example cancers, autoimmune disorders): • If applicable, how has living with COVID-19 affected their condition? • If applicable, how has the normal treatment pathway for their condition been affected? (For example, cancer treatment options, regularity of assessments, accessibility issues related to treatments)	**<u>Covid infection affecting MS</u>** Findings from the UK MS Register Covid cohort study found that infection regularly led to exacerbation of MS symptoms (Garjani et al. 2021).[6] In one Register study, 57% (n=203) of participants had an MS exacerbation during their infection. A fifth (20%; n= 82) developed new MS symptoms, and just over 50% (n= 207) experienced worsened pre-existing MS symptoms. Some participants reported both new MS symptoms and worsened pre-existing symptoms (n=59). Participants with a higher pre-Covid webEDSS (web-based Expanded Disability Status Scale) score and longer MS duration were more likely to experience worsening of their pre-existing MS symptoms during the infection. However, the study found that taking disease modifying treatments (DMTs) reduced the likelihood of developing new MS symptoms during Covid infection. A retrospective medical record review study found that Covid severity and lack of complete systemic recovery were associated with new or worsening neurologic symptoms in 36.9% of MS and related disorders (MSRD) patients.[7] The study found 41 patients (36.9%) had neurologic worsening post-COVID-19. Of those, 19 (46.3%) had pseudorelapses, 2 (4.8%) had relapses, and 24 (58.5%) patients reported worsening of pre-existing MSRD symptoms, or other new long-term neurologic symptoms. Neurologic worsening was associated with hospitalized (moderate or severe) COVID-19, treatment for COVID-19, and incomplete COVID-19 recovery but not with age, sex, MS type, race, disease duration, EDSS, vitamin D use, or disease modifying therapy use.

	Treatment pathway for MS Most people with MS who develop symptoms of Covid or test positive for the infection are able to continue with their regular MS treatments. However, evidence suggests that certain DMTs may be linked to an increased chance of having a more severe form of Covid, including a greater risk for hospitalisation. The ABN state that all DMTs should be available to people with MS but the potential benefits of any treatment should outweigh the risks, considering: the local rate of Covid infection, the individual's general health, their exposure to the virus (e.g., through occupation or caring responsibilities) and the DMT's impact on the risk of serious Covid-19 disease and the efficacy of a vaccine. ABN guidance recommends that certain therapies (Tysabri, Ocrevus, Lemtrada or Mavenclad) should be delayed until symptoms resolve. In cases of severe COVID infection, the DMT should be stopped and the prescribing team urgently consulted for further advice. ABN guidance also indicates that certain DMTs (sphingosine receptor modulators (fingolimod and Siponimod) and CD20 agents (ocrelizumab, rituximab and ofatumumab) may reduce antibody production following Covid vaccination. However, this would not increase any risk associated with the vaccine and therefore the ABN continue to encourage people with MS on these DMTs to have the vaccine.
Short term versus long term 9. For the people you represent who have tested positive for COVID-19, on	Research from the UK MS Register's 2021 community-based Covid-19 study indicates that for the majority of people with MS, infection with Coivd was relatively mild. While 5% of participants (4.7%, n=28) were hospitalised due to their Covid infection, this cohort was excluded from the study to avoid the potential confounding effect of hospitalisation on recovery from Covid.

average, how long did their symptoms last for? a) Did anyone have any long-term effects from COVID-19? Approximately what proportion does this represent? b) If yes, • What were they? (for example physical and mental impacts, impact on ability to work) • On average, how long did the effects last for? • What treatments did they need for the long-term effects of COVID-19?	The study found the average recovery time from Covid infection was 10 days (Garjani et al. 2021).8 However, almost 30% of people with MS (29.7%; n=165) had symptoms lasting for more than 4 weeks, and 12% (n=69) for more than 12 weeks. Participants with pre-Covid self-assessed EDSS scores greater than 7 (unable to walk more than 5 metres with walking aid), participants with probable anxiety and/or depression before infection, and women were more likely to report delayed recovery. Other MS-related factors such as disease duration or disease-modifying therapies did not appear to influence recovery from COVID-19. Of 60 participants who reported their symptoms at ≥12 weeks, 50 (83.3%) had non–MS-related symptoms such as breathing difficulties, sore throat, stomach ache and diarrhoea. Currently, there is little evidence on the treatment of long Covid in people with MS.

Current treatment for COVID-19 in the NHS	
10. What do patients or carers think of current treatments and care available in the NHS? - for preventing severe COVID-19 in people with high risk of hospitalisation - for treating people in hospital with severe COVID-19	Both carers and people with MS have indicated that they are relieved and grateful that these treatments are available. Many fear the risks of hospitalisation as a result of Covid, and what this would mean for their health and wellbeing. As outlined in Qs 9 and 15, our supporters indicate that accessing these treatments is working really in some areas, but in other areas of the country it is not clear how to access them, which causes concern, frustration and anxiety.
11. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?	
12. What impact does having these drugs available in the NHS have on your community?	Access to these treatments alleviate stress and concern in people with MS, and their carers. As outlined above, Covid infection is linked to worsening or new MS symptoms which can be distressing and significantly affect quality of life. Our Helpline still receives reports of people with MS choosing to shield in order to protect themselves from Covid infection. Having quick and safe access to treatments in the community has been a relief and gives vulnerable people a bit more confidence to return to their previous routines and activities.

13. Is there an unmet need for patients with this condition in relation to therapies for treating COVID-19? Are there any key subgroups of patients we should consider?	Some people with MS do not mount a sufficient response to Covid vaccinations, usually those on certain DMTs. We believe these groups should be able to access Evusheld for prophylactic use on the NHS in England. We are aware NICE are consulting separately on Evusheld and plan to respond to that in due course.
Hospital and community treatment settings 14. For those people that you represent who were <u>hospitalised</u> due to COVID-19 • At what point after being diagnosed with COVID-19 did they receive any form of treatment? • What did their treatment pathway look like? • How long did they spend in hospital?	**<u>15. Accessing treatments in the community</u>** The pathway for accessing community treatments relies on people with MS having NHS-issued lateral flow tests and reporting results online or to NHS 119. Results are used to pair with GP held data on MS diagnoses and the patient is contacted by the NHS Covid Medicines Delivery Unit (CMDU) to potentially offer antivirals, remaining eligible up to Day 5 of symptoms. The CMDU assess need and either send out treatment to be taken as a tablet at home, or arrange for to visit the NHS CMDU for a treatment that is given by infusion. People with MS are not automatically offered treatment. The MS Society became aware of a number of issues with accessing Covid treatments in Q1 and Q2 2022. Our Helpline received reports from people with MS that they were not directly contacted about their eligibility for treatments and were unsure about what to do if they tested positive. Some people were not aware of the requirement for Covid tests to be NHS-issued, instead of privately bought. Some people with MS, and their carers, also reported that awareness of eligibility and how to access treatments was low among some clinicians, with GPs referenced most frequently. This resulted in people being referred back to their MS teams for further advice which delayed the narrow window to access treatments if Covid positive. Our Helpline heard positive stories of people without transport being offered transport to and from infusion treatments. However, experiences do appear to have varied across the country.

If they had an underlying condition how did this impact the condition? 15. For the people you represent that had treatments for COVID-19 in <u>community settings</u>: • At what point after being diagnosed with COVID-19 did they receive any form of treatment from the NHS? • What did their treatment pathway look like? • Was there a preference for receiving tablets versus treatment with other administration methods (for example intravenously) • Can you tell us a bit about their experience of accessing these treatments? (for example	In consultation with our medical advisors, some clinicians reported challenges around the timeframe in accessing antivirals (e.g. receiving positive test results on day 4 of symptoms, tests reported over a weekend sometimes not promoting a response until Monday). They also reported that a small number of people with MS who registered positive test results reported receiving no follow up communication, possibly due to issues with the way their MS diagnosis is coded.

travelling to clinics/outpatient settings while testing positive for COVID-19) • Were there any issues with accessing these treatments?	
Patient population	
16. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	
17. For the people you represent, what do they think about the definition of 'high risk' used to determine access to treatments for preventing severe COVID-19. • Does the definition exclude any key 'high risk' patient groups?	

Equality	
18. Are there any potential equality issues that should be taken into account when considering COVID-19 and the available therapies?	The Office for National Statistics monitored the impact of the pandemic on disabled people in Great Britain. Key findings include[9]: • Disabled people were more likely to report feeling very uncomfortable or uncomfortable leaving their home because of the pandemic. In December 2021, 45% of disabled people reported feeling uncomfortable compared with 24% of non-disabled people. • When asked about their personal risk of catching Covid, 50% of disabled people thought they were very high risk or high risk, compared with 30% of non-disabled people. • Disabled people also reported being more concerned about new variants of Covid than non-disabled people (76% compared with 65%). These differences have remained consistent over time and underscore the importance of offering Covid therapeutics to disabled and immunocompromised people. Our Helpline still receives reports of people with MS choosing to shield in order to protect themselves from Covid infection, which has detrimental effects to their health wellbeing. We believe any opportunities to improve and strengthen access to Covid therapeutics to these groups would be welcome.
Other issues	
19. Are there any other issues that you would like the committee to consider?	

Key messages

20. In up to 5 bullet points, please summarise the key messages of your submission:

- Evidence suggests that Covid infection can worsen existing MS symptoms and/or see the development of new symptoms. Covid infection may also be linked to MS relapses in some cases, though further research is needed.
- Most people with MS who develop symptoms of COVID-19 or test positive for the infection are able to continue with their regular MS treatments. However, evidence suggests that certain DMTs may be linked to an increased chance of having a more severe form of COVID-19, including a greater risk for hospitalisation.
- Research prior to vaccine roll-out indicated that symptoms of long Covid were more likely in people with MS than the general population. Delayed recovery was more likely in people with advanced disability, probable anxiety/depression prior to infection, and in women.
- People with MS, their carers, and some clinicians have all reported issues with accessing Covid treatments in late 2021 and early 2022. Key drivers appear to be capacity issues within the CMDU, a lack of awareness of eligibility for these treatments among primary care and other health services, and confusion around how to access these treatments.
- Worry and anxiety around contracting Covid remains high among many people with MS, and their carers. This stems from fear of severe outcomes from Covid infection, and the possibility of reduced vaccine efficacy in some people due to certain MS treatments. This has led to a minority of people choosing to voluntarily shield over two years on from the outbreak of the pandemic, with negative impacts on their physical and mental health as a result. Maintaining and strengthening access to Covid treatments would make a huge difference to these groups, along with access to Evusheld as a prophylactic measure.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

You can provide a unique perspective on the technologies in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Faculty of Pharmaceutical Medicine**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with COVID-19? ☐ a specialist in the clinical evidence base for COVID-19 or the technologies? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Faculty of Pharmaceutical Medicine (FPM) is a charity and professional membership body. Our mission is to advance the science and practice of pharmaceutical medicine by working to develop and maintain competence, ethics and integrity and the highest professional standards in the specialty for the benefit of the public.
5b. Have you or the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatments for COVID-19	
6. What are the main aims of the treatments? (For example, to reduce specific long-term impact of COVID-19, lung damage, reduce length of stay in hospital) How does the aim differ per treatment?	The medicines cited have different uses and aims. Remdesivir, molnupiravir and nirmatrelvir and ritonavir, are all small molecule antiviral medicines. Small molecule respiratory antivirals should be used early (within 5-7 days), in a community-setting, following onset of symptoms, to support: • Reduction in the proportion of patients needing hospitalisation, ICU admission or dying from COVID or its complications • Reduction in the proportion of patients with persistent symptoms leading to longer term ill health • Faster return to normal health and ability to work Casirivimab and imdevimab, sotrovimab and tixagevimab and cilgavimab are monoclonal antibodies that, when used early following onset of symptoms of COVID, can reduce the proportion of patients needing hospital care or dying from COVID. However, the current Omicron variants are no longer inhibited by casirivimab and imdevimab or by sotrovimab in research studies and these agents should no longer be used as treatments, unless the circulating variant is shown to be inhibited by these agents in vitro or in vivo in animal studies.

	The combination of tixagevimab and cilgavimab has been shown to prevent infection and illness when given to high-risk patients prior to exposure to COVID. It may be used as a replacement for repeated vaccination to prevent COVID infection and illness in immunocompromised patients who cannot respond to vaccines. Baricitinib and tocilizumab, in contrast, are anti-inflammatory agents, which are used to treat the multisystem inflammatory disease which develops in patients later on in the COVID disease pathway following admission to hospital. If early antiviral treatment is successful in preventing need for hospitalisation these medicines would not be needed for the treatment of COVID-19. These treatments should be used together with dexamethasone in hospitalised patients needing high dose oxygen treatment with evidence of inflammation to: • Reduce the proportion of hospitalised patients needing ICU care or mechanical ventilation (tocilizumab only) • Reduce mortality (baricitinib or tocilizuzmab) A summary of how these treatments are used is present in the NICE Guidance (NG191) shown in Section 8 (UK: NICE https://www.nice.org.uk/guidance/ng191/resources/managing-covid-19-treatments-may-2022-v24.0-pdf-11070542125)
7. In your view, is there an unmet need for patients and healthcare professionals in relation to therapeutics for treating COVID-19?	The eligibility criteria for treatment should be reconsidered, to reduce hospitalisation and death among higher risk adults currently ineligible, and to also support earlier recovery and return to work among healthcare professionals and other essential workers. The majority of people at high risk of hospitalisation and death due to COVID as defined by the treatment label are not currently eligible for treatment. There is a need to consider treating health care professionals, so that they can return to work sooner and help to ease the burden of the "backlog" of 6 million plus patients waiting for treatments and operations for conditions other than COVID, rather than adding to that burden. There is a need to understand how to effectively use antivirals and monoclonal antibody treatments to prevent COVID in close contacts of COVID cases (post exposure prophylaxis); several prior trials investigating this approach failed to show benefit, but this may have been due to intervening too late and stopping treatment too early (nirmatrelvir/ritonavir) or using an inappropriate dose (tixagevimab and cilgavimab). Successful prevention of COVID in close contacts of cases in a care home was reported for bamlanivimab (Cohen MS, Nirula A, Mulligan M, et al. *Bamlanivimab prevents COVID morbidity and mortality in nursing home settings*. Presented at: Virtual Conference on Retroviruses and Opportunistic Infections 2021; March 6-10, 2021.) and in household contacts for

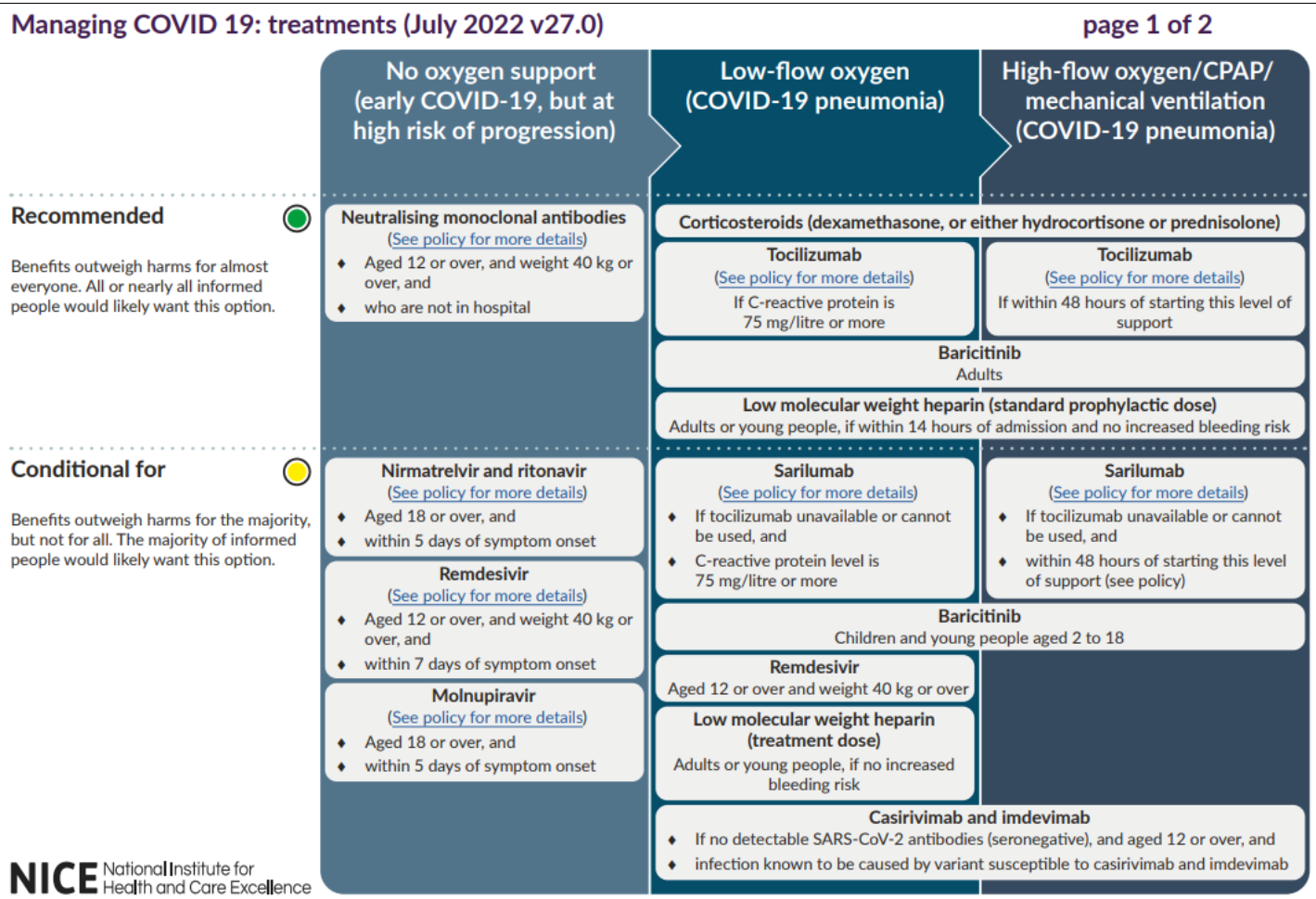
	Ronapreve (O'Brien MP, Forleo-Neto E, Musser BJ et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med. 2021 Sep 23;385(13):1184-1195. doi: 10.1056/NEJMoa2109682). There is a need to investigate whether early treatment of COVID illness prevents long COVID. This is currently still under investigation.
What is the expected place of the technologies in current practice?	
8. How is COVID-19 currently treated in the NHS?	Use of antiviral medications has been severely restricted in the UK and are used only in a small minority of patients to treat COVID illness. This approach has not noticeably limited hospitalisations for COVID illness in other higher risk adults/children and as the majority of the groups permitted access to treatment are immunocompromised and may not 'clear' the virus adequately, the approach increases the risk for emergence of transmissible treatment resistant viral variants. In addition, uptake of treatment has been low among this population – 14% estimated in one recent investigation, in which the authors also comment that in the group their algorithm detected as being at highest risk of hospitalisation and death only 3.6% received antiviral treatment (Julia Hippisley-Cox, Kamlesh Khunti, Aziz Sheikh, Jonathan S Nguyen-Van-Tam, Carol AC Coupland. *Q Covid 4 - Predicting risk of death or hospitalisation from COVID-19 in adults testing positive for SARS-CoV-2 infection during the Omicron wave in England*. medRxiv 2022.08.13.22278733; doi: https://doi.org/10.1101/2022.08.13.22278733). Sotrovimab is not effective in vitro (https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Sotrovimab/Pages/default.aspx) against the current Omicron virus strains, suggesting that this may not have been an appropriate treatment (it has been withdrawn from use in the USA for this reason). Other patients at high risk from COVID due to age or other medical conditions have not been permitted access to treatment, which may have further limited the impact of treatment on rate of hospitalisation and resulting mortality during recent waves caused by the omicron variants. Baricitinib and tocilizumab are used in hospitalised patients to reduce mortality.

• Are any clinical guidelines used in the treatment of COVID-19, and if so, which?	**Antivirals** **Pre-exposure** US Center for Disease Control Pre-exposure prophylaxis in the immune compromised: https://www.cdc.gov/mmwr/volumes/71/wr/mm7133e1.htm The CDC advises that Pre-exposure prophylaxis with Evusheld can help protect persons with moderate to severe immunocompromise who might not mount an adequate immune response after COVID vaccination, as well as persons for whom COVID vaccination is not recommended because of their personal risk for severe adverse reactions. In addition to early antiviral treatment if infected, persons who are moderately or severely immunocompromised can benefit from COVID pre-exposure prophylactic medication to help prevent severe COVID illness, as an adjunct to up-to-date vaccination for themselves and their close contacts, early testing, nonpharmaceutical interventions, and prompt access to treatment if they are infected. **Treatment** *NHS Interim clinical commissioning policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19*. Document first published: 9 December 2021 Page updated:14 June 2022. https://www.england.nhs.uk/coronavirus/publication/interim-clinical-commissioning-policy-neutralising-monoclonal-antibodies-or-antivirals-for-non-hospitalised-patients-with-covid-19/ The policy states that: antivirals or neutralising monoclonal antibodies (nMABs) are recommended to be available as a treatment option through routine commissioning for non-hospitalised adults with COVID-19 treated in accordance with the criteria set out in the document. The policy applies to non-hospitalised patients with COVID-19 who are symptomatic and showing no evidence of clinical recovery and covers the following treatment options: • First-line: nirmatrelvir plus ritonavir (antiviral) OR sotrovimab (nMAB), as clinically indicated • Second-line: remdesivir (antiviral) • Third-line: molnupiravir (antiviral)

	Please note that sotrovimab has been withdrawn from use in the USA as it is ineffective in vitro against the omicron variants. Despite its antibody construct, it cannot be expected to be as effective in vivo when it does not bid to or neutralise the virus. ADCC may cause increased lung damage in vivo. NICE treatment pathway matches NHS commissioning (NG191) This NICE Covid-19 rapid guideline: managing COVID-19 was updated 27 Juy 2022 https://www.nice.org.uk/guidance/ng191/chapter/Recommendations NIH (USA) treatment of non-hospitalised patients https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-nonhospitalized-adults/ with a similar list of treatments to the NHS commissioning policy : *For Patients Who Are at High Risk of Progressing to Severe COVID-19 Preferred therapies*. Listed in order of preference: • Ritonavir-boosted nirmatrelvir (Paxlovid) • Remdesivir Alternative therapies. For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. • Bebtelovimab • Molnupiravir Individuals aged >65 are eligible for treatment in the USA, but not in UK, unless they are also affected by the list of limited comorbidities considered to confer high risk. In addition, sotrovimab is not recommended for use in the USA as it not effective against the Omicron variants. USA CDC treatment *Summary of Guidance for Minimizing the Impact of COVID-19 on Individual Persons, Communities, and Health Care Systems* — United States, 11 August 2022 https://www.cdc.gov/mmwr/volumes/71/wr/mm7133e1.htm The CDC advised that antiviral medications (Lagevrio [molnupiravir], Paxlovid [nirmatrelvir and ritonavir], and Veklury [remdesivir]) and monoclonal antibodies (bebtelovimab) are available to treat COVID-19 in persons who are at increased risk for severe illnessincluding older adults, unvaccinated persons, and those with certain medical conditions (immunocompromised) Recent expansion of prescribing authority of nirmatrelvir/ritonavir (Paxlovid) to pharmacists intends to further facilitate access.

	WHO clinical care pathway Updated 22 April 2022 is in line with other guidance, but has a broader definition of treatment access including age >60 and obesity: https://www.who.int/tools/covid-19-clinical-care-pathway For patients with COVID-19 presenting with early onset of mild or moderate COVID-19 (non-severe symptoms): And with risk factors, for severe disease, consider including treatment with one of the following options: An antiviral nimatrelvir/ritonavir OR molnupiravir (contraindicated in pregnant or breastfeeding women and children) OR remdesivir (IV); OR neutralizing monoclonal antibodies (sotrovimab or casirivimab and imdevimab*). For patients with severe or critical COVID-19, the treatment care plan includes: • Interleukin-6 receptor blocker (tocilizumab OR sarilumab) OR JAK Inhibitor (baricitinib) • For seronegative patients, consider including neutralizing monoclonal antibodies (casirivimab and imdevimab*) * WHO suggests that monoclonal antibodies be used for the treatment of COVID-19 in cases where rapid viral genotyping is available and confirms infection with a SARS-CoV-2 variant that is susceptible to the neutralizing activity of the monoclonal antibody. NHS Interim Clinical Commissioning Policy: *Antivirals or neutralising monoclonal antibodies in the treatment of hospital-onset COVID-19* (Version 7) Publication date: 30 May 2022 Effective from: 13 June 2022 https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2022/03/Interim-Clinical-Commissioning-Policy_-Antivirals-or-neutralising-monoclonal-antibodies-in-the-treatment-of-ho.pdf states that: Neutralising monoclonal antibodies (nMABs) or antivirals are recommended to be available as a treatment option for COVID-19 through routine commissioning for adults and children (aged 12 years and above) in hospital with COVID-19 infection in accordance with the criteria [set out in this document]. • First-line: nirmatrelvir/ritonavir • Second-line: remdesivir (antiviral) • Third-line: sotrovimab (nMAB) **Anti-inflammatory treatments (dexamethasone, baricitinib, tocilizumab)** US NIH https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/hospitalized-adults--therapeutic-management/ Defines management of patients hospitalised for COVID according to admission status and oxygen requirement. European Respiratory Society Living Guideline:

	Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. James D. Chalmers, Megan L. Crichton, Pieter C. Goeminne, et al. Eur Respir J 2021; 57: 2100048. - August 01, 2022 UK: NICE https://www.nice.org.uk/guidance/ng191/resources/managing-covid-19-treatments-may-2022-v24.0-pdf-11070542125 (NB reference to use of casirivimab/imdevimab is no longer appropriate, as it is ineffective vs Omicron variant disease. It was replaced by sotrovimab but the same issue applies; the only current Mab which is effective at neutralising omicron variants is bebtelovimab, which is not currently MHRA approved)



• Is the pathway of care well	Community care pathways are poorly defined, with anecdotal evidence of regional differences in community use of antiviral therapies. Evidence of difficulty of accessing antiviral therapies is provided from patient surveys reported below.

defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	1) RAIRDA's survey report about difficulty accessing COVID-19 treatments at https://rairda.org/2022/06/21/survey-shows-poor-communication-around-covid-19-vaccine-and-treatments-for-people-with-rheumatic-conditions/ The findings suggest people with rheumatic conditions continue to experience persistent issues with communications for both fourth vaccine doses and COVID-19 antiviral treatments, with 40% people reporting no proactive contact from the NHS to inform them of their eligibility and half (50%) finding the process to get referred to a COVID medicines delivery unit (CMDU) by their GP/consultant to be 'very difficult'. 2) Kidney Care UK "OPEN Safely" report suggests that variation persists in accessing antibody/antiviral treatments – https://reports.opensafely.org/reports/antivirals-and-nmabs-for-non-hospitalised-covid-19-patients-coverage-report/#demographic *Extract from the Results* Between 11-Dec-2021 and 01-Jul-2022, a total of 115,200 non-hospitalised patients registered at a practice using TPP SystemOne software in England were identified as potentially being eligible for receiving an antiviral or nMAB for treating COVID-19. Of the 115,200 potentially eligible patients, only 22,120 (19%) received treatment from a CMDU. • Paxlovid: 6,020. • Sotrovimab: 10,980. • Remdesivir: 40. • Molnupiravir: 5,040. • Casirivimab: 50. Hospital care pathways are better defined with more consistent approaches taken to care in hospital.
• At what point after being diagnosed with COVID-19 do people receive any form of	The majority of patients receive no treatment as they are not within the narrow band of 500,000 patients considered at high risk. A very small number of patients permitted access to antiviral medicines receive treatment within 1-5 days of first onset of illness but by no means all of those eligible are receiving treatment. Groups of patients with high-risk conditions not included in the list of conditions eligible for treatment comprise many of the patients needing hospital care. In hospital, care includes supportive care, oxygen therapy, anticoagulation and anti-inflammatory treatments including dexamethasone and baricitinib or tocilizumab.

treatment from the NHS?	
• How does the pathway differ by patient group (by age, underlying conditions, risk of hospitalisations, vaccination status)?	The list of high-risk patients who are eligible for any antiviral treatment pathway are listed below. Unfortunately, an ONS survey in May collected between 11 and 25 May 2022 among those who were at highest risk from COVID-19 and potentially suitable for antibody and antiviral out-of-hospital treatments for COVID-19 showed around two-fifths (41%) were not aware they needed to submit the result from a free government-issued lateral flow device to access out-of-hospital treatments. Patient surveys have reported the high-risk patient categories are complex to interpret and some are refused treatment. High risk patient categories: https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report/def • metastatic or locally advanced inoperable cancer • Down's syndrome and other genetic disorders • Solid cancer • lung cancer (at any stage) • people receiving any chemotherapy (including antibody-drug conjugates), PI3K inhibitors or radiotherapy[footnote 6] within 12 months • people who have had cancer resected within 3 months[footnote 7] and who received no adjuvant chemotherapy or radiotherapy • people who have had cancer resected within 3 to 12 months and receiving no adjuvant chemotherapy or radiotherapy are expected to be at less risk (and thus less priority) but still at increased risk compared with the non-cancer populations • Haematological diseases and recipients of haematological stem cell transplant (HSCT) o allogeneic HSCT recipients in the last 12 months or active graft versus host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases) o autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases)

	○ individuals with haematological malignancies who have received CAR-T cell therapy in the last 24 months, or radiotherapy in the last 12 months ○ individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months • all people who do not fit the criteria above, and are diagnosed with: ○ myeloma (excluding monoclonal gammopathy of undetermined significance (MGUS)) ○ AL amyloidosis ○ chronic B-cell lymphoproliferative disorders (chronic lymphocytic leukaemia, follicular lymphoma) ○ myelodysplastic syndrome (MDS) ○ chronic myelomonocytic leukaemia (CMML) ○ myelofibrosis • all people with sickle cell disease • people with thalassaemia or rare inherited anaemia with any of the following ○ severe cardiac iron overload (T2 * less than 10ms on magnetic resonance imaging) ○ severe to moderate iron overload (T2 * greater than or equal to 10ms on magnetic resonance imaging) plus an additional co-morbidity of concern (for example, diabetes, chronic liver disease or severe hepatic iron load on MRI) ○ individuals with non-malignant haematological disorders (for example, aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (for example, anti-CD20, anti-thymocyte globulin (ATG) and alemtuzumab) within the last 12 months ○ Renal disease renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who have:

	○ received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab (anti-CD20), anti-thymocyte globulin) ○ an additional substantial risk factor which would in isolation make them eligible for monoclonals or oral antivirals ○ not been vaccinated prior to transplantation ○ non-transplant renal patients who have received a comparable level of immunosuppression. Please refer to the section on 'Immune-mediated inflammatory diseases' below for a list of qualifying immunosuppressive therapies ○ patients with chronic kidney disease (CKD) stage 4 or 5 (an eGFR less than 30ml per min per 1.73m2) without immunosuppression • Liver diseases ○ people with cirrhosis Child-Pugh class A,B and C, whether receiving immune suppressive therapy or not. Those with decompensated liver disease (Child-Pugh B and C) are at greatest risk ○ people with a liver transplant ○ people with liver disease on immune suppressive therapy (including people with and without cirrhosis) – please refer to the section on 'Immune-mediated inflammatory diseases' below for a list of qualifying immunosuppressive therapies • Solid organ transplant recipients • Immune-mediated inflammatory disorders ○ people who have received a B-cell depleting therapy in the last 12 months ○ people who have been treated with cyclophosphamide (IV or oral) in the 6 months prior to positive PCR ○ people who are on biologics or small molecule JAK-inhibitors (except anti-CD20 depleting monoclonal antibodies) or who have received these therapies within the last 6 months

	○ people who are on corticosteroids (equivalent to greater than 10mg per day of prednisolone) for at least the 28 days prior to positive PCR ○ people who are on current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine/mercaptopurine (for major organ involvement such as kidney, liver and/or interstitial lung disease), methotrexate (for interstitial lung disease) and/or ciclosporin ○ people who exhibit at least one of: (a) uncontrolled or clinically active disease (that is required recent increase in dose or initiation of new immunosuppressive drug or IM steroid injection or course of oral steroids within the 3 months prior to positive PCR); and/or (b) major organ involvement such as significant kidney, liver or lung inflammation or significantly impaired renal, liver and/or lung function) • Immune deficiencies ○ common variable immunodeficiency (CVID) ○ undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) ○ hyper-IgM syndromes ○ Good's syndrome (thymoma plus B-cell deficiency) ○ severe combined immunodeficiency (SCID) ○ autoimmune polyglandular syndromes or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) ○ primary immunodeficiency associated with impaired type 1 interferon signalling ○ x-linked agammaglobulinaemia (and other primary agammaglobulinaemias) ○ any person with secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy • HIV/AIDS

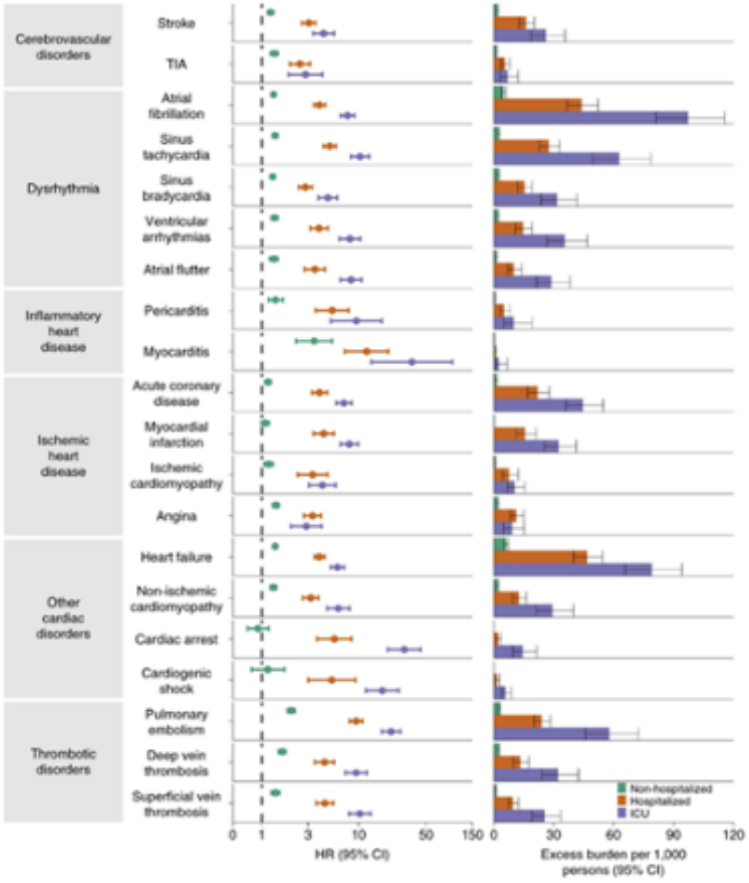
	○ people with high levels of immune suppression, have uncontrolled or untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis ○ people on treatment for HIV with CD4 less than 350 cells per mm3 and stable on HIV treatment or CD4 greater than 350 cells per mm3 and additional risk factors (for example, age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, alcoholic dependency)[footnote 9] • Rare neurological and severe complex life-limiting neurodisability conditions. An NHS England and Improvement (NHSEI) expert group has identified the key conditions are: ○ multiple sclerosis ○ motor neurone disease ○ myasthenia gravis ○ Huntington's disease A triage system may be in place to restrict access to ICU care when services are overwhelmed. This may disadvantage those of older age and greater frailty at times of peak demand.
Hospital and community treatment settings • How does the pathway differ by setting (for example community	Symptomatic patients in the community can only receive treatment if they are in a high-risk group (see above) and their symptoms show no signs of improvement. Patients in hospital must also be in the high-risk group to receive treatment if they develop COVID during their stay. The likelihood is that those that do get treatment will receive an oral medication according to NHS commissioning guidance. Patients who are hospitalised will likely receive oxygen, but community patients will not, and most hospitalised patients will receive a steroid and if they deteriorate whilst on an anti-inflammatory (baricitinib/tocilizumab). As noted previously, there are limited community services available, with antiviral treatments being delivered by COVID medicine delivery units (CMDUs) based in A+E departments. However, these treatments should ideally be delivered by home-based care and greater use of oral medications could be enhanced by enabling pharmacy prescription under a patient group directive.

versus hospital)?	Patients developing hypoxia in the community are admitted to hospital for oxygen therapy and other treatment of more severe illness which may include dexamethasone and baricitinib or tocilizumab. Length of stay in hospital depends on whether or not ICU care is required. A requirement for invasive ventilation may lead to prolonged admissions and older adults are usually requiring longer stays in hospital (https://www.medrxiv.org/content/10.1101/2022.03.16.22271361v1. Latest NHS data (from March 22) shows median time in hospital around 5 days, with a small peak after the January 21 wave, presumably in unvaccinated patients (https://digital.nhs.uk/supplementary-information/2022/average-length-of-stay-in-hospital-for-patients-with-covid-19-or-suspected-covid) and length of stay was reduced in the 'Omicron' period and a lower proportion of subjects require ICU admission than in previous waves, which is noted on ONS by change in ICU occupancy ((https://www.cdc.gov/mmwr/volumes/71/wr/pdfs/mm7104e4-h.pdf, https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-50-severity-omicron/).
• How long on average do people spend in hospital?	Because of the large excess of community-based vs hospitalised COVID cases, total cases of long COVID after community infection exceed those cases post hospitalisation. One can assume that the incidence of common symptoms is also common in hospitalised patients but the post-acute sequalae are often the most significant and may have life-long impact or even be life threatening; deaths within the acute phase will be counted as COVID deaths in ONS; deaths within the 4-12 weeks are 'ongoing symptomatic' and may not be counted as COVID deaths; beyond 12 weeks they are counted as Long COVID. There is research evidence that admission to hospital with COVID increases serious cardiovascular, respiratory and mental disorders. From Department of Veterans Affairs (USA) data – patients who are hospitalised have increased risk of long term cardiovascular disorders (https://www.nature.com/articles/s41591-022-01689-3) compared to both current and historical matched controls after following patients for 12 months.
• What proportion of people hospitalised	

develop long-covid?

Fig. 5: Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes compared with the contemporary control cohort by care setting of the acute infection.

From: Long-term cardiovascular outcomes of COVID-19



Risks and burdens were assessed at 12 months in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (green), individuals hospitalized for COVID-19 (orange) and individuals admitted to intensive care for COVID-19 during the acute phase (first 30 d) of COVID-19 (blue). Outcomes were ascertained 30 d after the COVID-19-positive test until the end of follow-up. The contemporary control cohort served as the referent category. Within the COVID-19 cohort, non-hospitalized (*n* = 138,462), hospitalized (*n* = 16,760), admitted to intensive care (*n* = 3,388) and contemporary control cohort (*n* = 5,637,647). Adjusted HRs and 95% CIs are presented. The length of the bar represents the excess burden per 1,000 persons at 12 months, and related 95% CIs were also presented.

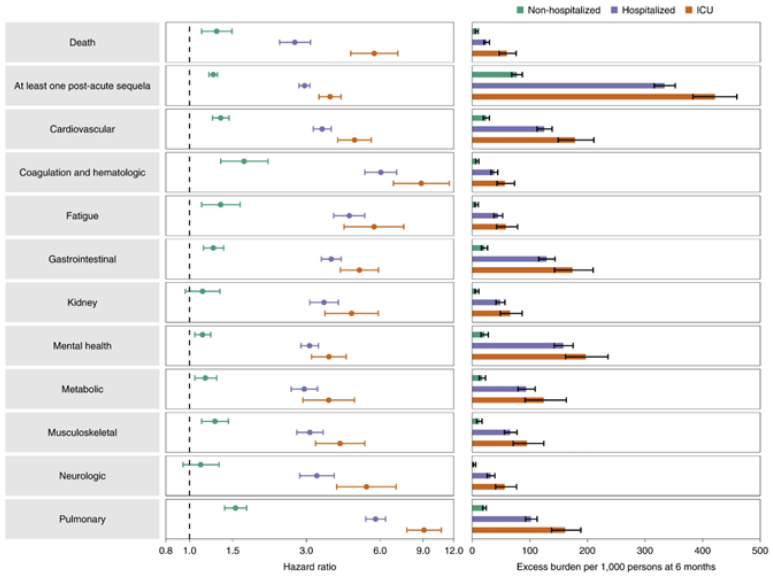
Professional organisation submission

A further study demonstrated similar results for psychiatric post-acute sequalae for those hospitalised compared to non hospitalised (BMJ2022;76:e068993 http://dx.doi.org/10.1136/bmj-2021-068993 Accepted: 8 January 2022,)

Whilst new variants may be less severe, in that the percentage of patients admitted to ICU is much lower, the risk for patients once admitted to ICU is not likely to be that different. This was reenforced by a study exploring break through infections in a vaccinated population in a case control Veterans Affairs study for patients who had events post 30 days as measured up to 6 months after the infection. The risk of having at least one post-acute sequela was evident in non-hospitalized people (HR = 1.25 (1.20, 1.30); burden of 77.60 (68.40, 87.04)), was further increased in those who were hospitalized (HR = 2.95 (2.80, 3.10); burden of 334.10 (315.90, 352.53)) and was highest in those admitted to ICU (HR = 3.75 (3.38, 4.16); burden of 421.39 (383.37, 459.56)).

Fig. 2: Risk and 6-month excess burden of post-acute sequelae in those with BTI by acute phase care setting.

From: Long COVID after breakthrough SARS-CoV-2 infection



Risk and 6-month excess burden of death, at least one post-acute sequela and post-acute sequelae by organ system are plotted by care setting of the acute phase of the disease (not hospitalized, hospitalized and admitted to ICU). Incident outcomes were assessed from 30 days after the positive SARS-CoV-2 test to the end of follow-up. Results are in comparison of BTI (non-hospitalized n = 30,273; hospitalized n = 3,667; admitted to ICU n = 811) to the contemporary control group with no record of a positive SARS-CoV-2 test (n = 4,983,491). Adjusted HRs (dots) and 95% CIs (error bars) are presented, as are estimated excess burden (bars) and 95% CIs (error bars). Burdens are presented per 1,000 persons at 6 months of follow-up.

• What proportion of people offered treatment for COVID-19 in the community develop long-covid?	Ref: Al-Aly, Z., Bowe, B. & Xie, Y. *Long COVID after breakthrough SARS-CoV-2 infection*. Nat Med 28, 1461–1467 (2022). https://doi.org/10.1038/s41591-022-01840-0 The Post-Hospitalisation COVID-19 study (PHOSP-COVID) is a prospective, longitudinal cohort study recruiting adults (aged ≥18 years) discharged from hospital with COVID-19 across the UK. Recovery was assessed using patient-reported outcome measures, physical performance, and organ function at 5 months and 1 year after hospital discharge, and stratified by both patient-perceived recovery and recovery cluster. The proportion of patients reporting full recovery was unchanged between 5 months (501 [25·5%] of 1965) and 1 year (232 [28·9%] of 804). Factors associated with being less likely to report full recovery at 1 year were female sex (odds ratio 0·68 [95% CI 0·46–0·99]), obesity (0·50 [0·34–0·74]) and invasive mechanical ventilation (0·42 [0·23–0·76]). The authors found a substantial deficit in median EQ-5D-5L utility index from before COVID-19 (retrospective assessment; 0·88 [IQR 0·74–1·00]), at 5 months (0·74 [0·64–0·88]) to 1 year (0·75 [0·62–0·88]), with minimal improvements across all outcome measures at 1 year after discharge in the whole cohort and within each of the four clusters. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00127-8/fulltext The Office of National Statistics Survey reports that up to 3% of the UK population may be currently suffering from long COVID. https://www.ons.gov.uk/. As only a minority of people are offered treatment for COVID in the community, we do not know whether or not such treatment can prevent the development of long COVID. The majority of these patients are those that received no treatment for COVID. Vaccination appears to reduce the incidence of long COVID. In an international survey, vaccination was reported to alleviate symptoms of long COVID in ~50% of cases (Strain WD, Sherwood O, Banerjee A et al. *The Impact of COVID Vaccination on Symptoms of long COVID: An International Survey of People with Lived Experience of long COVID*. Vaccines. 2022;10:652. doi: 10.3390/vaccines10050652. PMID: 35632408; PMCID: PMC9146071.) In addition, a study conducted among users of the Zoe App suggested that persistent symptoms for >28 days post COVID were less frequent in double vaccinated people (Antonelli M, Penfold RS, Merino J et al. *Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study*. Lancet Inf Dis 2022. 22; 43-55. DOI: https://doi.org/10.1016/S1473-3099(21)00460-6). These data suggest that antiviral treatment of breakthrough disease could further reduce the incidence of long COVID, although this has yet to be demonstrated by specific research.
Long-covid • What treatments are offered for	Long COVID remains poorly understood with no approved treatments. Treatments for long COVID are largely condition specific, for example treatment of diabetes. Ceban et al (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8935463/) found 59 trials exploring treatments including, biologics and small molecules, dietary supplements, homeopathic treatments and procedures. The authors concluded there was relatively little consistency in approach. This is further complicated by the different definitions of disease, outlined below: Post-acute COVID and long COVID

people with long-covid? What are the symptoms of long-covid?	Post-COVID conditions are being referred to by a wide range of names, including long COVID, post-acute COVID-19, long-term effects of COVID, post-acute COVID syndrome, chronic COVID, long-haul COVID, late sequelae, and others, as well as the research term post-acute sequalae of SARS-COV-2 infection (PASC). RCGP, SIGN NICE 19 May 22 https://app.magicapp.org/#/guideline/EQpzKn/section/n3vwoL https://www.nice.org.uk/guidance/NG188 The RCGP guidelines comprise mostly recommendations for palliative care SIGN/NICE RCGP agreed definitions: • Acute COVID-19 - Signs and symptoms of COVID-19 for up to 4 weeks. • Ongoing symptomatic COVID-19 - Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks. • Post-COVID-19 syndrome - Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed. In addition to the clinical case definitions, the term 'long COVID' is most commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more) CDC (USA) published guidance on long COVID and background to some of the common definitions. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-workup.html WHO have also published on Post COVID-19 conditions and define it as a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children. There is no minimal number of symptoms required for the diagnosis; though symptoms involving different organs systems and clusters have been described.

• On average, how long do the symptoms of long-covid last?	https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 The most serious life-threatening, post-acute and long COVID diseases or induced exacerbation of disease may not be cured. They are stroke, diabetes, chronic kidney disease and chronic lung disease. They are well reviewed in Montani et al. Montani D, Savale L, Noel N, et al. Post-acute COVID-19 syndrome. Eur Respir Rev 2022; 31: 210185 [DOI: 10.1183/16000617.0185-2021]. Data from the ONS survey suggests that 43% of affected patients have symptoms which persist for at least 1 year, and 21% of affected patients for 2 years, following the initial COVID illness. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/ conditionsanddiseases/articles/coronaviruscovid19/latestinsightsn The PHOSP-COVID and VA datasets in hospitalised patients suggest little difference in the proportion of patients with persistent symptoms 6 months and 1 year post recovery, suggesting symptoms may persist life-long.
• What impact would the technologies have on the	Early intervention with effective antiviral treatment may reduce need for hospitalisation and death by 50-80%. If the group eligible for antiviral treatment were expanded to include all those at risk of hospitalisation which, according to ONS data, includes a much larger section of the at-risk population than those defined currently, especially older patients, then the number of patients hospitalised for COVID could be reduced significantly. If, of the percentage of patients hospitalised, the numbers with ongoing symptomatology remains as high as previous

current pathway of care?	epidemiology, 25-30%, this would reduce ongoing burden of care. Early intervention might therefore reduce the incidence of patients developing long COVID, but this remains to be proven.
9. Will the technologies be used (or are they already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technologies and current care?	If used in the labelled population, oral antivirals could reduce both short and long term healthcare burden as described in Section 8. For example, had community antivirals been used broadly in July, the 12,000 hospitalisations per week could have been reduce to 6000 (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19/latestinsights), with subsequent knock-on impact on the proportion likely to develop long covid reducing the later, longer-lasting, burden of care required for these patients. Deploying the technology to healthcare staff could even, within the oral antiviral SmPCs, reduce length of absence and hospitalisation (many HCPs are over 60). However, more broad deployment, as in Canada, is likely to reduce length of disease – as has been noted following antiviral treatment for influenza and data from remdesivir trials - and could get HCPs back to work faster as they reduce length of viral shedding. It would also reduce the long COVID healthcare burden in HCPs. In some countries, such as New Zealand and USA, oral antivirals are dispensed through pharmacies. Here in the UK pharmacists and GPs/Practice nurses/paramedical staff could also supply antiviral medications and medications given by sc/IM injection. Some patients, such as pregnant women, will still require parenteral treatment which can be delivered in the infusion centres that have already been established.
• In what clinical setting should	Antiviral treatment – Predominantly primary (community) care

the technologies be used? (For example, primary or secondary care, specialist clinics.)	Baricitinib/tocilizumab – secondary care
• What investment is needed to introduce the technologies? (For example, for facilities, equipment, or training.)	An education programme for GPs, specialists and government decision makers to understand the utility of these technologies, as well as the entire scope of patient groups that would benefit as well as other groups eg healthcare professionals. This is essential as it applies to antivirals for all respiratory disorders including influenza and RSV. Purchase of sufficient medications to enable a course of treatment to be offered to symptomatic patients with confirmed COVID and high risk conditions (population est 17.2 million people aged >/=50 years of age; 5% incidence approx 1 million courses per annum)
• Do you expect any of the new technologies to help prevent long-covid or reduce the length of stay in hospital?	<u>Ongoing symptomatic treatment and Long COVID</u> See section 8, the most effective ways of preventing long COVID are vaccination and pre-exposure prophylaxis to prevent contracting the infection, followed by antivirals to prevent hospitalisation. <u>Length of stay</u> • Anti-inflammatories have demonstrated reduction in progression to ICU and all-cause mortality. Whilst the former reduces length of stay the latter may increase it. However, as ICU patients may have very long periods in hospital (as demonstrated between the

	difference between mean and median hospital stays in ONS data Section 8) the resulting effect is almost certainly to reduce hospital stay. • Remdesivir used in hospital has demonstrated a reduction in stay. The original remdesivir clinical data on which the drug was given emergency use authorisation was ACTT-1 study (Biegel JH, Tomashek LE et al. Remdesivir for the treatment of Covid-19 – final report. N Engl J Med 2020; 383:1813-1826 DOI: 10.1056/NEJMoa2007764) which demonstrated faster recovery from COVID-19 among remdesivir treated patients than those given placebo.
10. Are there any groups of people for whom the technologies would be more or less effective (or appropriate) than the general population?	Targeting the higher risk populations – those aged >50(minimum) or >65 (per influenza vaccination strategy), health and social care workers (enabling earlier return to work), adults and adolescents with high-risk comorbidities (chronic lung disease, cardiovascular disorders, immune compromised, cancer, renal disease, pregnant women)
The use of the technologies	
11. Do you consider that the use of these technologies will result in any	COVID is a self-limiting condition in the majority of the population unless associated with debilitating long COVID (which can occur in non-hospitalised patients), hospitalisation or death. Long COVID may cause significant disability in a small number of subjects but as only 3%-8% of patients report long COVID symptoms over a prolonged period, this is unlikely to be captured by a QALY estimation. Long COVID has debilitated many young and fit patients and, as with bacterial pneumonia where QALY is a challenging measure due to patients losing many healthy years if they recover, estimating a QALY is challenging in such patients.

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
12. Do you consider any of these technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits?	Because the NHS has been severely impacted by COVID and delivery of care is restricted still in proportion to the number of beds required for COVID cases, reducing the number of individuals requiring hospital care will increase capacity within the NHS to conduct other activities.
• Are the technologies a 'step-change' in the	Reducing the need for hospital care by 50-80% may be considered a step change in management. Reducing in-hospital mortality from 14 to 12%, while statistically significant, may not represent such a large benefit as would be delivered by preventing need for hospital care in the first place.

management of COVID-19?	
• Does the use of these technologies address any particular unmet need of the patient population?	Approx 1.7 million people are at higher risk of hospitalisation and death from COVID, currently only 0.5 million people meet the highly restricted definition of those considered eligible for antiviral treatment in the community. Enlarging the pool of eligible patients will meet the otherwise unmet need of 1.2 million people. The wider at risk group of people are aware of their risks and trying to voice their concerns. However, many are finding it a challenge to identify who are decision makers https://www.kidneycareuk.org/news-and-campaigns/news/5-key-tests-of-the-governments-plan-for-living-with-covid-19-the-support-required-for-people-at-high-risk/. There are major unmet medical needs for reducing the burden of ongoing symptomatic care and long COVID that would be fulfilled by broader expansion of deployment of community care treatments.
13. How do any side effects or adverse effects of these technologies affect the management of COVID-19 and the patient's quality of life?	Clinical trial evidence suggests that the antiviral treatments are well tolerated and do not require significant monitoring during in practice use other than those requiring IV administration. No additional safety concerns have arisen during wider use of these treatments in the US and Europe to date. No additional safety concerns have been identified from use of these treatments in the UK. Of those who took the ONS survey in May for antivirals, approximately three-quarters (74%) of those who took the treatment offered after testing positive felt it reduced their symptoms and 63% did not experience any side effects; the majority (94%) would repeat the treatment if offered it again. For those in hospital or ICU generally reported adverse event rates drop against a background of other significant health care issues.
Sources of evidence	

14. Does the clinical evidence on the technologies reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	Other clinical evidence from round the world is relevant to UK clinical practice.
• What, in your view, are the most important outcomes, and were they measured in the clinical evidence?	The clinical trials leading to approval of antiviral medicines were conducted during the alpha and Delta waves, with the most critical outcomes being hospitalisation and death due to COVID and all cause mortality. These have all been measured but due to falling rates and the importance of ongoing symptomatic disease and long COVID these outcomes may need to be supplemented. If these technologies are deployed to reduce all aspects of the healthcare burden then incidence of ongoing symptomatic disease, Long COVID, length of disease, hospital stay, duration of virus shedding etc all become more important, as does the burden of COVID on treatment for non COVID disease within the NHS and the impact on waiting lists.
• If surrogate outcome measures were used, do they adequately predict long-	The only surrogate outcome for clinical effectiveness of an antiviral is the impact on quantitative virus shedding and duration of infectivity, which correlate with length of illness, albeit imperfectly and only if deployed early in the course of disease. All-cause mortality is a controversial endpoint for infection and other studies, particularly in ICU as other factors may impact this outcome. Equally, hospitalisation may be miscategorised, for example in the ONS data the primary reason for hospitalisation may or may not be related to COVID. However, infection and illness may exacerbate other disorders, which in turn leads to hospitalisation. Prior work (Casscells SW, Granger E, Kress AM, Linton A, Madjid M, Cottrell L. Use of oseltamivir after influenza infection is associated with reduced incidence of recurrent adverse cardiovascular

term clinical outcomes?	outcomes among military health system beneficiaries with prior cardiovascular diseases. Circ Cardiovasc Qual Outcomes. 2009 Mar;2(2):108-15. doi: 10.1161/CIRCOUTCOMES.108.820357. Epub 2009 Mar 5. PMID: 20031822. Madjid M, Curkendall S, Blumentals WA. The influence of oseltamivir treatment on the risk of stroke after influenza infection. Cardiology. 2009;113(2):98-107. doi: 10.1159/000172796. Epub 2008 Nov 15. PMID: 19018144; PMCID: PMC2814019. Enger C, Nordstrom BL, Thakrar B, Sacks S, Rothman KJ. Health outcomes among patients receiving oseltamivir. Pharmacoepidemiol Drug Saf. 2004 Apr;13(4):227-37. doi: 10.1002/pds.845. PMID: 15255089. Dutkowski R, Thakrar B, Froehlich E, Suter P, Oo C, Ward P. Safety and pharmacology of oseltamivir in clinical use. Drug Saf. 2003;26(11):787-801. doi: 10.2165/00002018-200326110-00004. PMID: 12908848.) with antiviral therapies for influenza has shown that early intervention does reduce hospitalisations and deaths following influenza illness in high-risk patients.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Clinical trial evidence suggests that the antiviral treatments are well tolerated and do not require significant monitoring during in practice use other than those requiring IV administration. No additional safety concerns have arisen during wider use of these treatments in the US and Europe to date. No additional safety concerns have been identified from use of these treatments in the UK. Of those who took the ONS survey in May for antivirals, approximately three-quarters (74%) of those who took the treatment offered after testing positive felt it reduced their symptoms and 63% did not experience any side effects; the majority (94%) would repeat the treatment if offered it again. For those in hospital or ICU generally reported adverse events drops against a background of other significant health care issues. Follow up of patients receiving nirmatrelvir/ritonavir (Paxlovid) has suggested recurrent viral shedding and mild symptoms may occur in 1-2% of treated subjects within 5-10 days of completing an initial course of treatment. A second course of treatment appears to enable recovery in these cases.
15. Are you aware of any new evidence for the treatments since the publication of	

the assessment report?	
16. How do data on real-world experience compare with the trial data?	Real world evidence available (Vasan A, Foote M, Long T. Ensuring Widespread and Equitable Access to Treatments for COVID-19-19. JAMA. Published online July 29, 2022. doi:10.1001/jama.2022.13554) has suggested that the efficacy noted in clinical trials in earlier waves of illness is sustained in treated vs untreated groups of high-risk subjects.
17. What issues do you foresee with the data and how do you think this may impact treatment effectiveness for future variants? (For example, the data available is heterogeneous and includes treatment effectiveness	Several of the monoclonal antibody agents are no longer as effective in vitro for omicron vs earlier variants: there is a need for revised monoclonals targeting conserved protein antigens. As a result, the majority of these treatments should no longer be considered for use; only bebtelovimab has retained activity against Omicron strains while sotrovimab and ronapreve are no longer effective in vitro. Tixagevimab/cilgavimab Evusheld retains activity, but should be administered at a higher dose (600mg vs 300mg) to retain effectiveness. All monoclonal antibody therapies need to be reviewed for activity vs any emergent variants to ensure effectiveness is retained. Current evidence has demonstrated that remdesivir, molnupiravir and nirmatrelvir have all retained efficacy vs all variants (as would be expected given that these target highly conserved viral enzymes assisting virus replication, rather than the spike surface antigen binding to host cell receptors).

pooled over different variants of COVID-19 (primarily delta). People with different vaccination status could also impact the treatment effectiveness calculations.)	
Equality	
18a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes. The risk from COVID for individuals on immediate and long-term health is not equal across the population, differentially adversely affecting • Older people. This group could be defined as those aged >50 (minimum) or those aged >65 (per influenza vaccination strategy) • Adults and adolescents with high risk, including those with co-morbidities (chronic lung disease, cardiovascular disorders, immune compromise, cancer, renal disease) • Pregnant women.

	• Patients requiring care for non-COVID conditions (e.g. cancer) as availability and quality of care is being affected due to the impact of COVID on the Health and Social Care workforce. • People without access to technology and those with language barriers need particular attention to modes of access to care and treatment.
18b. Consider whether these issues are different from issues with current care and why.	This treatment potentially offers benefits for these patient groups that are not currently available.
Key messages	

19. In up to 5 bullet points, please summarise the key messages of your submission.

- Clinical trial data generated pre vaccination in the alpha and delta variant COVID epidemics suggests that early use of small molecule antiviral medications in high-risk patients starting within the first 5-7 days of onset of symptoms reduce need for hospitalisation and death by 50-80% as do monoclonals when the COVID variant is susceptible.
- Whilst absolute proof that antiviral treatment reduces long term morbidity the risk of continuing symptomatology in hospitalised patients is greater almost 30% and most cardiovascular symptomatology lasts more than 1 year.
- The use of antiviral medications in the UK has been restricted to those at the greatest risk of death. This has contributed to 10,000 or more patients being admitted to hospital weekly in the most recent wave, further reducing capacity within the over stretched health service and limiting the ability of the NHS to catch up with waiting lists and return to acceptable service levels for non COVID illnesses
- Real world evidence from the US suggests that proactive deployment of antiviral treatment in the community can reduce hospitalisations due to COVID within a highly vaccinated population
- Broadening access to antiviral medications to include all high-risk patients may reduce the burden of COVID related hospitalisations and enable the NHS to function more effectively
- The risk from COVID for individuals on immediate and long-term health is not equal across the population and current deployment policy may be discriminatory if vulnerable patients have no access to needed protection from COVID infection that is likely to hospitalise them

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

You can provide a unique perspective on the technologies in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UK Clinical Pharmacy Association (Critical Care)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with COVID-19? ☒ a specialist in the clinical evidence base for COVID-19 or the technologies? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Not-for-profit association of clinical pharmacists from across UK. Aim to promote best practice in clinical pharmacy to maximise patient benefits. Comprised of several specialist sub-groups, including many of the leading practitioners in their fields.**
5b. Have you or the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	**I have received no personal funding from any of the manufacturers.** **UKCPA organisational funding received from:** **Gilead - £600, annual UKCPA corporate membership fee** **Pfizer - £12,000, annual UKCPA corporate sponsorship fee including funds held to exhibit at UKCPA events**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatments for COVID-19	
6. What are the main aims of the treatments? (For example, to reduce specific long-term impact of COVID-19, lung damage, reduce length of stay in hospital) How does the aim differ per treatment?	Tocilizumab, baricitinib- To reduce the potentially life-threatening inflammatory effects of covid infection, mainly on lungs. A secondary effect would be to reduce severity of infection, and reduce length of hospital stay. Nirmaltrelvir/ritonavir, molnupiravir, remdesivir- Antiviral agents to reduce viral load, minimising impact of infection. First two largely used in out-patients to prevent hospital admission in highest risk patients; remdesivir more for in-patients (as requires intravenous administration) to reduce length and severity of symptoms. Sotrovimab, casirivimab/ imdevimab, tixagevimab/ cilgavimab- Monoclonal antibodies designed to enhance the immune system, mostly in those with impaired immunity, enabling the body to fight the virus. Currently largely seen as out-patient options to prevent hospital admission.
7. In your view, is there an unmet need for patients and healthcare professionals in	We are still learning about aspects of the condition, so still scope for novel agents and modified dosing regimes or combinations.

relation to therapeutics for treating COVID-19?	
What is the expected place of the technologies in current practice?	
8. How is COVID-19 currently treated in the NHS?	1) Vaccination 2) Early treatment of high risk patients 3) Symptomatic treatment if acutely unwell
• Are any clinical guidelines used in the treatment of COVID-19, and if so, which?	Majority of clinicians follow a series of Clinical Commissioning Policies produced by the UK Chief Medical Officers for these agents. Tixagevimab/ cilgavimab still under evaluation, so no guideline in place.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. Minimal variation, though some questions about optimal dosing, retreating with antivirals and efficacy of MABs in particular against newer variants. Questions over cost-effectiveness of early treatment of high risk patients, as no indication of baseline morbidity with current variants/ vaccination.
• At what point after being diagnosed with COVID-19 do people receive any form of treatment from the NHS?	Highest risk patients (defined by CMOs) treated as soon as possible after positive test to ensure early action to minimise potential for deterioration. General population only treated if there is significant deterioration.

• How does the pathway differ by patient group (by age, underlying conditions, risk of hospitalisations, vaccination status)?	Under 18s treated less aggressively due to perceived lower risks. High risk patients, for early treatment, are defined in the “McInnes report. High levels of vaccination mean non-vaccinated are not considered any differently.
Hospital and community treatment settings • How does the pathway differ by setting (for example community versus hospital)? • How long on average do people spend in hospital? • What proportion of people hospitalised develop long-covid? • What proportion of people offered treatment for COVID-19 in the community develop long-covid?	• Early treatment of high risk patients is largely oral therapy as out-patients. Treatment of symptomatic patients is largely in hospital. Nowadays fewer patients need ICU level care. • Not aware of current length of stay figures as has varied over time with introduction of new treatments, vaccination status and variants, e.g. length of stay was longer in the second pandemic surge. Few have major illness, and many are in for only a few days. Frail patients may have prolonged stay due to isolation requirements, or lack of care provision in community. • Not clear. Whether long-covid “symptoms” are a result of post ICU syndrome, genuine physical complications of covid (eg venous thromboembolism, lung damage) or a post viral syndrome or a combination of all three is not clear. Questions whether all cases can be considered in the same way. • No proven therapies exist for long covid, though increased ICU follow up may help some aspects of post-ICU syndrome where this is a major part of the problem.
Long-covid	See above

• What treatments are offered for people with long-covid? What are the symptoms of long-covid? On average, how long do the symptoms of long-covid last?	
• What impact would the technologies have on the current pathway of care?	Current therapies not thought to have a particular impact on long covid, though appropriate general treatment may reduce some long-term effects resulting from physical damage (eg lung function)
9. Will the technologies be used (or are they already used) in the same way as current care in NHS clinical practice?	Already used as current therapy
• How does healthcare resource use differ between the technologies and current care?	No difference
• In what clinical setting should the technologies be used? (For example,	Early treatment of high risk patients- largely in Primary Care Symptomatic treatment largely in Secondary Care

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technologies? (For example, for facilities, equipment, or training.)	Arrangements for supply of early antivirals and nMABS could be improved. Currently different models are in place according to local circumstances and resources, but often involve secondary care in what should be a largely primary care activity, and may not be very convenient for patients. It would be useful to investigate different models
• Do you expect any of the new technologies to help prevent long-covid or reduce the length of stay in hospital?	As already in common use, and less severe symptoms evident, minimal effect on length of stay. Further information on long covid is required for understanding what might work.
10. Are there any groups of people for whom the technologies would be more or less effective (or appropriate) than the general population?	There remains little good evidence of the efficacy of early treatment in the perceived high risk patient group. However difficult to study against no treatment on ethical grounds, so probably needs to be continued based on assumptions.
The use of the technologies	
11. Do you consider that the use of these technologies will result in any substantial health-	No

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
12. Do you consider any of these technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits?	Yes. Previously limited treatment options.
• Are the technologies a 'step-change' in the management of COVID-19?	Long action of tixagevimab/cilgavimab could be an effective preventative in addition to vaccination in highest risk patients
• Does the use of these technologies address any particular unmet need of the patient population?	Yes. Novel treatments for a new infection
13. How do any side effects or adverse effects of these technologies affect the	Side effects do not appear to be a major problem.

management of COVID-19 and the patient's quality of life?	
Sources of evidence	
14. Does the clinical evidence on the technologies reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the clinical evidence?	Effective treatments reducing mortality
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials	No, though increasing concern about reactivation of viral activity after initial treatment

but have come to light subsequently?	
15. Are you aware of any new evidence for the treatments since the publication of the assessment report?	Recent data on efficacy of sotrovimab against new variants Sotrovimab to prevent severe COVID-19 in high-risk patients infected with Omicron BA.2 - Journal of Infection Also evolving evidence on the role of pharmacogenetics which may lead to use of specific therapies (eg JAK inhibition) from GenOMICC programme.
16. How do data on real-world experience compare with the trial data?	Largely appears consistent in practice.
17. What issues do you foresee with the data and how do you think this may impact treatment effectiveness for future variants? (For example, the data available is heterogeneous and includes treatment effectiveness pooled over different variants of COVID-19	A large proportion of the evidence relates to studies carried out before large scale vaccination. Morbidity appears to have reduced since then, and also new virus variants have become predominant. The impact of some treatments could therefore be over-estimated as regards the current virus, while efficacy could also be reduced.

(primarily delta). People with different vaccination status could also impact the treatment effectiveness calculations.)	
Equality	
18a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
18b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

19. In up to 5 bullet points, please summarise the key messages of your submission.

- New technologies have been implemented rapidly and seem to have had a significant effect.

- Still early days in the knowledge of best treatment options- still potential for dose optimisation and combination therapy
- An evaluation of the cost-effectiveness of early treatment of high risk patients might be beneficial
- Further studies on the efficacy of antivirals and particularly MABs against new variants are required.
-

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Therapeutics for people with COVID-19 [ID4038]

Thank you for agreeing to give us your organisation's views on these technologies and their possible use in the NHS.

You can provide a unique perspective on the technologies in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UK Kidney Association**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with COVID-19? ☐ a specialist in the clinical evidence base for COVID-19 or the technologies? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The leading professional body for the UK renal community, dedicated to improving lives by supporting professionals in the delivery of kidney care and research. Funded by membership fees and NHS capitation fees.
5b. Have you or the organisation received any funding from the	UKKA - AstraZeneca: £89220, event sponsorship/corporate membership UKKA - GSK: £4995, grant UKKA - Pfizer: £175000, research project work UKKA - Roche: £10500, corporate membership

manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and	

purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatments for COVID-19	
6. What are the main aims of the treatments? (For example, to reduce specific long-term impact of COVID-19, lung damage,	The treatments vary in their mechanisms of actions and aims: The antivirals _ Remdesivir molnupiravir, nirmatrelvir and ritonavir, (paxlovid hereafter for ease) - Predominantly for treating active early infection either pre hospital (all of them) in symptomatic patients or in hospital - (remdes only) with different guidance depending on whether immunocompromised or not The neutralising mAbs – for improving clearance of virus pre exposure (evusheld) or once infected pre hospital (sotrovimab) or in hospital (ronapreve no longer in use and reduced efficacy vs omicron) tixagevimab and cilgavimab (evusheld)

reduce length of stay in hospital) How does the aim differ per treatment?	casirivimab and imdevimab (ronapreve) sotrovimab The anti-inflammatories for treating hospitalised patients with covid pneumonitis – baricitinib improved outcomes regardless of oxygen requirement whereas tocilizumab is limited to use for those requiring oxygen and CRP >75. tocilizumab baricitinib, All the treatments used pre hospital aim to reduce the risk of more severe disease requiring hospitalisation and the in hospital treatments for reducing likelihood of requiring invasive ventilation or death from covid. None of the treatments reduces transmission and I do not know if any been shown to reduce the risk of long covid though if COVID infection prevented e.g with pre exposure prophylaxis (PrEP) then it is likely Long covid will be prevented. However the primary aim of these treatments is to reduce severity of acute COVID infection

7. In your view, is there an unmet need for patients and healthcare professionals in relation to therapeutics for treating COVID-19?	Yes. The groups most at risk of doing badly now are those highlighted in the latest QCovid reports (https://www.medrxiv.org/content/10.1101/2022.08.13.22278733v1 and OpenSafely https://www.medrxiv.org/content/10.1101/2022.07.30.22278161v1 - the absolute risk of death / severe disease has definitely decreased in all groups but immunocompromised individuals and those with advanced chronic kidney disease (CKD stages 4 and 5) are now at hugely relative risk of doing badly. And that is in face of ONS estimates that 13% of CEV (ie 65,000 out of 500,000) individuals continue to shield – ie are limiting their exposure to virus and probably influencing outcomes in this way. Nearly all these drugs were trialled on variants that are no longer dominant so the applicability and appropriatedness in the omicron era has largely not been tested. Ronapreve no longer used as was shown to be ineffective in vitro (tho was that true in vivo; data suggests sotrovimab also has reduced effectiveness in vitro but RWE suggests quite effective still. The drugs are approved for use based on quite rigid criteria – within hospital settings it is often easier to be a bit more flexible in application but CMDUs are very rigid in interpretation – so if a highly at risk patient says they don't feel ill they are denied treatment as "asymptomatic", similarly if there are delays in their referral to the CMDU they are often denied treatment. This is likely very variable around the country. It makes sense to target the nMAbs to those with no antibody responses to vaccines yet antibody is by no means routine in the populations we know likely to make poor antibody responses eg those with solid organ transplants, those with autoimmune diseases who have had B cell depleting therapies, those with blood cancer etc.

	From a patient perspective the uncertainty about risk and the unavailability of evusheld is causing anguish in the kidney community – many patients voluntarily shield, have lost their jobs, their social networks as they feel completely unprotected. The mental health toll is immense.
What is the expected place of the technologies in current practice?	
8. How is COVID-19 currently treated in the NHS?	According to the NHSE guidance that has sequentially come out. Refer to the CAS alerts for non hospitalised and hospitalised patients – https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103208 https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103207 There are now really quite complicated algorithms. Many trusts have tried to simplify these. There is separate guidance on use of oxygen, anticoagulants etc.
• Are any clinical guidelines used in the treatment of COVID-19, and if	As above

so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In theory the pathway is clearly defined but how well and flexibily this is applied I suspect varies hugely across the country. Some trusts have set up detailed guidance (or did until recently). This is particularly useful for complex patients e.g. those with persistent virus due to immunocompromise, those who are heavily immunosuppressed – weighing the risk benefit of adding baricitinib / tocilizumab is not necessarily straightforward and in many trusts it is likely that the default is to be risk averse and not use these treatments.

• At what point after being diagnosed with COVID-19 do people receive any form of treatment from the NHS?	As soon as lateral flow positive AND symptomatic, CEV patients (as definited by NHSE) can be referred to CMDU for prehospital treatment. They need to be referred and treated within 5 days of presentation. There is waning recognition of this pathway, patients need to be aware of it (especially now the CEV list has been abandoned and it wasn't up to date anyway) and patients cannot refer themselves directly – need to be referred by GPs – difficult over a weekend or in the current GP workload crisis. Otherwise their specialists refer but they should be able to self refer by filling in an econsult given the time restraints. If they are admitted to hospital and found to be covid+ (incidental finding) there is a pathway but routine asymptomatic testing in most groups about to stop so they could well be infected, at risk of worse outcomes and infect others around them. If sick with covid pneumonitis there is a clear treatment pathway.
• How does the pathway differ by patient group (by age, underlying conditions	A large proportion of kidney patients are eligible for pre hospital treatment by dint of advanced CKD, solid organ transplantation or being immunosuppressed for autoimmune kidney disease. Just being old (despite probably still being the biggest risk factor for doing badly) doesn't not entitle to pre hospital treatment. Nor does having had very severe covid / long covid previously.

, risk of hospitalisations, vaccination status)?	
Hospital and community treatment settings • How does the pathway differ by setting (for example community versus hospital)? • How long on average do people spend in hospital?	As above LoS very variable and likely reduced in recent months PHospCOVID will shed light on proportion of patients getting long covid…. https://pubmed.ncbi.nlm.nih.gov/35472304/ It is estimated there are now millions of people living with long covid – COVID-Zoe will shed light ONS has recently suggested 2 million - https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/infections We do not yet know if kidney patients disproportionately affected (due to high rates of infection, more severe infections etc) and indeed some symptoms of long covid will be difficult to discern from those of advanced CKD

• What proportion of people hospitalised develop long-covid? • What proportion of people offered treatment for COVID-19 in the community develop long-covid?	
Long-covid • What treatments are offered for people	Diverse, very much depends if have access to long covid clinics. We do not know how common or severe long covid is in Kidney patients and many symptoms may overlap with those of their underlying disease or kidney dysfunction. This is currently an unmet need

with long-covid? What are the symptoms of long-covid? On average, how long do the symptoms of long-covid last?	
• What impact would the technologies have on the current pathway of care?	These technologies are in use (bar Evusheld) and have had major impact. Pre hospital treatment has almost certainly improved outcomes for vulnerable patients BUT there are disparities in uptake and access that need to be addressed - https://www.medrxiv.org/content/10.1101/2022.08.17.22278893v1 - particularly in minority groups who are overrepresented amongst those with kidney disease

9. Will the technologies be used (or are they already used) in the same way as current care in NHS clinical practice?	They are all in routine use in the NHS bar evusheld. I suspect there will be a loss of expertise as severe covid becomes more infrequent (we hope) and that is likely to lead: a) to loss of timely referral for pre hospital treatment (especially now testing more difficult, people having to pay for lateral flows, routine testing of asymptomatic high risk patients e.g. those on dialysis, has been dropped) b) Loss of timely in hospital treatments – most a time restricted; people already overlook given remdesivir regardless of timing and for 10 days in the immunosuppressed. More likely to lead to late / no delivery of necessary meds; The complexity of the current pathway, the introduction of recommendation to use baricitinib even in the absence of oxygen requirement – is this treating too many people (the data are not from the omicron era?) and if then need oxygen the safety of combining tocilizumab and baricitinib especially in those with advanced CKD / heavily immunosuppressed already.
• How does healthcare resource use differ between the technologies and	Evusheld not available The technologies are part of current care tho it is not clear how widely everything implemented. CMDUs were

current care?	
• In what clinical setting should the technologies be used? (For example, primary or secondary care, specialist clinics.)	Currently all should be administered via CMDUs or secondary care. In time it may be appropriate to be able to prescribe oral antivirals from primary care but given their complex drug interactions this might not be practicable.
• What investment is needed to introduce the technologies? (For	This is all after the fact. The CMDUs are designed to give though for instance I think very few offering 3 days of IV remdesivir as just too difficult for patients to attend when infected and at a distance. So resource should be designed for more local hubs to administer the drugs with oversight from the centre

example, for facilities, equipment, or training.)	
• Do you expect any of the new technologies to help prevent long-covid or reduce the length of stay in hospital?	Yes All of them if given in a timely manner have evidence to reduce severity / LoS – less clear about long covid
10. Are there any groups of people for whom the technologies	Kidney patients are very disadvantaged due to these drugs being problematic if kidney function reduced and because of drug interactions with drugs commonly used by kidney patients. **Several of the drugs cannot be used in the face of reduced kidney function:** **Remdesivir** – cannot be used in those with an eGFR<35msl/min unless on haemodialysis.

would be more or less effective (or appropriate) than the general population?	Excludes a lot of patients especially as many of those with less severe CKD get acute kidney dysfunction early on in a severe infection. **Mulnopirivir** – no data on use in dialysis patients, said not to need dose reduction in renal impairment but really very little data **Paxlovid** – not recommended in those with eGFR <30mls/min and dose reductions needed (which are complex for patients) if eGFR 30-60mls/min **Bariticinib** cannot be used if eGFR <30mls/ min and dose reduction advised between eGFR 30-60mls/min
The use of the technologies	
11. Do you consider that the use of these technologies will result in any substantial health-related benefits that	Well the patients more likely to survive but that should be captured. Key issues that I do not have the answer for and should be included in the modelling: 1) Reduced rates of admission 2) Reduced length of stay 3) Reduced use of ICU / HDU beds 4) Reduced rates of long covid and more rapid return to work

are unlikely to be included in the quality-adjusted life year (QALY) calculation?	5) Reduced mental health issues due to stress of inadequate response to vaccine and no access to PrEP
12. Do you consider any of these technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits?	Yes – Particularly the one that is not available – PrEP with evusheld or others – could be a real game changer. Many immunosuppressed kidney patients continue to shield as they fear they don't respond to vaccines (many studies attest to the reduced response rates already – see work from OCTAVE and OCTAVE-DUO, multiple publcations from Imperial cohorts (lead author Willicombe M), also work from Crick – (Beale R and Carr E key authors). And ongoing MELODY study will provide data on serology and infection rates before the end of 2022 in nearly 30,000 immunosuppressed patients (solid organ transplants, blood cancer and rare autoimmune diseases). Yet antibody testing not routinely available so patients don't know if protected or not. Need to consider giving PrEP to All at risk or stratify by ab testing and give to those with no response. Won't provide complete protection but very likely

	To reduce severity and need for hospitalisation From published data (e.g. see data from Israel https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciac625/6651663?login=false and see most recent from France https://www.kireports.org/article/S2468-0249(22)01720-X/fulltext Would allow those at risk to participate in society again – work, school, etc.
• Are the technologies a 'step-change' in the management of COVID-19?	Yes. First wave massive mortality for kidney patients – especially those on dialysis. Many factors but without a doubt the introduction of vaccines, in hospital treatments and since late Dec pre hospital treatment, mortality has clearly declined (see open safely data) BUT CKD and immunosuppressed patients now have a hugely increased relative risk of death / severe disease vs others. Absolute rates lower but huge cause for concern to our patients.
• Does the use of these technologies address any particular unmet	Yes Evusheld – as above. Need PrEP for those who do not respond to vaccines (probably in the region of 20-30% of Immunosuppressed patients. They are currently living in fear of life threatening infection. Need easier access to pre hospital treatments and need to continue to offer nMAbs as most of the other drugs not Able to be used in those with impaired kidney function / solid organ transplants.

need of the patient populatio n?	
13. How do any side effects or adverse effects of these technologies affect the management of COVID-19 and the patient's quality of life?	There were some reports of severe nausea and vomiting with mulnopirivir leading to toxic levels of anti rejection Medicine tacrolimus – which in turn contributed to severe AKI. Need to know from yellow card system how common However, mulnopirivir now very suboptimal in protection offered and probably should no longer be. All patients with significantly impaired eGFR can't have most of these drugs (see earlier) or cannot have paxlovid Because of drug interactions so their options very limited. Huge cause for concern. Only option pre hospital now is Sotrovimab and in hospital tocilizumab (unless on haemodialysis) can have remdesivir. So prevention MUCH better Option than treatment – need access to PrEP with evusheld
Sources of evidence	
14. Does the clinical evidence on the technologies reflect current UK clinical practice?	Yes for everything except PrEP – been strictly controlled by NHSE based on evidence. Some flexibility would be welcome e.g. not having to have CRP 75 to get tocilizumab pre escalation of ventilation. Evidence now largely based on Wuhan and delta strain – need ongoing data on omicron and upcoming variants. The outlier is Evusheld – not available in UK, being used routinely in 32 other HIC. We are definitely an outlier.
• If not, how could the results be	I don't know the data well enough but given that age remains the biggest risk for doing badly, age alone might be A consideration for post exposure pre hospital prophylaxis. Kidney patients benefit from being considered if CKD4 or 5

extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the clinical evidence?	Given the change in variants, the most important outcomes now should be: Not requiring hospitalisation As well as not requiring HDU/ICU / death. There is good evidence for evusheld, and for the pre exposure drugs but not sure current NHSE rules cover all those In the evidence. Immunosuppressed were often excluded from the evidence especially in the early studies.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Do we know? Requiring ICU/HDU clearly predicts doing worse long term but we don't yet know the long term impact of COVID That didn't require hospitalisation on long covid, on long term kidney function, on flares of autoimmunity or rejection Episodes in transplant patients. These could be significant and viruses in general known to trigger these and if could Prevent with PrEP would have big long term impact

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Need yellow card data but concerns re AKI and mulnopirivir (possibly secondary to nausea and vomiting and resulting Tacrolimus toxicity)
15. Are you aware of any new evidence for the treatments since the publication of the assessment report?	Mostly cited above but ongoing publications from OpenSafely, OCTAVE and OCTAVE duo soon to publish
16. How do data on real-world experience compare with the trial data?	MELODY will publish in autumn / winter 2022 Most real world data has shown significant protection ongoing from nMAbs pre or post exposure despite lab assays not Showing such good neutralisation.

17. What issues do you foresee with the data and how do you think this may impact treatment effectiveness for future variants? (For example, the data available is heterogeneous and includes treatment effectiveness pooled over different variants of COVID-19 (primarily delta). People with different vaccination status could also impact the treatment effectiveness calculations.)	Much of the data (even that coming out now) is completely out of date, was based on a time when dealing with Wuhan or delta and not omicron, when were not routinely using tocilizumab, when the main feature was hyperinflammation. Need ongoing and rapid responses to new variants. That this MTA is not reporting til mid 2023 is an absolute travesty. These drugs generally became available pari passu with top line data (pre publication) of the trials particularly RECOVERY. Yet despite good quality trial data, RWE and MHRA approval, there is no availability of Evusheld in advance of the Winter wave which will come. We must not lose the rapid response approach – people will die waiting and possibly unnecessarily We need routine anti S ab screening for patients at risk of poor vaccine responses – this was required for ronapreve Use but has been dropped. Should be available for guiding use of PreEP and choosing best post exposure treatment

Equality	
18a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patients from minority backgrounds have greater rates of CKD, less likely to have transplants and have been the groups Amongst those with the worst outcomes from COVID. As mentioned above there is evidence of inequity of access to Post exposure pre hospital treatment in these groups. Improvements need to be made to ensure optimal treatment available and ideally PrEP for these patients.
18b. Consider whether these issues are different from issues with current care and why.	
Key messages	

19. In up to 5 bullet points, please summarise the key messages of your submission.

- The access to pre hospital post exposure treatments is excellent but choice remains very limited for patients with kidney disease /
  Solid organ transplants. Need to maintain access to nMAbs even if less cost effective.
- Need to offer Pre exposure prophylaxis (currently approved but not available) for those at risk from poor vaccine responses and poor
  Outcomes from COVID infections. This should not wait til the MTA reports in spring/ summer 2023. The need is now.
- In hospital treatment – limited options again for patients with kidney disease and access to nMAbs should be considered (RECOVERY
  Is currently evaluating Sotrovimab in patients hospitalised with covid pneumonitis – earlier studies were not in this group). – Ronapreve
  Was very helpful in this setting with Delta variant.
- Need rolling trials evaluating impact of these drugs in the more vulnerable (CKD, immunosuppressed) groups and evidence base should
  Include RWE.

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Professional organisation submission

Therapeutics for people with COVID-19 [ID4038]

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You can provide a unique perspective on the technologies in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted] & [redacted]
2. Name of organisation	UK Renal Pharmacy Group

3. Job title or position	[redacted] & [redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with COVID-19? ☐ a specialist in the clinical evidence base for COVID-19 or the technologies? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Renal Pharmacy Group is a group of pharmacists and technicians with an interest in renal. We are a charity and part of the UK Kidney Association. We are sponsored by industry partners to enable a yearly conference.
5b. Have you or the organisation received any funding from the manufacturer(s) of the technologies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	1. AstraZeneca – annual RPG conference funding for 2022 = £5000

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatments for COVID-19	
6. What are the main aims of the treatments? (For example, to reduce specific long-term impact of COVID-19, lung damage, reduce length of stay in hospital) How does the aim differ per treatment?	Sotrovimab, paxlovid, remdesivir and molnupiravir – aim is to reduce severity of disease and prevent hospital admission for patients who are deemed at highest risk from COVID-19. Ronapreve (casirivimab + imedevimab) had same aim but this treatment option was withdrawn end 2021 as it was shown to be ineffective against Omicron variants, which were and remain the dominant circulating strain(s). Tocilizumab– reduce mortality Baricitinib – reduce mortality especially in context of viral pneumonia syndrome Tixagevimab and cilgavimab – specifically to be used in patients with no COVID antibodies who have not mounted a response to vaccination due to their attenuated immune system or who were not able to be vaccinated. It is to be used as pre-exposure prophylaxis in patients who are not currently infected with COVID.
7. In your view, is there an unmet need for patients and healthcare professionals in	Yes there is, for patients with a eGFR<30ml/min who are not on dialysis, there are less treatment options as paxlovid and remdesivir can't be used in this patient cohort due to paucity of data. There is some limited experience of using remdesivir on a case by case basis. A safety and dosing trial is due to start later this

relation to therapeutics for treating COVID-19?	year for Paxlovid use in patients with CKD (<30ml/min) or on dialysis. Baricitinib is also excluded for use in patients with eGFR <15 or on haemodialysis.
What is the expected place of the technologies in current practice?	
8. How is COVID-19 currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of COVID-19, and if so, which?	Extensive NICE guidance (e.g. 173, 165, NG191) CAS alerts, MHRA – EAMS. From our experience most hospital COVID guidelines reflect current national COVID guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes well defined, however there can be differences of opinion in some nuanced clinical situations. Service delivery capacity can also impact on treatment choice for non-hospitalised COVID+ patients.
• At what point after being diagnosed with COVID-19 do people receive any form of treatment from the NHS?	High risk patients who are symptomatic and showing no evidence of clinical recovery are offered COVID treatment (antiviral or nmab) within 5 days of symptom onset or positive covid test via CMDU triaging – flagged via NHS webportal or GP/HCP email to local CMDU. , All patients receive appropriate treatment if admitted to hospital and requiring oxygen therapy as per hospital antimicrobial guidelines in line with national COVID guidelines.

• How does the pathway differ by patient group (by age, underlying conditions, risk of hospitalisations, vaccination status)?	Most hospital adult guidelines, in our experience are hierarchical in approach and risk stratify patient on clinical condition. Some treatments are considered on individual risk/benefit basis e.g. use of tocilizumab in someone who is recently immunosuppressed.
Hospital and community treatment settings • How does the pathway differ by setting (for example community versus hospital)? • How long on average do people spend in hospital? • What proportion of people hospitalised develop long-covid? • What proportion of people offered treatment for COVID-19 in the community develop long-covid?	2 x settings (community & hospital) both have protocolised treatment pathways as per national guidelines
Long-covid	No patient experience with long covid

• What treatments are offered for people with long-covid? What are the symptoms of long-covid? On average, how long do the symptoms of long-covid last?	
• What impact would the technologies have on the current pathway of care?	
9. Will the technologies be used (or are they already used) in the same way as current care in NHS clinical practice?	Yes – the technologies should continue to be commissioned via evidence based clinical pathway national guidelines to ensure all patients have access to the same treatment options, guided by their clinical presentation and symptoms.
• How does healthcare resource use differ between the technologies and current care?	CMDU work load within secondary care is largely additional work taken on by service users whose patients are high risk, vulnerable groups for severe COVID infection. This work is not currently commissioned by ICS. We would like to highlight that this additional work should be funded to ensure sustainability.
• In what clinical setting should the technologies be used? (For example,	

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technologies? (For example, for facilities, equipment, or training.)	Facilities for IV administration, staffing – currently largely unfunded in secondary care (eg CMDU triaging and drug delivery/administration) and service provided is an additional service on top of routine workload. Service provision needs to be sustainable.
• Do you expect any of the new technologies to help prevent long-covid or reduce the length of stay in hospital?	Yes – more preventative therapies would hopefully prevent people from being admitted with covid
10. Are there any groups of people for whom the technologies would be more or less effective (or appropriate) than the general population?	
The use of the technologies	
11. Do you consider that the use of these technologies will result in any substantial health-	

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
12. Do you consider any of these technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits?	
• Are the technologies a 'step-change' in the management of COVID-19?	Yes they are a 'step change' in COVID management until other therapies are identified via randomised controlled clinical trials.
• Does the use of these technologies address any particular unmet need of the patient population?	
13. How do any side effects or adverse effects of these technologies affect the	

management of COVID-19 and the patient's quality of life?	
Sources of evidence	
14. Does the clinical evidence on the technologies reflect current UK clinical practice?	UK hospital /CMDU guidelines reflect national advice as per CAS alerts/NICE guidance/MHRA
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the clinical evidence?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials	

but have come to light subsequently?	
15. Are you aware of any new evidence for the treatments since the publication of the assessment report?	Remdesivir – has been safely used in dialysis patients, a 3-5 day course could safely be used in patients with an eGFR<30ml/min who are not on dialysis on a risk/benefit basis. Clinical evidence to support this awaited. Paxlovid dosing and safety study in the US for patients with CKD (eGFR<30ml/min) or on dialysis. Some anecdotal individual case reports of reduced doses being used in CKD (eGFR<30ml/min).
16. How do data on real-world experience compare with the trial data?	
17. What issues do you foresee with the data and how do you think this may impact treatment effectiveness for future variants? (For example, the data available is heterogeneous and	

includes treatment effectiveness pooled over different variants of COVID-19 (primarily delta). People with different vaccination status could also impact the treatment effectiveness calculations.)	
Equality	
18a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patients with an eGFR<30ml/min who are not on dialysis are subject to drug choice restrictions arising from paucity of drug dosing data in CKD e.g. remdesivir, paxlovid, baricitinib (eGFR <15ml/min). Limited treatment options can translate to less effective treatment being offered. Routine testing of antibody status should be used to identify at risk immunocompromised individuals via their specialist clinic follow up to guide use of pre-exposure preventative therapies (if/when available).
18b. Consider whether these issues are different from issues with current care and why.	

Key messages
19. In up to 5 bullet points, please summarise the key messages of your submission. • Treatment option inequality for patients with eGFR<30ml/min who are not on dialysis are subject to drug choice restrictions arising from paucity of drug dosing data in CKD e.g. remdesivir, paxlovid, baricitinib (eGFR <15ml/min). • Routine testing of antibody status should be used to identify at risk immunocompromised individuals via their specialist clinic follow up to guide use of pre-exposure preventative therapies (if/when available). • staffing – currently largely unfunded in secondary care and service provided (eg CMDU triaging and drug delivery/administration) is an additional service on top of routine workload. Service provision needs to be sustainable. • •

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal
Therapeutics for people with COVID-19 [ID4038]
NHS organisation submission (ICB and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes or No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes or No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? Yes or No An expert in treating the condition for which NICE is considering this technology? Yes or No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the taxpayer. During the pandemic, NHS England has been a decision-making member of the RAPID C-19 collaboration and also led on the development of UK wide clinical access policies, for subsequent approval by the Chief Medical Officers.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Currently there are various Chief Medical Officer approved UK-wide interim clinical commissioning policies in place which support the use some of the drugs listed within the MTA scope, namely: • Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies in the treatment of hospital-onset COVID-19 - nirmatrelvir/ritonavir, remdesivir and sotrovimab • Interim clinical commissioning policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19 - nirmatrelvir/ritonavir, remdesivir, sotrovimab and molnupiravir • Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised due to COVID-19 (adults and adolescents 12 years and older) • Interim Clinical Commissioning Policy: IL-6 inhibitors (tocilizumab or sarilumab) for hospitalised patients with COVID-19 (adults) • Interim clinical commissioning policy: Baricitinib for patients hospitalised due to COVID-19 (adults and children aged 2 years and over) All policies are available at: Coronavirus » Rapid Clinical Policy development: COVID-19 (england.nhs.uk) or via CAS - Coronavirus (COVID-19) Alerts (mhra.gov.uk) These policies are all interim and have been developed under agreed pandemic-specific governance arrangements which have produced rapid UK wide clinical policies during the pandemic. In most cases, the policies will be superseded by the obligations which follow the publication of NICE Technology Appraisal guidance recommendations as these will place statutory obligations on the relevant commissioner for the COVID treatment concerned (in most cases this will be Integrated Commissioning Boards (ICBs) in England).

7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is currently via: • Secondary care (hospital provider trusts in England), for hospital-onset COVID-19 (for people considered to be those at the highest risk of developing severe complications from COVID-19) and for people hospitalised due to COVID-19 • Assessment of patients by a COVID-19 Medicine Delivery Unit (CMDU) for people presenting in the community; with administration or supply via the CMDU. This route if available for people considered to be at the highest risk of developing severe complications from COVID-19, under the UK clinical access policy. These service arrangements may be amended at local level as we transition to ICB led 'BAU' commissioning arrangements Planning continues on the potential for wider deployment of COVID therapeutics, including oral antivirals (AVs), for example via GPs and community pharmacies. Current use of nirmatrelvir/ritonavir, remdesivir, sotrovimab and molnupiravir is guided by risk category, as defined at: https://www.gov.uk/government/publications/highest-risk-patients-eligible-for-covid-19-treatments-guide-for-patients/highest-risk-patients-eligible-for-new-covid-19-treatments-a-guide-for-patients). Use of these agents, as detailed in the NICE MTA scope, refers to use in line with their marketing authorisations, which is a wider cohort of patients.
8. What impact would the technology have on the current pathway of care?	Treatment access to the medicines covered under the scope of the MTA are already available to the England (and wider UK) population within the criteria of the relevant published clinical commissioning policies. Impact is dependent on a number of elements, including cohort coverage, infection rates, prevailing (sub)-variant(s), vaccination status, response and duration of immunity. CMDUs have been set up specifically to support treatment of prioritised community cohorts during the pandemic. Future models, including the potential for wider deployment, are being planned with ICB colleagues. There may be differing, and potentially significant impacts should there be material new waves of infection, waning vaccine immunity and / or emergence of new variants.

The use of the technology

9. To what extent and in which population(s) is the technology being	The following therapies are currently in use, in line with eligibility criteria in the UK wide clinical access policies detailed above:

used in your local health economy?	• Remdesivir: people at highest risk, with COVID-19, presenting in the community; people at highest risk with hospital-onset COVID-19; people hospitalised with COVID-19 • Tocilizumab or sarilumab: people hospitalised due to COVID-19 (adults) • Casirivimab and imdevimab: not currently recommended due to concerns regarding retained activity against current variants • Baricitinib: people hospitalised due to COVID-19 (adults and children aged 2 years and over) • Sotrovimab: people at highest risk, with COVID-19, presenting in the community; people at highest risk with hospital-onset COVID-19 • Molnupiravir people at highest risk, with COVID-19, presenting in the community • Nirmatrelvir/ritonavir: people at highest risk, with COVID-19, presenting in the community; people at highest risk with hospital-onset COVID-19 • Tixagevimab and cilgavimab: not currently used
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Potentially, but this will depend on the specific recommendations made by NICE in comparison with current CMO led access decisions. For example, AVs and MABs used in the community setting are currently only routinely available for people at highest risk of COVID-19; use in line with marketing authorisations would extend use to a wider cohort of people. There is some wider trial based access to oral antivirals via the PANORAMIC trial. Are the recommendations likely to be contingent? For example, in relation to: • prevailing levels of infection and virulence (such as severity of outcomes (risk of hospitalisation; death))? • variant/sub-variant virus and associated severity of infections? • advice on variants and neutralisation capability of COVID-19 monoclonal antibody therapies from MHRA/UKHSA?
10a. How does healthcare resource use differ between the technology and current care?	The COVID-19 medicines currently available in England, in line with the interim policies detailed above, have been either: • Procured and funded by the DHSC (remdesivir, sotrovimab, molnupiravir, nirmatrelvir/ritonavir and casirivimab and imdevimab (noting this combination is not currently recommended) • Procured via usual routes and reimbursed by DHSC (baricitinib, tocilizumab)

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The therapies are currently used in the following settings: • Secondary care (baricitinib, tocilizumab, nirmatrelvir/ritonavir, remdesivir, sotrovimab and molnupiravir) • Community settings, currently via the CMDUs (nirmatrelvir/ritonavir, remdesivir, sotrovimab and molnupiravir) Work is underway under the leadership of ICBs to agree future service delivery models. It is expected that future delivery may be accessed via a primary care 'front door'
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	NHS England is working directly with NICE to determine appropriate estimates of NHS treatment administration costs for the medicines covered within the scope of the MTA. NHSE has highlighted the importance of considering the resources required for the whole patient pathway, including testing, patient transport, medicine delivery / courier costs etc. Funding of COVID-19 therapeutics has been via the DHSC during the Pandemic. The NHS will need to fund these treatments, dependent on a positive recommendation, after publication of the NICE MTA (subject to the usual timing requirements for funding to be made available).
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Current interim policies require that SARS-CoV-2 infection is confirmed by either: Community and hospital-onset: • Polymerase chain reaction (PCR) testing OR • Lateral flow test Hospitalised due to COVID-19: • SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or where a multidisciplinary team (MDT) has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis Starting and stopping criteria for each medicine / healthcare setting differ and are set out in the relevant published interim clinical commissioning policies
11. What is the outcome of any evaluations or audits of the use of the technology?	N/A

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	A review of access to COVID medicines to highest risk patients in community settings has highlighted areas of potential inequality of access common to some other areas of healthcare access (including COVID vaccination). For example, access is lower than expected for those in younger or older age groups, for those in more deprived groups, and for those with black African, black Caribbean or mixed race ethnicity.
12b. Consider whether these issues are different from issues with current care and why.	An inequalities impact assessment would need to properly consider whether these identified risks were likely to be mitigated or extended under NICE's MTA recommendations, once available.

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CMDU Deployment Costs – Position Statement

Summary

This paper highlights the key stages of producing guidance on the coding of COVID-19 activity undertaken by COVID Medicine Delivery Units (CMDUs) and details how indicative local tariffs were calculated.

Cost of IV administration

In July 2021 coding guidance was provided by the National Specialised Commissioning team on how to code COVID-19 patients who were being treated within acute or community Hospital settings, in mobile facilities or at home under the published UK wide clinical access policy for non-hospitalised patients at highest risk . Advice was to utilise the following combination of codes:

- Primary diagnosis code (ICD10): U071: COVID-19, virus unidentified
- OPCS codes were:
    - X891: Monoclonal antibodies Band 1 or
    - X892: Monoclonal antibodies Band 2.

Any spells coded as above would group to HRG code DX21: COVID-19 infection. Neither core HRGs DX21A or DX21B (age dependent) had national tariffs at the time in 2021/22, and still don't.

It was suggested that non-admitted patient care treatment could be recorded in the Outpatient CMDS and that the diagnosis field, which is not routinely completed, be used to include the U071 code and relevant OPCS codes (X891 / X892).

An indicative local tariff of £362 per spell plus Market Forces Factor (MFF) was suggested. This figure was based on national tariffs for similar treatments with a 10% COVID uplift.

The costs of any drugs were being met nationally by the Department of Health & Social Care (DHSC). The costs of any administration of the drugs were expected to be made available from local system envelopes.

Costing Exercise

Around 100 CMDUs were set up and went live on December 2021 across England. These were to enable patients with the highest risk of severe illness, hospitalization or death to access treatments and reduce their risk of hospitalisation.

Due to the speed with which these units had to be set up, there was no 'one size fits all' structure. However, they did all have the following elements in common:

1) Telephone triage
2) Clinical assessment to ensure suitability
3) Provision of clinical information and ability to prescribe
4) A pharmacy pick up or delivery service for oral antivirals and/or an infusion service for monoclonal antibodies (and later also redesivir)

It was decided in January 2022, once the CMDUs had been in operation for 1 month, that a bottom up costing exercise would be conducted. This had the aim of determining an average unit cost per patient treated with:

- Oral Antivirals
- IV treatments including Neutralising Monoclonal Antibodies (nMABs)

A number of CMDUs assisted in this data collection exercise & provided a detailed breakdown of costs, including:

Pay costs

1. Medical staff
2. Other clinical staff
3. Admin support

All of which were split into:

- Admin (non-patient facing activity)
- Triage (patient facing contact)
- Treatment costs (either dispensing oral antivirals or delivery of IV infusions)

Non-Pay costs (also split into categories of admin, triage & treatment)

1) Clinical consumables
2) Medicine courier costs
3) Travel costs
4) Stationery
5) Taxi & other vehicle hire
6) Room hire
7) Office equipment
8) Patient travel expenses

To ensure the costing exercise outcome would be as accurate as possible, the CMDUs involved were representative of different delivery models. These included:

1) Infusions given in the renal unit of an acute hospital & outreach via a Hospital at Home service
2) Triage & assessment within an acute hub with treatments provided by another local acute provider
3) ICS-wide CMDU with clinical triage provided by the local Clinical Commissioning Group (CCG) & treatment provided by all hospitals in the patch
4) Triaging provided by a health & care provider with oral antivirals dispensed by local hospital or infusions provided by local urgent treatment centre (UTC)
5) GP hub triaged patients with the adoption of GP virtual wards that following up with oximeters after treatment. All treatment provided by local acute providers
6) Nursing team provision of initial contact and triage, consultant discussed treatment options and the nursing team arranged the treatment slot – all within the local acute provider

Limitations

- Due to the rapidly changing nature of the pandemic with unexpected peaks and troughs of activity and the speed at which CMDUs were set up, the structure and resourcing needs were constantly evolving, meaning that costings are likely to have continued to change. . For example, using Paxlovid as an additional oral antiviral treatment ***had not been implemented*** at this point. It was well documented that this drug had many contra-indications and was expected to be resource intensive because of this.

- CMDUs did not have permanent staffing structures, Instead CMDUs were typically staffed on the basis of clinicians working in CMDUs alongside other front-line clinical duties or on the basis of overtime It is recognized that CMDUs were established during parallel winter and other operational pressures on the NHS.

- CMDUs participating in the cost exercise found it difficult to estimate staff time on administration, triage and treatment.

The outcome of this costing exercise was:

- The average unit cost per patient treated with oral antivirals was £410
- The average unit cost per patient treated with nMABs (IV infusion) was £820

Therapeutics for people with COVID-19. An economic evaluation

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

Paul Dark is the National Deputy Medical Director of a National Institute for Health and Care Research Clinical Research Network. He is a Local Principal Investigator for both the RECOVERY and REMAP-CAP platform trials, NIHR Urgent Public Health (UPH) pandemic research Advisory Group Lead Link for REMAP-CAP and specialist member of NIHR UPH Advisory Group. His NHS host hospital Research and Innovation Department has been contracted and paid to provide advice on the use of tocilizumab for Roche and sotrovimab for GlaxoSmithKline both in COVID-19. He supported the activity as a named NHS expert employed by the Northern Care Alliance NHS Foundation Trust (Salford Care Organisation) but received no personal payments. Matt Stevenson provided advice to Astra Zeneca Rare Diseases regarding an unrelated intervention in an unrelated disease area. There are no other conflicts of interest within this project team.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Metry A, Pandor A, Ren S, Shippam A, Clowes M, Dark P, McMullan R, Stevenson M. Therapeutics for people with COVID-19. An economic evaluation. School of Health and Related Research (ScHARR), 2022.

Keywords: COVID-19; cost-benefit analysis; economic evaluation; cost-effectiveness; cost-utility analysis

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). Over six million deaths worldwide have been associated with COVID-19.

Objective. To assess the cost-effectiveness of treatments used for the treatment of COVID-19 in hospital or used in the community in patients with COVID-19 at high-risk of hospitalisation.

Setting: Treatments provided in UK hospital and community settings.

Methods: Clinical effectiveness estimates were taken from the COVID-NMA initiative and the metaEvidence initiative. A mathematical model was constructed to explore how the interventions impacted on patient health, measured in quality-adjusted life years (QALYs) gained. The costs associated with treatment, including those of hospital care, were also estimated and used to form a cost per QALY gained value which was compared with thresholds published by the National Institute for Health and Care Excellence (NICE). Estimates of cost-effectiveness compared against current standard of care (SoC) were produced in both the hospital and community settings at three different levels of efficacy: mean, low and high. Public list prices were used for interventions with neither confidential patient access schemes, nor confidential list prices considered. Confidential information relating to the proportion of high-risk people who were hospitalised could not be used in this report. Results incorporating confidential data were provided to the NICE appraisal committee.

Results: The treatments were estimated to be clinically effective although not all reached statistical significance. All treatments in the hospital setting, or community, were estimated to plausibly have a cost per QALY gained value below NICE's thresholds when compared with SoC. Although almost all drugs could plausibly have cost per QALYs above NICE's thresholds. However, there is considerable uncertainty in the results as the prevalent SARS-CoV-2 variant, vaccination status, history of being infected with SARS-CoV-2 and SoC have all evolved since pivotal studies were conducted which could have significant impact on the efficacy of each drug. For drugs used in high-risk patients in the community setting, the proportion of people at high-risk who need hospital admission was a large driver of the cost per QALY.

Limitations: No studies were identified that were conducted in current conditions. This may be a large limitation as the SARS-CoV-2 variant changes. No head-to-head studies of interventions were identified.

Conclusions: The results produced could be informative to decision makers, although conclusions regarding the most clinical—and cost-effectiveness of each intervention should be tentative due to the evolving nature of the decision problem and the use of list prices only. Comparisons between interventions should also be treated with caution due to potentially large heterogeneity between studies,

Future work: Research assessing the relative clinical effectiveness of interventions within head-to-head studies in current conditions would be beneficial. Contemporary information related to the probability of hospital admission and death for patients at high-risk in the community would improve the precision of the estimates generated.

Word Count 470

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See the NIHR Journals Library website for further project information.

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FIGURES

Plain English Summary

COVID-19 is an infectious disease that can cause death and long-term ill-health. Treatments exist that can be provided in hospital to reduce the number of deaths from COVID-19. Treatments also exist which can be provided in the community for people at high-risk of needing to be admitted to hospital to reduce the number of admissions and to reduce the number of deaths from COVID-19. However, the value for money of these treatments have not been estimated. We took the clinical effectiveness of nine treatments from published literature sources and built a model that estimated the value for money of six treatments compared with care without these treatments. Three treatments were excluded due to confidential prices. The results of the model showed that many treatments in a hospital setting had estimates of cost-effectiveness that would normally be seen to be good value for money using the thresholds published by the National Institute of Health and Care Excellence. The same was true for some treatments in a community setting. However, it is also possible that these treatments are not good value for money. The benefit of the drugs and value for money is highly uncertain as studies trying to estimate the gain have been done with 1) previous variants of the virus causing COVID-19 being widespread, 2) where the proportion of people who have had vaccinations or who had previously had COVID-19 is low, and 3) where standard treatment was that when COVID-19 was first identified, and not the drugs used now. Because of these differences, and the unknown price of some interventions, we cannot confidently say which (if any) treatments helps patients the most, or which treatment represents the best value for money. Further research, in current conditions, would improve the accuracy of our answers.

Scientific Summary

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). At the time of writing (October 2022) there had been over 620 million confirmed cases and over six-and-a-half million deaths worldwide associated with COVID-19. For the UK, these values are nearly 24 million cases and 190,000 deaths.

In addition to the widespread vaccination programme, treatments exist that can help people who have been hospitalised due to COVID-19 (casirivimab and imdevimab (henceforth casirivimab/imdevimab), tocilizumab, remdesivir, baricitinib, and baricitinib with remdesivir) or be used in patients who have COVID-19 and are at high-risk of needing hospitalisation (casirivimab/imdevimab, molnupiravir, nirmatrelvir and ritonavir (henceforth nirmatrelvir/ritonavir), remdesivir, sotrovimab, and tixagevimab and cilgavimab (henceforth tixagevimab/cilgavimab)). For reasons related to urgency, these treatments, unlike interventions in other disease areas, have not received positive guidance from the National Institute of Health and Care Excellence before being routinely used. As the pandemic subsides there is more need for a formal evaluation of the clinical and cost-effectiveness of these treatments.

Objectives

The objective of this study is to summarise the current knowledge related to the clinical efficacy of the interventions and to conduct an economic evaluation that estimates the cost-effectiveness of each intervention against standard of care (SoC), as of October 2022. A full incremental analysis is performed whilst noting the caveats in the comparison of all interventions simultaneously.

Methods

Given the timescale of the project, where there was less than three months between the publication of the final scope and the deadline of a report for consultation, a literature review following best practice was not possible. Instead, a pragmatic, alternative approach was undertaken where evidence was taken from two living systematic reviews (supported by the COVID-NMA initiative and the metaEvidence initiative) in line with current best practice guidelines. For interventions related to use in hospitals, data were extracted on time to death, clinical improvement, and time to discharge. For interventions which are used in the community for patients at high-risk of hospitalisation, data were extracted on the risks of hospitalisation or death, and the risks of death. These measures of efficacy were assumed generalisable to October 2022 despite changes in background conditions which include the SoC, the percentage of people who have been vaccinated and a change in the dominant SARS-CoV-2 variant. This is noted as a large limitation as drugs that have looked effective in previous variants have not worked as well in later variants.

A mathematical model was constructed that used the data from the living systematic reviews to simulate the experiences of patients in hospital, and requirement for supplemental oxygen, until discharge or death in hospital. Due to the (conditional) marketing authorisations of the interventions, the model was developed such that results could be produced for the supplemental oxygen group and the non-supplemental oxygen group separately. The model structure used an eight-point ordinal scale that was used in clinical trials to categorise patients during their admissions. Outputs from this model included the costs associated with interventions and care, and the quality-adjusted life-years (QALYs) gained by the patient both within the hospital episode and after discharge, incorporating decrements in health-related quality of life associated with the lasting impact of COVID-19. For interventions used in the hospital, these values allowed a cost per QALY gained to be calculated for each treatment compared with SoC, and for completeness, a full incremental analysis to be conducted.

The costs of each intervention were taken from public sources where available. However, tocilizumab and baricitinib have confidential patient access schemes agreed, which discount the price of the intervention, and are not considered in this document, but were provided to the NICE Appraisal Committee in a separate confidential appendix. The price of three treatments (casirivimab/imdevimab, molnupiravir and tixagevimab/cilgavimab) were not publicly available at the time of writing and the cost-effectiveness results for these three drugs are contained in a confidential appendix.

For patients at high-risk of hospitalisation treated in the community, a decision tree was put before the hospital model, which simulated the reduced need for hospitalisation associated with early treatment. The total costs and QALYs associated with treatment options were estimated to allow an evaluation of the cost per QALY of each treatment against SoC and for completeness, a full incremental analysis to be undertaken. The modelling did not assess the logistical aspects of treatment in the community, but the External Assessment Group notes that this could be a large factor in deciding which treatments could be preferred, as oral treatments could be more acceptable to patients and healthcare systems than treatments that are given intravenously or subcutaneously. The costs of providing treatment within the community was provided by NHS England.

Three scenarios were run changing the efficacy of interventions. The ‘mean efficacy’ estimate used the mean of each distribution extracted from the living systematic reviews, the ‘high efficacy’ estimate used the most favourable limits of the 95% CIs, and the ‘low efficacy’ estimate used the least favourable limits of the 95% CIs.

Eight scenario analyses were performed, explored the impact of changing: i) the duration of long COVID (ranging from half to double that of the base case); ii) changing the rate of hospital admission in the community with people being at ‘high risk’ of hospitalisation from a value of 2.79% to 1.00%,

5.00% and 10.00%; iii) changing the average age of patients at high-risk of hospitalisation in the community from 55 years to 50 and 60 years; iv) using a HR of unity for all interventions in relation to time to hospital discharge and time to clinical improvement; v) changing the baseline distribution of supplemental oxygen requirements from that associated with SoC (19% no supplemental oxygen, 55% high flow oxygen, 16% non-invasive ventilation, and 10% invasive ventilation) to an arbitrarily less severe baseline distribution (25% no supplemental oxygen, 60% high flow oxygen, 10% non-invasive ventilation, and 5% invasive ventilation) for patients who have received an intervention in the community; vi) changing the cost per year associated with long COVID to £2500 per year rather than £1013 per year; vii) assuming a utility decrement of 0.02 per day for patients receiving IV treatment in the community; and viii) changing the SMR for people during the period of long COVID from 7.7 to 5.0 and 10.0.

Results were presented in terms of incremental cost-effectiveness ratios (ICERs) measured in cost per QALYs gained and also using incremental net monetary benefit (NMB). An advantage of NMB is that interventions can be compared using different assumptions on efficacy for different interventions, and interventions can be omitted without the need to recalculate efficiency frontiers.

Results

Due to changes between the conditions when the pivotal studies were undertaken and the current conditions in terms of the SoC, the percentage of people who have been vaccinated and a change in the dominant SARS-CoV-2 variant all results should be treated with caution. The results also do not incorporate confidential price discounts for baricitinib and tocilizumab, nor were any cost-effectiveness results presented for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab which had confidential list prices. These analyses were seen by the NICE appraisal committee which also incorporated confidential data taken from the PANORAMIC study.

All treatments used for hospitalised patients, had a median hazard ratio (HR) for death below 1, indicating a benefit, although all confidence intervals (CIs) crossed unity apart from those for tocilizumab and baricitinib. The overlapping CIs, and heterogeneous studies meant that no firm conclusions could be made regarding the relative efficacy of these treatments. There was less data relating to the relative risks (RRs) of clinical improvement at 28 days and the HRs for the time to discharge, although these were generally close to unity and had CIs that crossed unity. No clear conclusions could be made on the relative efficacy of treatments for these two measures.

All treatments used in the community had favourable median RRs for hospitalisation and death at 28 days, although due to wide CIs no firm conclusions could be made regarding the relative efficacy of these treatments. The median RR associated with death at 28 days were favourable for all interventions,

except for remdesivir where the median estimate was unity. The CIs were wide and spanned 1 for all treatments except for molnupiravir and nirmatrelvir/ritonavir. As such, no clear conclusions relating to the relative efficacy of the interventions could be made regarding avoiding death at 28 days.

For hospitalised patients requiring supplemental oxygen, all treatments had estimated ICERs compared with SoC below £11,000 in both the mean efficacy and high efficacy scenarios. However, in the low efficacy scenario only baricitinib and tocilizumab generated more QALYs than SoC. Baricitinib had an estimated ICER under £8,000, whilst tocilizumab had an estimated ICER under £29,000. For hospitalised patients not requiring supplemental oxygen, all treatments had estimated ICERs compared with SoC below £11,000 in both the mean efficacy and high efficacy scenarios. However, in the low efficacy scenario, only baricitinib generated more QALYs than SoC with an estimated ICER below £4000 for baricitinib.

For interventions used in the community, the estimated ICERs compared with SoC were more varied. In the mean efficacy scenario, the estimated ICERs were below £7000 for nirmatrelvir/ritonavir, below £22,000 for sotrovimab, and below £30,000 for remdesivir. In the high efficacy scenario, the estimated ICERs were below £7000 for nirmatrelvir/ritonavir, below £20,000 for sotrovimab, and below £26,000 for remdesivir. In the low efficacy scenario, the estimated ICERs were below £9000 for nirmatrelvir/ritonavir, below £26,000 for remdesivir, and below £39,000 for sotrovimab.

Only one of the scenario analyses noticeably changed the ICERs, which was changing the proportion of people with COVID-19 in the community at high-risk of hospitalisation who are hospitalised when treated with SoC. Treatments became more cost-effective as the admission proportion increased. The average age of people in the community with COVID-19 at high-risk of hospitalisation also had a marked impact on the ICERs with younger people making the drugs more cost-effective. The assumed duration of long COVID had a lower impact on the ICERs than the previous scenarios, although shorter durations of long COVID were associated with the treatments becoming more cost-effective. The ranges in the ICERs assuming mean efficacy for the drugs, when using 1% and 10%, rather than 2.79% as assumed in the base case, were: nirmatrelvir/ritonavir (£23,189, £272) remdesivir (£84,027, 7213) and sotrovimab (£62,342, £4583).

Conclusions

There is considerable uncertainty in the efficacy of treatments compared to SoC observed in the studies due to the small number of events, which results in wide CIs for HRs and RRs. Some treatments (tocilizumab and baricitinib in the hospitalised setting and molnupiravir and nirmatrelvir/ritonavir in the community setting) were estimated to have a statistically significant benefit related to death due to COVID-19, however, this may also have been shown for other treatments if the pivotal studies had had

larger sample sizes. However, the dominant SARS-CoV-2 variant, the SoC, and the percentage of people who have had a vaccination, have all changed since the pivotal studies were undertaken meaning that the efficacies for treatments are highly uncertain. This is demonstrated by sotrovimab having favourable median and mean efficacies in prevention hospitalisation, but this drug is not authorised in the USA, as it is unlikely to be effective against the Omicron BA.2 subvariant, Further the WHO has made strong recommendations against the use of sotrovimab. Given potential further changes in the variant, the results presented in this report, and within the confidential appendix, should be treated with caution.

Word Count 1899

ABBREVIATIONS

Abbreviation	Description
ACTT-1	Adaptive COVID-19 treatment trial
AUC	Area under the curve
BNF	British national formulary
CI	confidence interval
COVID-19	Coronavirus disease 2019
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External assessment group
ECMO	Extracorporeal membrane oxygenation
eMIT	electronic market information tool
EQ-5D-3L	EQ-5D 3-level
EQ-5D-5L	EQ-5D 5-level
HDU	High dependency unit
HFO	High flow oxygen
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IPD	Individual patient-level data
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
KM	Kaplan-Meier
LFO	Low flow oxygen
MAV	Medical attended visits
NHS	National health service
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NMA	Network meta-analyses
NMB	Net monetary benefit
ONS	Office for National Statistics
OS	Overall survival
PANORAMIC	Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community clinical study
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RECOVERY	Randomised Evaluation of COVid-19 thERapY
REES	Remdesivir Effectiveness Evaluation Study
RR	Relative risk
SAE	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMR	Standardised mortality ratio
SoC	Standard of care
WHO	World health organization
WTP	Willingness to pay

1. BACKGROUND

1.1 Description of the underlying health problem

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). At the time of writing (June 2022) there had been more than 540 million cases of COVID-19 worldwide and more than 6 million deaths; in the UK these values were more than 22 million cases and over 175,000 deaths.[1] In the UK, there have been waves of infections (peaking in late December 2021 and early January 2022), and waves of death (peaking in January 2021).[1]

The ratio of notified infections to death in the UK has changed markedly over time, being approximately 5 to 1 in April 2020, 45 to 1 in January 2021; and 700 to 1 in January 2022 (authors' calculations based on worldometer data[1]). Factors associated with the change in ratio include:

- better ascertainment of COVID-19 cases, which previously may have been left unobserved particularly early in the pandemic especially when mild or asymptomatic
- increasing level of protection in the population, both acquired from previous SARS-CoV-2 infection and vaccine-induced
- improved levels of treatment, such as the use of dexamethasone
- the likelihood of more frail people dying in earlier waves; and
- the change in variants of SARS-CoV-2

Should the risk of death following COVID-19 remain at low levels and SARS-CoV-2 becomes endemic in society, then treatments for patients with COVID-19 may no longer be treated differently to interventions for other conditions such as breast cancer or heart disease. If this were the case, then it could be considered logical and acceptable that pharmacological treatment for COVID-19 would be appraised by the National Institute for Health and Care Excellence (NICE) using its standard methods.[2] This is in line with the best practice recommendations for the assessment of diagnostics and therapeutics for COVID-19 published by HORIZON 2020.[3]

The SARS-CoV-2 variants have changed noticeable throughout the COVID-19 pandemic. Between February 2021 and May 2021, the Alpha variant was predominant, but was replaced by the Delta variant which was the main variant until December 2021 when Omicron became established. Since then, there has been a period where Omicron BA2 has been the predominant variant and in July 2022, Omicron BA5 was estimated to be the cause of 75% of identified SARS-CoV-2 variants.{UK Health Security Agency, 2022 #4395}

1.2 The NICE scope

In April 2022, NICE issued a scope[4] for the assessment of therapeutics for people with COVID-19; the NICE website also hosts the final protocol written by the External Assessment Group (EAG).[5] This scope was revised and finalised in August 2022;[6] the key changes being that lenzilumab was removed as an intervention and tixagevimab and cilgavimab was added as an intervention. The remit of the final scope was to appraise the clinical and cost-effectiveness of eight interventions for treating (i) people with mild COVID-19 at high-risk of progressing to severe COVID-19 and (ii) people with severe COVID-19. The comparators included the established management in clinical practice with or without corticosteroids and appropriate respiratory support, and the other interventions. The components of the decision problem are discussed more fully in Section 1.4. The deadline for the original EAG report sent to stakeholders was the 30th of June 2022, allowing less than three months for the estimates of the clinical effectiveness of each intervention to be made, for the mathematical models to be adapted and run, the results to be interpreted and the report to be written.

The NICE scope[6] did not include secondary infections to NHS staff, or the wider population, which may be unfavourable to the interventions. The impact of transmission may be reduced as the modelled population are those with COVID-19 who are therefore symptomatic and who have been either hospitalised or referred for treatment. In this circumstance, it is likely that peak viral load has passed and that the modelled population would avoid unnecessary contact with other people. The scope also does not cover the potential benefits of interventions in maintaining the capacity for operations or in avoiding delays in patients' treatment that could arise due to either a reduced number of patients in hospital with COVID-19, or reduced staff absence due to COVID-19. Were this benefit, which has been termed 'enablement', included in the model this would likely be favourable to the interventions.

Reinfections and readmission were not listed in the NICE scope and have not been considered in the modelling due to the lack of data and time constraints. It is uncertain whether this omission is favourable or unfavourable to particular interventions as subsequent adverse events could reduce the estimated QALY gains from avoiding adverse events in the first hospitalisation due to treatment, but the interventions could also confer additional protection from a secondary infection.

The scope focusses on treating patients with COVID-19. It does not include prophylactic treatment for patients who are at high-risk but who do not have COVID-19.

1.3 Description of current service provision

Patients with severe COVID-19 are typically hospitalised with the intensity of treatment dependent on the severity of the condition. Patients may be treated in intensive care units (ICUs), be provided with high-flow oxygen or low-flow oxygen, and be treated with interventions, including those in the NICE scope and with corticosteroids.

1.4 The Decision Problem

This section has been sub-divided into sections detailing the population, interventions, comparators, outcome measures, and subgroups.

1.4.1 Population

The population considered within the EAG report has been divided into two broad groups. The first group consists of people who have been hospitalised due to COVID-19 and the second group consists of people who are at high-risk of requiring hospital care due to COVID-19. Patients who were hospitalised for reasons other than COVID-19 and contracted COVID-19 in hospital and were at high-risk of requiring hospital care for COVID-19 were categorised within the second group. For brevity, all patients not hospitalised due to COVID-19 who are at high-risk of hospitalisation will be termed 'non-hospitalised patients' noting the aforementioned caveat regarding patients who contract COVID-19 in hospital, whereas patients who have been hospitalised directly because of COVID-19 are referred to as 'hospitalised patients'.

Following discussions with NICE, the definition for patients at high-risk was aligned to that considered within the Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community (PANORAMIC) clinical study,[7] with the exception that being aged 50 years or over was not considered to be a high-risk factor.

The aim of treatment differs between both groups. For patients hospitalised due to severe or critical COVID-19, the aim of treatment is to reduce the immunoinflammatory response of the body and prevent clinical deterioration. For non-hospitalised patients, the aim of treatment is to prevent viral replication and damp inflammation, thus reduce the probability of the development of severe symptoms that could lead to hospitalisation or death.

1.4.2 Interventions

The interventions listed within the NICE scope[6], are shown in Table 1 to Table 3 based on marketing authorisation in the UK at the time of writing. Table 1 contains the interventions with marketing authorisation in the UK, Table 2 contains the interventions with conditional marketing authorisation in the UK, and Table 3 contains the interventions with no marketing

authorisation in the UK. Each table contains the generic name of the intervention, its branded name and the company manufacturing it, the class of intervention, the mode of administration and recommended dose. Table 1 provides the indication for the drug, whilst Table 2 and Table 3 provide the population in key studies for the intervention.

Multiple interventions are indicated for the prevention of severe COVID-19. Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or saturation of peripheral oxygen <90% on room air and would require hospitalisation.[8]

1.4.3 Comparators

The comparators within the decision problem include all of the interventions contained in Table 1 to Table 3, when used in the same position as a particular intervention and additionally standard of care (SoC) which would be dependent on the severity of the patient's illness. SoC is defined as any treatment widely accepted by the National Health Service (NHS), which is routinely funded by the NHS with no strong rationale to appraise it, for example supplemental oxygen and dexamethasone. SoC has evolved throughout the COVID-19 pandemic, which means that randomised controlled trials (RCTs) conducted comparing interventions against SoC may not be directly comparable as SoC has improved over time.

Table 1: Interventions with marketing authorisation in the UK as of the 28th of June 2022

Generic treatment name (branded name and company)	Class	Mode of administration, (recommended dose)	Indication relevant to the decision problem
Casirivimab/imdevimab (Ronapreve, Regeneron and Roche)	mAb	IV/SC (600mg of both drugs administered together as one infusion. An SC injection is permitted if an IV approach would lead to a delay)	Treatment of acute COVID-19 infection
Molnupiravir (Lagevrio, Ridgeback Biotherapeutics and Merck Sharp & Dohme)	Antiviral	Oral (800mg twice daily for 5 days)	Treatment of mild to moderate COVID-19 in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness
Tocilizumab (RoActemra, Roche)	Immunomodulator	SC/IV (8 mg/kg administered once IV with 0.9% sodium chloride over one hour) One additional infusion of tocilizumab 8 mg/kg may be administered. The interval between the two infusions should be at least 8 hours	Treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation

IV - intravenous, mAb – monoclonal antibody, SC – subcutaneous

Table 2: Interventions with conditional marketing authorisation in the UK as of the 28th of June 2022

Generic treatment name (branded name and company)	Class	Mode of administration, (recommended dose)	Therapeutic indication in the SmPC relevant to the decision problem
Nirmatrelvir/ritonavir (Paxlovid, Pfizer)	Antiviral	Oral (300mg (nirmatrelvir) and 100mg (ritonavir) twice daily for 5 days)	Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19
Remdesivir (Veklury, Gilead)	Antiviral	IV (200 mg loading dose on day 1 for all patients, then dependent on patient characteristics). • For adults and adolescents with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment): 100 mg daily IV for five to ten days) • For Adult patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19: IV (100 mg daily IV for three days)	Treatment of COVID-19 in: • adults and adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) or • adults with pneumonia not requiring supplemental oxygen
Sotrovimab (Xevudy, GlaxoSmithKline and Vir Biotechnology)	mAb	IV (500mg over 30 minutes)	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
Tixagevimab/cilgavimab† (Evusheld, Astra Zeneca)	mAb	Intramuscular injection (single dose of 300mg of tixagevimab and 300mg of cilgavimab)	Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19

IV - intravenous, mAb - monoclonal antibody, SC – subcutaneous, SmPC – summary of product characteristics

† As of the 15th of September 2022

Table 3: Interventions with no marketing authorisation in the UK as of the 28th of June 2022

Generic treatment name (branded name and company)	**Class**	**Mode of administration, (recommended dose)**	**Population in key studies if no marketing authorisation or conditional marketing authorisation exists**
Baricitinib (Olumiant, Eli Lilly)	Immunomodulator	Oral (4mg daily, the optimal duration is currently unclear)	Studied in clinical trials, as a monotherapy, in people with COVID-19
Baricitinib (Olumiant, Eli Lilly) and R**emdesivir** (Veklury, Gilead)	Immunomodulator and antiviral	As for the component drugs	Studied in clinical trials in people aged 18 years and older, hospitalised with COVID-19

IV – intravenous, mAb – monoclonal antibody

1.4.4 Outcome Measures

The NICE scope[6] lists nine possible outcomes to explore: mortality; requirement for respiratory support; time to recovery; hospitalisation (requirement and duration); time to return to normal activities; virological outcomes (viral shedding and viral load); post-COVID-19 symptoms; adverse effects of treatments; and health-related quality of life (HRQoL). All model outcomes, except virological outcomes were assessed; these were excluded as these would be of more relevance to decision problems that included transmission and due to the prioritisation of other endpoints given the limited time available.

The cost-effectiveness of the eight treatments were expressed in terms of incremental cost-effectiveness ratios (ICERs) which were reported in terms of cost per quality-adjusted life year (QALY) gained. A patient lifetime horizon was used to take differential mortality between treatments into account.

1.4.5 Subgroups

Due to time constraints, the only subgrouping considered was related to whether oxygen was required upon admission to hospital entry. This was considered important as the licensed indication and the clinical outcomes for some of the appraised interventions depend on the level of oxygen support required. The EAG is aware that other possible criteria for selecting subgroups include but are not limited to: age; immune system competence; comorbidities; seroprevalence; vaccination status; and the predominant SARS-CoV-2 variant but did not have the time to explore the impact of these characteristics.

2. CLINICAL-EFFECTIVENESS

2.1 Methods for the Rapid Evidence Review

Given the timelines of the project, the EAG could not follow best practice for systematically reviewing the clinical evidence relevant to the decision problem. Following discussions with NICE, a pragmatic, alternative approach was undertaken relying on the use of data extracted by third parties which are referred to as 'living systematic reviews'. This is in line with the best practice recommendations for the assessment of diagnostics and therapeutics for COVID-19 published by HORIZON 2020.[3] The methods used, assumptions taken, and the summarised results are provided in this chapter.

2.1.1. Rationale for using living systematic reviews

COVID-19 clinical research has accelerated dramatically worldwide, with over 5000 registered trials investigating therapeutic interventions for COVID-19.[9] The need for rapid information on COVID-19 has resulted in a paradigm shift, especially in the communication of scientific results. Traditional systematic reviews can date quickly but 'living' systematic reviews search for evidence much more regularly than standard reviews and incorporate relevant new evidence as it becomes available. This is important in the context of COVID-19, in which the evidence-base is rapidly changing as new data emerge. The ability of a 'living' systematic review and network meta-analysis (NMA) to regularly update and incorporate relevant new evidence as it becomes available makes it the best type of evidence synthesis, in the opinion of the EAG, to inform this pragmatic rapid evaluation. This approach has been recommended by best practice recommendations[3] which stated that "*HTA agencies should consider the use of existing "living" clinical evidence reviews and meta-analyses to inform their clinical effectiveness decisions"* as *"Using these sources will reduce duplication of work and may allow for quicker assessments.*"

The EAG did not have the time to attempt to untangle the impact of differences between studies in terms of aspects such as the dominant SARS-CoV-2 variant, SoC, vaccination status, outcome definition, and age of participants and caution that the results may not be directly comparable between interventions. The EAG also did not have time to: validate the data within the living systematic reviews; to quality assess the component studies; or to remove studies that were not using the appropriate doses. To recognise this uncertainty the EAG has run 'mean', 'high' and 'low' efficacy scenarios in the cost-effectiveness analyses (see Section 3.4) to allow decision makers an indication of how cost-effectiveness changes with different efficacy assumptions.

2.1.2. Selection criteria for the living systematic reviews

Several living systematic reviews that incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple COVID-19 treatments, have been robustly developed and published.[9-12] Two sources were selected as they provided detailed relevant outcome data from individual studies and up-to-date evidence synthesis to inform the model.

The first source is the COVID-NMA initiative,[10, 13] supported by the World Health Organization (WHO) and Cochrane which is a living systematic review of registered randomised trials, in which all available evidence related to COVID-19 is regularly collected, critically appraised, and synthesised using pairwise comparisons and NMA methods. These analyses are updated every two weeks and results can be accessed via a web interface (https://covid-nma.com/).

The second source is the metaEvidence initiative,[11] supported by the University Hospital of Lyon and the University of Lyon which is also a living meta-analysis and evidence synthesis of therapies for COVID-19 and is an emerging online resource that provides direct access to the efficacy and safety results reported in the studies for potential drugs for the treatment of COVID-19. The risk of bias, synthesised by meta-analysis, is also reported. The analyses are updated within a target time of less than 24 hours with results accessed through a web interface (http://www.metaevidence.org/COVID19.aspx).

Other sources of evidence, which primarily informed living guidelines,[9, 12] did not report the extracted outcome data from individual studies. As such, they precluded further synthesis and evaluation.

2.1.3. Assumption of transportability of relative treatment effects

A consequence of the need to use data from the living systematic reviews was that there was reduced scope for the EAG to undertake nuanced analyses with a key limitation being that the EAG had to assume that all relative treatment effects were generalisable to different settings. This meant that for each intervention, the same treatment effects, either hazard ratios (HRs) or relative risks (RRs), were assumed to be applicable regardless of study characteristics which include: the age, perceived severity, vaccination status, and history of SARS-CoV-2 infection of patients; the SoC at that time; the geographical location; and the dosage of the intervention used. The EAG acknowledge that this assumption may be incorrect, which adds additional uncertainty to the clinical- and cost-effectiveness results.

2.1.4 Inclusion criteria and data extraction

Selected data were extracted for the interventions contained in Table 1, Table 2 and Table 3. Key model outcomes such as time to death, clinical improvement at day 28 or day 60 (defined as a hospital

discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery) and incidence of serious adverse events (SAEs) were initially extracted from the COVID-NMA living systematic review[10]. Where relevant outcome data were not available, these data were extracted from the metaEvidence living systematic review.[11] All data extractions (undertaken between the 16th of March to the 18th of May, updated between the 25th to the 31st of May 2022 and updated again on 6th September 2022) were undertaken by one reviewer (AS) and checked by a second reviewer (AP), with any discrepancies resolved by a third reviewer (SR). All data and evidence synthesis analyses were extracted from forest plots, tables and text generated by the COVID-NMA and metaEvidence web interface; checking of the extracted data by the EAG against the original RCT publications for accuracy could not be undertaken within the timescales of the project.

2.1.5 Adjustments made for changing SoC, SARS-CoV-2 variant, vaccination status and prior infection

The conditions under which each study was conducted were heterogeneous. Across time SoC has changed markedly, most particularly with reference to the widespread use of corticosteroids such as dexamethasone and change in SARS-CoV-2 variants. The vaccine roll-out in England has provided protection that was not available to patients recruited to early studies, similarly, there is likely to be an increased level of protection associated with prior infection. Ideally there would be attempts to establish the impact of different circumstances on the observed clinical effectiveness of interventions in studies, although this was not possible within the timescales of the project. As such, the EAG had to make a simplistic assumption that none of the changes were treatment effect modifiers, and that given this, the relative benefits observed in the studies were generalisable and could be applied to the estimated outcomes for patients with COVID-19 in England in Summer 2022.

One notable comment is that there is a belief raised by stakeholders and confirmed by the clinical authors of this report that casirivimab/imdevimab does not work for the Omicron variant of SARS-CoV-2. Further guidance from the USA Food & Drug Administration that '*sotrovimab is not authorized in any US state or territory at this time*' (5th April 2022) as it is unlikely to be effective against the Omicron BA.2 sub-variant.[14] Additionally, less than a fortnight before the report was completed, the WHO offered strong recommendations against the use of casirivimab/imdevimab in patients with COVID-19 and against the use of sotrovimab in patients with non-severe COVID-19.[15] As such, it is likely that the 'low' efficacy scenario described in Section 3.4 may be the most appropriate scenario for casirivimab/imdevimab and for sotrovimab in patients with non-severe COVID-19, with the results from the 'mean' and 'high' efficacy scenarios reserved for consideration if there is a change in the SARS-CoV-2 variant. The robustness of any estimate of efficacy is uncertain.

Another stakeholder comment was the belief that monoclonal antibodies may have better effectiveness than antivirals in reducing supplemental oxygen use in patients treated in the community that are subsequently hospitalised. Clinical opinion provided to the EAG suggests that the effect of antivirals is uncertain. The EAG believe that the sensitivity analyses undertaken in conjunction with an incremental net monetary benefit approach, shortened to net monetary benefit (NMB) approach (see Section 3.4 for further details) would allow the committee to consider alternative assumptions.

2.2 Results of the Rapid Evidence Review

This section reports key results from the analyses described in Section 2.1. A brief description of each included RCT, reproduced from the COVID-NMA Initiative,[10] is presented in Appendix 1. Appendix 1 also presents a summary of the extracted data for each intervention and relevant outcomes from the living systematic reviews. The assumed clinical effectiveness for each intervention in hospitalised patients is detailed in Table 4, and in Table 5 for patients at high-risk of hospitalisation treated in the community. The interventions are listed in order of current marketing authorisation and alphabetical order. The values reported in Table 4 and in Table 5 are used to inform the economic evaluation. All measures of treatment effect, such as RRs and HRs and 95% CIs were taken directly from the living systematic reviews unless specified. The individual studies informing Table 4 and Table 5 are detailed in Appendix 1. Where data were not available for clinical improvement or time to discharge a value of 1.0 was used as the model results were not sensitive to these values within the observed range associated with other interventions.

Table 4: Summarised clinical effectiveness data in patients hospitalised due to COVID-19

Intervention	Estimated efficacy (95% CI)	Source of evidence (number of studies informing the estimate)
Time to death HR		
Casirivimab/imdevimab	0.81 (0.53 – 1.23)	COVID-NMA[10] (1 study)
Tocilizumab	0.77 (0.65 – 0.91)	COVID-NMA[10] (9 studies)
Remdesivir	0.77 (0.57 – 1.04)	COVID-NMA[10] (3 studies)
Baricitinib	0.61 (0.47 – 0.78)	COVID-NMA[10] (2 studies)
Baricitinib/remdesivir	0.65 (0.39 – 1.09)	COVID-NMA[10] (1 study)
Clinical improvement RR at 28 days		
Casirivimab/imdevimab	1.02 (0.99 – 1.04)	COVID-NMA[10] (2 studies)
Tocilizumab	1.05 (1.00 – 1.11)	COVID-NMA[10] (15 studies)
Remdesivir	1.04 (0.99 – 1.10)	COVID-NMA[10] (4 studies)
Baricitinib	1.02 (1.00 – 1.05)	COVID-NMA[10] (3 studies)
Baricitinib/remdesivir	1.07 (1.01 – 1.14)	COVID-NMA[10] (1 study)
Time to discharge HR		
Casirivimab/imdevimab	1.24 (1.05 – 1.47)	metaEvidence[11] (2 studies)
Tocilizumab	1.05 (0.88 – 1.25)	metaEvidence[11] (2 studies)

CI - confidence interval, HR - hazard ratio, RR - relative risk

Table 5: Summarised clinical effectiveness data for patients at high-risk of hospitalisation due to COVID-19

Intervention	Estimated efficacy (95% CI)	Source of evidence (number of studies informing the estimate)
Hospitalisation or death RR		
Casirivimab/imdevimab	0.28 (0.18 – 0.44)	COVID-NMA[10] (3 studies)
Molnupiravir	0.68 (0.50 – 0.94)	COVID-NMA[10] (3 studies)
Nirmatrelvir/ritonavir	0.13 (0.07 – 0.27)	COVID-NMA[10] (1 study)
Remdesivir	0.28 (0.10 – 0.74)	COVID-NMA[10] (1 study)
Sotrovimab	0.20 (0.08 – 0.48)	COVID-NMA[10] (1 study)
Tixagevimab/cilgavimab	0.50 (0.29 – 0.86)*	metaEvidence[11] (1 study)
All-cause mortality RR at 28 days		
Casirivimab/imdevimab	0.51 (0.09 – 2.95)	COVID-NMA[10] (3 studies)
Molnupiravir	0.19 (0.04 – 0.86)	COVID-NMA[10] (4 studies)
Nirmatrelvir/ritonavir	0.04 (0.00 – 0.63)	COVID-NMA[10] (1 study)
Remdesivir	1.00 (0.02 – 50.23)**	COVID-NMA[10] (1 study)
Sotrovimab	0.20 (0.01 – 4.16)	COVID-NMA[10] (1 study)
Tixagevimab/cilgavimab	1.00 (0.32 – 3.06)	COVID-NMA[10] (1 study)

CI - confidence interval, HR - hazard ratio, RR - relative risk

* An odds ratio was provided in the source and the authors calculated the RR.

** There were no deaths reported in either arm. This estimate is calculated assuming a continuity factor of 0.5 deaths and 1 extra observation was added to each arm

To aid interpretation of the clinical efficacy data for interventions used to treat patients in hospital, plots of i) the HR for death at 28 days, ii) the RR for clinical improvement at 28 days, iii) the HR associated with time to discharge, iv) the probability that the intervention, based on the distribution extracted for clinical efficacy, is associated with more deaths at 28 days, and v) the ranked position of each intervention in 1000 joint samples of efficacy for all are shown in Figure 1, Figure 2, Figure 3, Figure 4 and Figure 5 respectively. Figure 1, Figure 2, and Figure 3 consist of two horizontal lines for each intervention which sit on a vertical line. The vertical line shows the lower and upper 95% confidence intervals (CI) whilst the lower horizontal line provides the median value, and the upper horizontal line provides the mean value from the distribution. When the mean and the median values are close these become indistinguishable in the figures.

As seen in Figure 1, all treatments have a beneficial mean estimate for the HR associated with death. The CIs of each treatment overlap showing that there is considerable uncertainty in the ranked order of

clinical effectiveness. A similar conclusion related to the ranking of interventions for clinical improvement can be drawn from Figure 2, and for the ranking of treatments in relation to time to discharge from Figure 3, although only two interventions reported data on this measure.

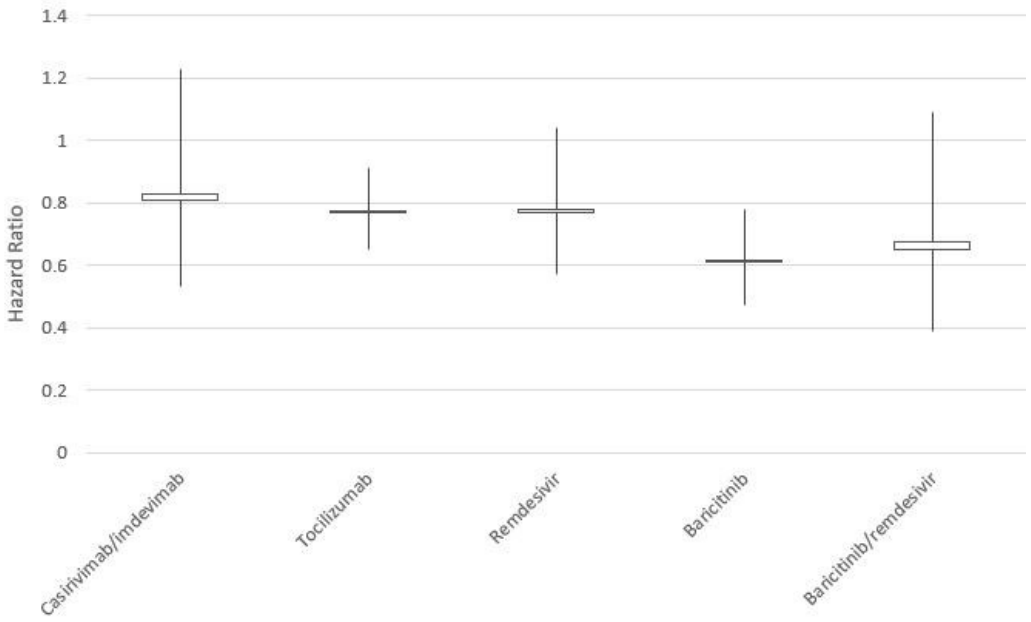

Figure 1: The hazard ratio of avoiding death for interventions used to treat patients in hospital

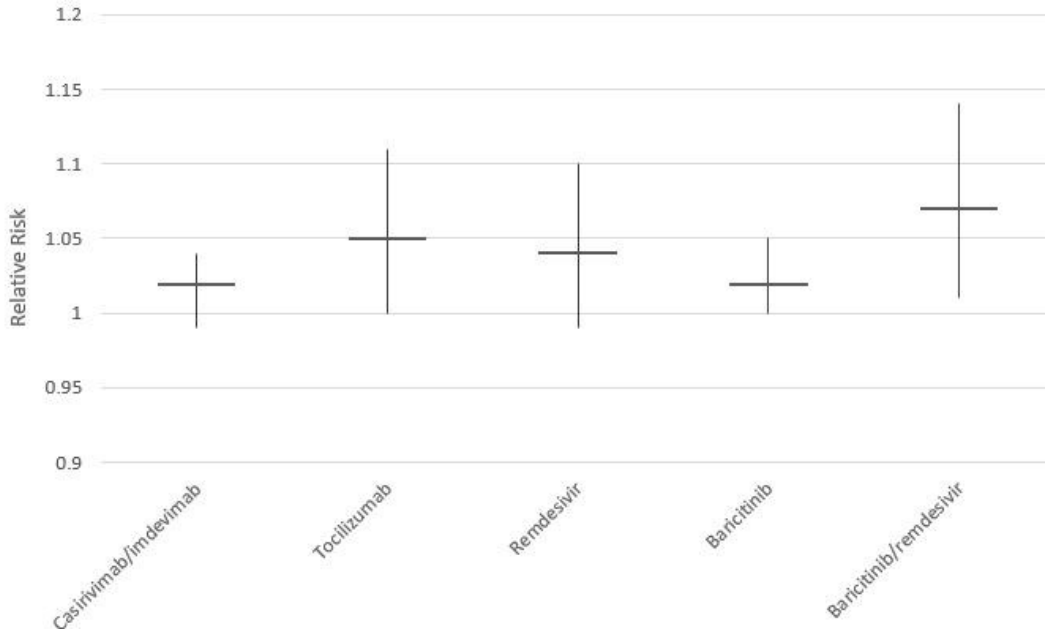

Figure 2: The relative risk of clinical improvement at 28 days for interventions used to treat patients in hospital

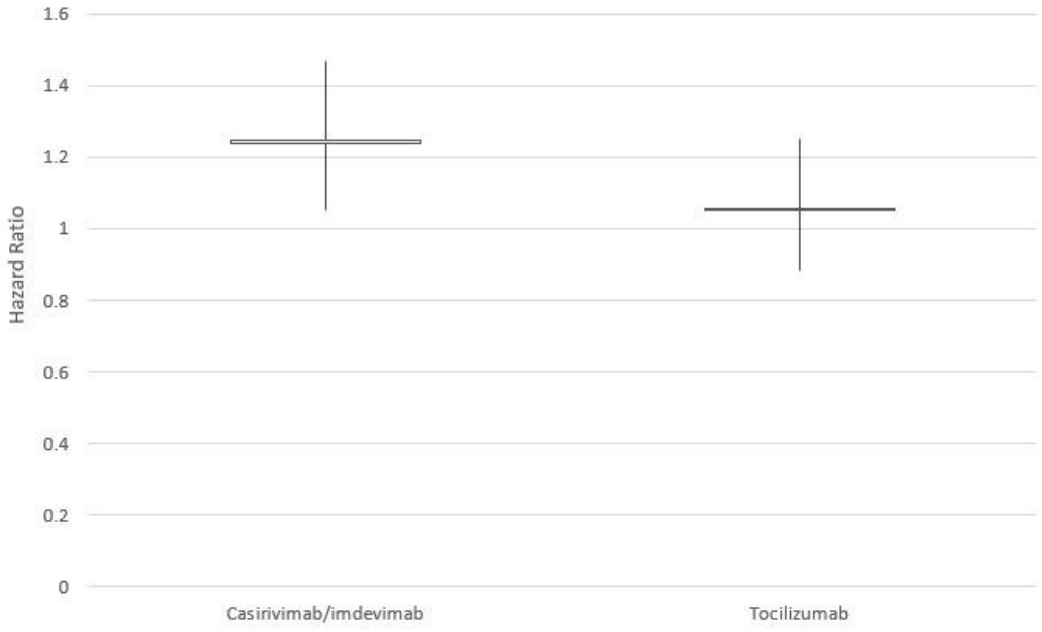

Figure 3: The hazard ratio of discharge for interventions used to treat patients in hospital

Figure 4 indicates the probability that each intervention is associated with greater deaths than SoC at 28 days. For tocilizumab and baricitinib, this probability is extremely low. For casirivimab/imdevimab the probability is in excess of 0.15.

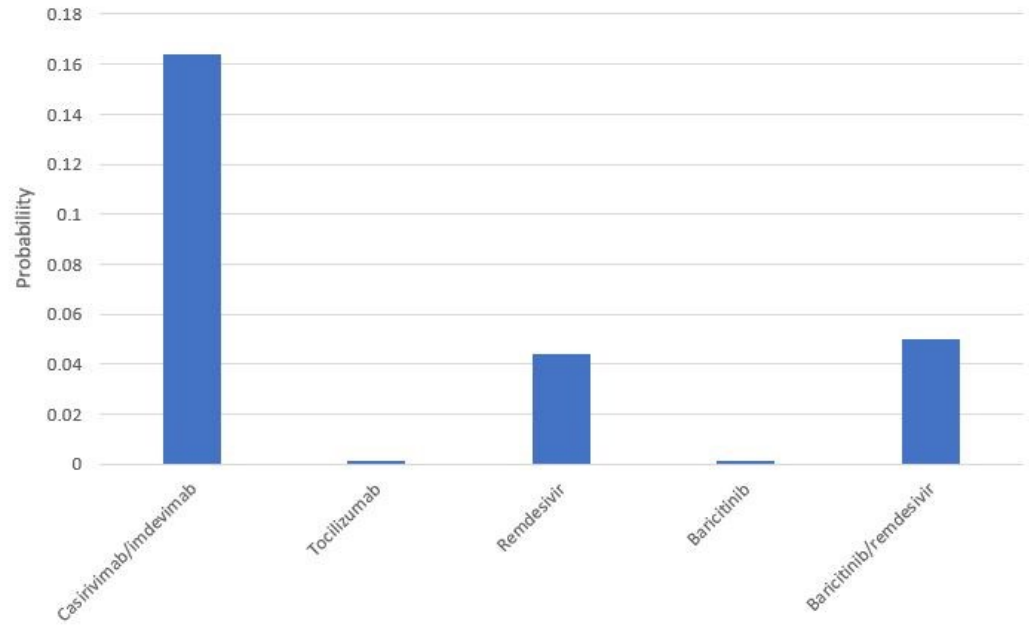

Figure 4: The probability that the intervention used in hospital is associated with increased mortality based on the lognormal distribution derived from the living systematic reviews

The EAG simulated 1000 sets of draws for each intervention assuming that all distributions are independent and recording the order of treatments from most efficacious to least efficacious. For each treatment, the proportion of simulations in which an intervention is in each rank position is shown in Figure 5. There is considerable uncertainty in the results; for example, baricitinib is the intervention with the greatest estimated probability of being ranked first, yet has similar probabilities of being ranked second, or of being third, fourth, and fifth combined. To add additional uncertainty, the assumption that the efficacy estimate is generalisable to different settings may be incorrect due to differences in factors such as SoC, predominant SARS-CoV-2 variant, and vaccination status.

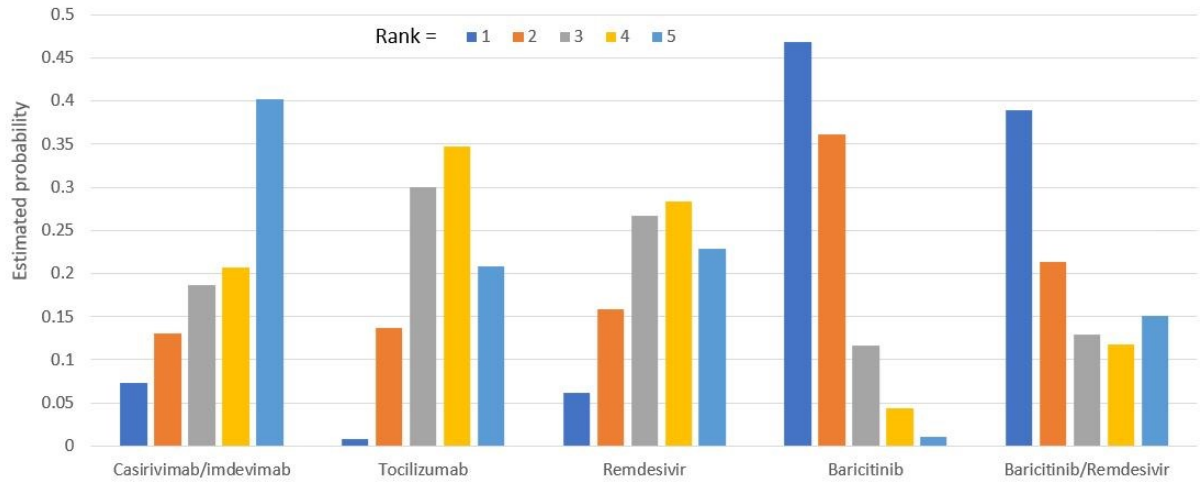

Figure 5: The estimated probability that each intervention is ranked first through to fifth for hazard ratio for mortality

To aid interpretation of the clinical efficacy data for interventions used to treat patients in the community, plots of i) the RR for avoiding hospitalisation or death at 28 days, ii) the RR for avoiding death at 28 days, iii) the probability that the intervention, based on the distribution extracted for clinical efficacy, is associated with more deaths at 28 days and iv) the ranked position of each intervention in 1000 joint samples of efficacy for all interventions are shown in Figure 6, Figure 7, Figure 8 and Figure 9 respectively. Figure 6 and Figure 7 consist of two horizontal lines for each intervention which sit on a vertical line. The vertical line shows the lower and upper 95% CIs whilst the lower horizontal line provides the median value, and the upper horizontal line provides the mean value from the distribution. When the mean and the median values are close these become indistinguishable in the figures.

From Figure 6, it can be seen that no CI crosses unity, although the widths of the CIs differ, with that of nirmatrelvir/ritonavir having most precision, although the CI associated with this intervention overlaps with that of casirivimab/imdevimab, remdesivir, and sotrovimab indicating considerable

uncertainty in the most clinically effective intervention even if the assumption of generalisable efficacy holds.

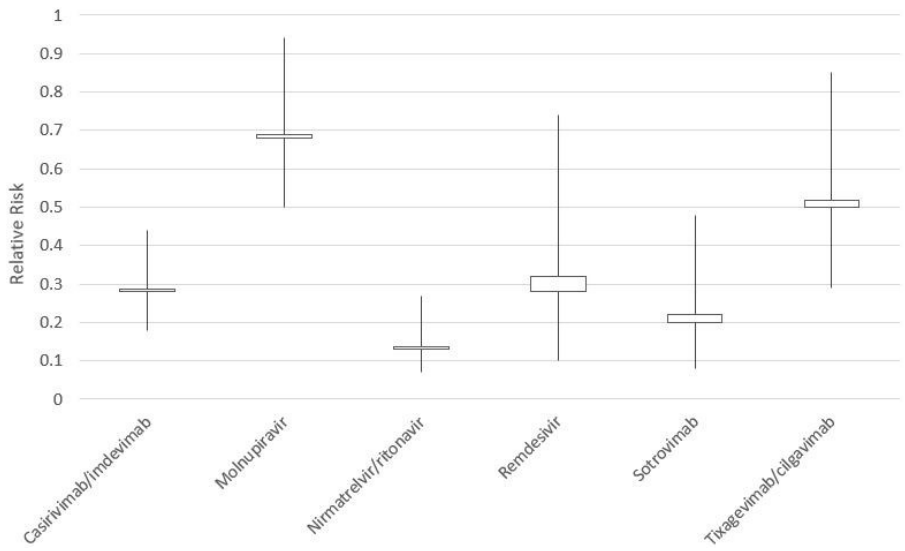

Figure 6: The relative risk of avoiding hospitalisation or death at 28 days for interventions used to treat patients in the community

For the avoidance of death at 28 days, Figure 7 indicates wide CIs for all treatments excluding molnupiravir and nirmatrelvir/ritonavir, in which the upper confidence limits do not exceed 1.0. The wide CIs are primarily related to the sample size and the small number of observed events in each arm.

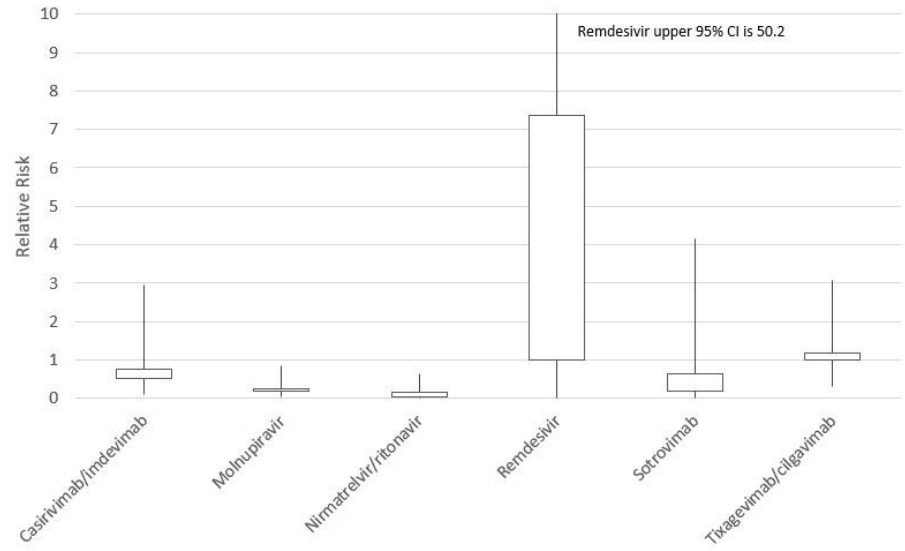

Figure 7: The relative risk of avoiding death at 28 days for interventions used to treat patients in the community

These wide CIs mean that there is a considerable probability (of more than 0.1) that all interventions except molnupiravir and nirmatrelvir/ritonavir could increase the risk of death, although this is a frequentist interpretation of the distribution and does not consider any correlation between reduced hospitalisation rates and the reduced probability of death. The actual correlation could be important in the cost-effectiveness analyses as it may be seen as unlikely that an intervention that causes a statistically significant reduction in the composite endpoint of hospitalisation or death would cause an increase in the number of deaths, although this could be implied by a lack of statistical power.

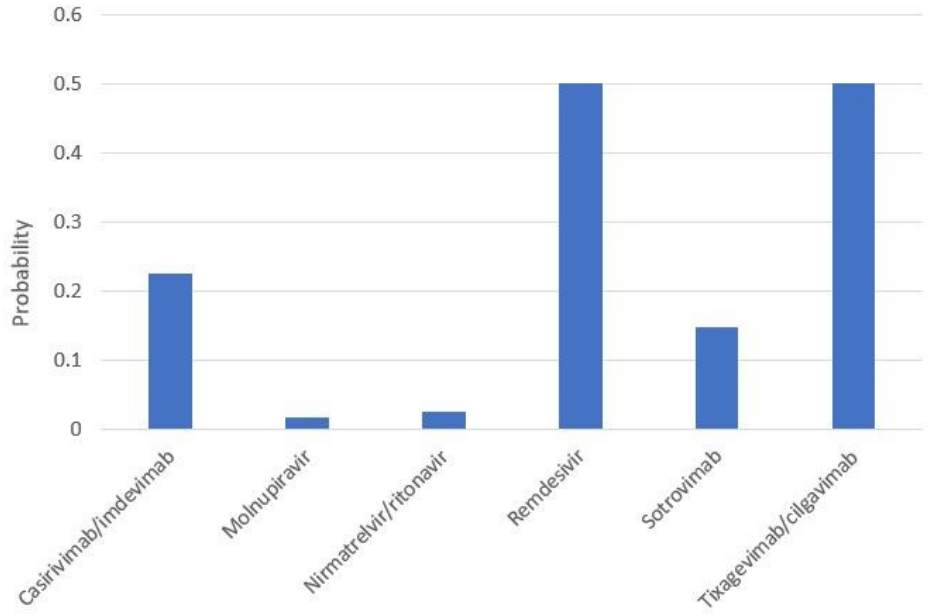

Figure 8: The probability that the intervention is associated with increased mortality based on the lognormal distribution derived from the living systematic reviews

The EAG simulated 1000 sets of draws for each intervention assuming that all distributions are independent and recording the order of treatments from most efficacious to least efficacious. For each treatment, the proportion of simulations in which an intervention is in each rank position is shown in Figure 9. There is considerable uncertainty in the results; for example, whilst nirmatrelvir/ritonavir has a large, estimated probability (greater than 60%) of being ranked first, it has a 19% chance of being ranked third or lower. To add additional uncertainty, the assumption that the efficacy estimate is generalisable to different settings may be incorrect.

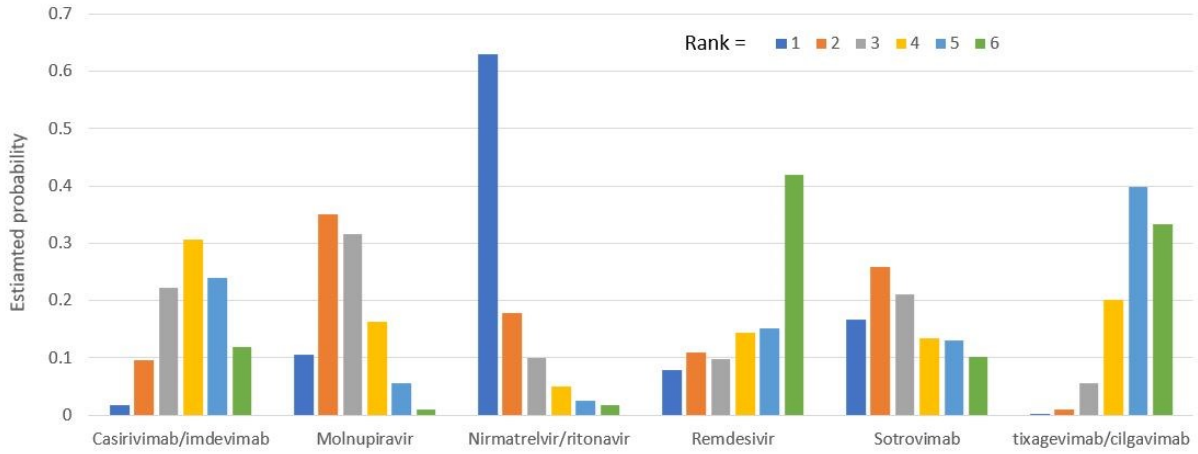

Figure 9: The estimated probability that each intervention is ranked first through to sixth for preventing mortality at 28 days

The interventions should be reviewed for activity against future variants. If it is shown that these confer more or less protection than against the predominant variant in the key clinical studies, then decision makers may choose to select the 'high' or 'low' efficacy results to guide estimates of cost-effectiveness.

3. METHODS FOR THE COST-EFFECTIVENESS ANALYSIS

A provisional working plan was available in the published NICE final scope.[4] The model framework for assessing the cost-effectiveness of treatments for people hospitalised due to COVID-19 is an adaptation of the approach taken by Rafia *et al*.[16] This decision was made for two principal reasons. Firstly, that there is an overlap in the authors for both the Rafia *et al*. paper and this report, meaning that the model was available to the team reducing model construction time. Secondly, this model structure was used in a preliminary appraisal of remdesivir that was undertaken by a NICE panel meeting;[17] whilst no formal documents related to this meeting has been released an author of this report (MS) was on the panel and believes that no significant issues were raised relating to the model structure.

For non-hospitalised patients, the model structure was based on that outlined in an unpublished report by the NICE Decision Support Unit which provided an early economic evaluation of neutralising monoclonal antibodies and oral antivirals for treating COVID-19 prior to hospitalisation.[18] This consisted of a decision-tree approach where patients who ultimately required hospital admission were evaluated in the hospital-based structure, whereas those that didn't, remained in the community.

This section initially describes the model structures briefly, with later sections providing detail on the population of the parameter values used to generate the results within this report. Cost data were expressed in pound sterling, reflecting prices for the year 2022. Costs were estimated from an NHS and Personal Social Services perspective. The costs and consequences of each strategy were estimated for a lifetime horizon with an annual discount rate of 3.5% being applied for costs and benefits expressed in QALYs.

Due to the timescales of the project no systematic review was undertaken for inputs such as costs and utility values. The default values were taken from a mixture of Rafia *et al*.,[16] data sourced from papers known to the authors, pragmatic, non-systematic searches and from suggestions made by stakeholders at consultation.

3.1 Model Structures

3.1.1 General model structure for hospitalised patients

The economic model was developed in Microsoft Excel and uses a partitioned survival approach (often referred to as area under the curve (AUC) approach) with three mutually exclusive health states; (a) discharged from hospital and alive, (b) hospitalised with or without COVID-19 and (c) death from any cause (COVID-19 or due to other causes).

Movements between health states were not explicitly modelled. Instead, the partitioned model estimates health state occupancy at each time interval. Figure 10 shows a simplified schematic of the model structure. A daily cycle length is used until the end of parametric extrapolation, at day 70, after which a weekly cycle length is used. An initial daily cycle length was chosen to allow changes in treatment and/or hospitalisation and oxygen requirements that happen early in a patient's stay to be modelled at a granular level. A cohort partitioned survival approach was used due to the limited time, the absence of individual patient data (IPD) that may allow a more complex model structure and the need to not explicitly model transitions between health states as would be required by a state transition model. A limitation of the partitioned survival approach is that it is not possible to track individual patients in the model which may have allowed a better representation of the patient experience.

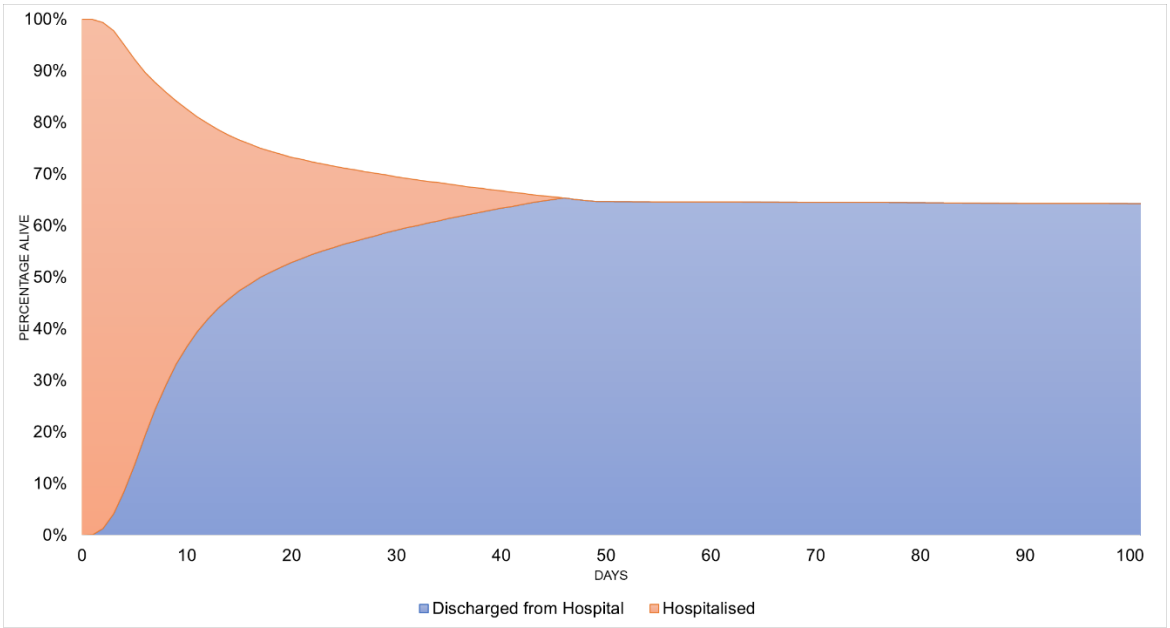

Figure 10: Simplified schematic of model structure (values are for illustration only)

Whilst in hospital, the 8-point ordinal scale of clinical status (an inverted version of the scale originally developed for severe influenza requiring hospitalisation as recommended by the WHO) used in the Adaptive COVID-19 Treatment Trial (ACTT-1) RCT,[19] and in the Remdesivir Effectiveness Evaluation Study (REES)[20] is used. This ordinal scale is described in Table 6 and is used in the model to (1) define the population at baseline in terms of oxygen requirements at the start of treatment, and (2) estimate changes in hospital/oxygen requirements during the hospital stay.

Table 6: Eight-points ordinal scale of clinical status used in ACTT-1[19]

	Clinical status
1	not hospitalised and no limitations of activities
2	not hospitalised, with limitation of activities, home oxygen requirement, or both
3	hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control or other nonmedical reasons)
4	hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions)
5	hospitalised, requiring any supplemental oxygen such as low-flow oxygen (LFO)
6	hospitalised, requiring non-invasive ventilation (NIV) or use of high-flow oxygen (HFO) devices
7	hospitalised, receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)
8	Death

When evaluating the interventions, patients enter the hospital model based on the marketing authorisation, where this has been granted, or in relation to the population in the key studies. Table 7 provides information in which ordinal scales the interventions can be used in line with their marketing authorisation (or anticipated marketing authorisation) of each intervention in Table 1 to Table 3. Scale values of 1 or 2 describe patients with COVID-19 in the community whilst values 3 or higher describe patients in hospital. Only the latter group are relevant for the hospital model, although scale 3 does not require ongoing medical care.

Table 7: The ordinal scale points at which treatments can be provided according to marketing authorisation or anticipated marketing authorisation

	Ordinal Scale						
Intervention	1	2	3	4	5	6	7
Cas and imd							
Molnupiravir	Δ	Δ	Δ				
Tocilizumab					†	†	†
Nirm and rit	Δ	Δ	Δ				
Remdesivir	⅄	⅄	⅄	⅄	⅄	⅄	
Sotrovimab	Δ	Δ	Δ				
Tix and cilg	Δ	Δ	Δ				
Baricitinib							
Bari and rem							

Cas and imd – casirivimab/imdevimab; Nirm and rit – nirmatrelvir/ritonavir; Tix and cilg – tixagevimab/cilgavimab Bari and rem – baricitinib and remdesivir

Δ – with one risk factor for developing severe illness, † - when receiving corticosteroids, ⅄ - in patients with pneumonia

Interventions are permitted for use in cells shaded green and not permitted in cells shaded peach

Movements (improvement or worsening) between the different hospitalisation/oxygen requirements over time is modelled with each scale being associated with cost and HRQoL implications. During their hospital stay, patients are distributed according to their hospital/oxygen requirement derived from the placebo arm of the ACTT-1 study and additional assumptions where necessary. Figure 11 provides an illustration of movement between ordinal scales for patients who needed supplemental oxygen on hospital entry and when treated with SoC. The area above Ordinal Scale 7 denotes patients who have died; the area below Ordinal Scale 3 signifies patients discharged from hospital.

Following Rafia *et al.*[16] the model assumes that all patients are discharged at 70 days. This may underestimate the costs and QALY losses associated with hospital care for the most efficacious drugs, although this is not expected to be a large limitation as the proportions of patients estimated to be in hospital at day 70 is very small. For example, in the mean efficacy scenario this proportion was zero for all interventions.

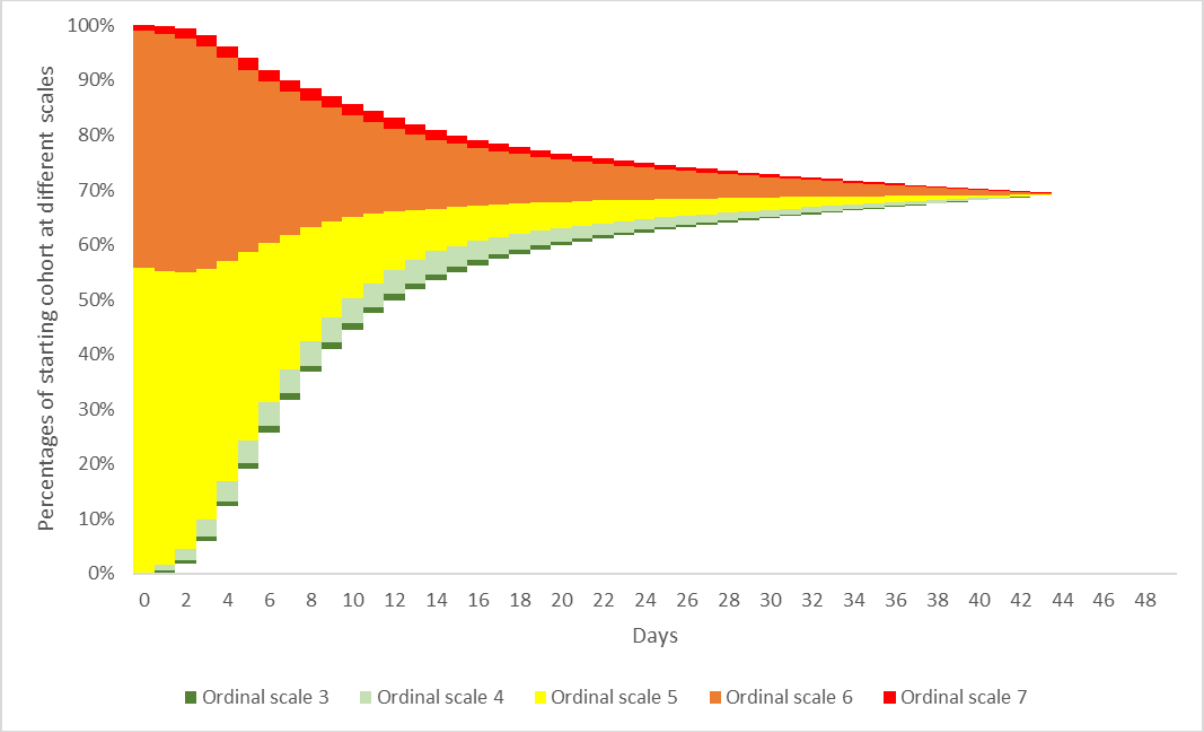

Figure 11: Illustration of ordinal scale occupancy during hospital stay of a cohort admitted to hospital requiring supplemental oxygen and receiving SoC treatment

Pivotal clinical trials/studies for treatments for COVID-19 used in this economic evaluation tend to follow patients and typically collect key clinical outcomes after 28 days of follow-up. It is, therefore, necessary to extrapolate beyond the duration of studies to capture the life expectancy and HRQoL following hospital discharge from COVID-19. Following discharge, patients who were hospitalised with COVID-19 are at an elevated risk of death;[21] emerging evidence suggest that some patients discharged continue to experience symptoms and have a reduced quality of life,[22-31] may require re-admission due to COVID-19,[19, 32-36] and are at an elevated risk to experience multi-organ dysfunctions[21] (such as respiratory diseases, diabetes, cardiovascular, liver and kidney diseases) and may require long term management/monitoring.[37] Within the model, HRQoL reductions and additional costs associated with COVID-19 have been included; for brevity this has been termed 'long COVID'. In addition, the possibility of patients having an increased risk of death following COVID-19 has been modelled using a standardised mortality rate (SMR) applied to the mortality rates for an age- and sex-matched population.

Consequently, a seven-step approach is employed:

- Step 1: use of a parametric function (hazard spline model with 3 knots) fitted to the relevant outcomes (time to death and time to discharge) for all patients on the SoC arm in RECOVERY study[38] for the first 28 days, as used in Rafia *et al*.[16]

- Step 2: This parametric function is adjusted to reflect the outcomes at day 28 as reported in the literature to reflect the benefit of using corticosteroids, which represent the current SoC for patients in need of supplemental oxygen.[37] The model was calibrated as detailed in Section 3.2.2.
- Step 3: Treatment effect in the form of hazard ratios (HRs) or RRs for the interventions were applied to the SoC curves. Data were missing for some interventions with respect to the HR for discharge and the HR for clinical improvement (see Section 2.2). The EAG noted that these HRs were not large drivers of the cost-effectiveness results, and that there was no clear relationship between the two HRs and other results, such that an estimation could be made. As no values for interventions with data were markedly different from unity when compared with SOC, the EAG decided to use the values for SoC where data were missing, with a sensitivity analysis undertaken using a HR of 1.0 for all interventions which is likely to be favourable to casirivimab/imdevimab in relation to time of discharge and baricitinib/remdesivir in relation to clinical improvement.
- Step 4: As shown in Figure 11, ordinal scale occupancy in hospital is assumed to last until the distribution for overall survival (OS) and the distribution for time to discharge intersect. It was assumed in the model that none of the hospitalised cohort would remain in hospital after 70 days.
- Step 5: parametric extrapolation is employed to estimate the rates of death between day 28 until day 70 in the base case.
- Step 6: use of mortality rates from the general population, adjusted by an SMR for the assumed mean duration of long COVID to reflect the elevated risk of death in patients with COVID-19 discharged from hospital.
- Step 7: use of unadjusted mortality rate from the general population after the assumed mean duration of long COVID.

3.1.2 General model structure for non-hospitalised patients

The model structure used for assessing interventions for patients with COVID-19 and at high-risk of hospitalisation is depicted in Figure 12. This is comprised a decision tree which simulates whether hospitalisation is required, and for those patients who are hospitalised, whether supplemental oxygen is required on admission. Patients who are hospitalised were assumed to enter a partitioned survival model as described in 3.1.1.

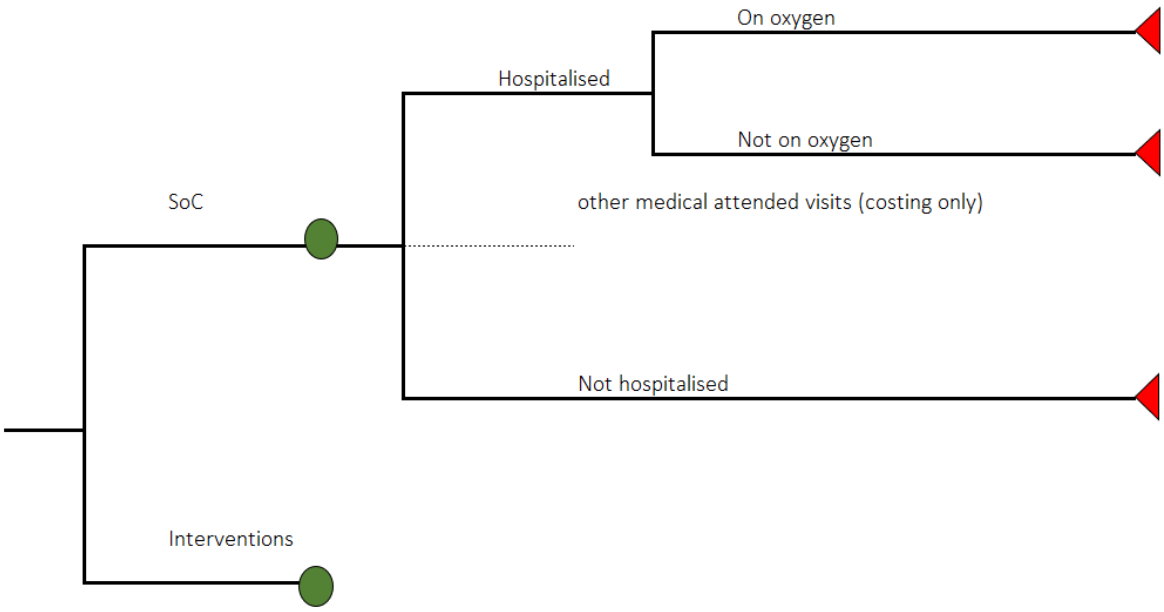

Figure 12: Structure of the decision tree used for the non-hospitalised cohort

In the report sent to stakeholders, the hospitalisation rates for patients on SoC was assumed to be 1.8% calculated from data in Nyberg *et al*.[39] which was doubled for patients at high-risk based on data in Hippisley-Cox *et al*.[40] and clinical advice. Stakeholders responded to this, with Glaxo Smith Kline (GSK) providing data from an interim analysis based on 3865 high-risk non-hospitalised patients in North-West London, with a COVID-19 diagnosis or positive polymerase chain reaction test between the 1st of December 2021 and the 30th of April 2022 who did not receive treatment with a monoclonal antibody or an antiviral. The cohort had a median age of 52 years and 86% had received two or more vaccinations. 108 patients had an inpatient admission with a primary diagnosis of COVID-19 within 29 days of COVID-19 diagnosis equating to a rate of 2.79%. This value has been used in the base case. The EAG notes that the value provided by GSK aligns with the definition of high-risk detailed in a report[41] produced for the Department of Health and Social Care, but believes that this, along with the sensitivity analyses conducted will be informative for decision making. Data from Hippisley-Cox *et al*.[42] in pre-print form indicated an average risk of hospitalisation following a SARS-CoV-2 positive test was 1.45% based on approximately 1.3 million people in England, although the EAG notes that it would expect the value based on a positive SARS-CoV-2 test to be lower than based on having COVID-19 (which is people with SARS-CoV-2 who are symptomatic). The risk of hospitalisation was markedly increased in patients with Down's syndrome, patients with kidney transplant, chemotherapy grade B or C and rare neurological conditions with midpoint HRs greater than 4. Many conditions were associated with increased risks of hospital admission, although vaccination and prior SARS-CoV-2 infection were associated with lower risks. The data from Hippisley-Cox *et al*.[42] did not indicate that the estimate provided by GSK was implausible.

A few working days before the report submission the EAG also received data, in confidence, from the PANORAMIC study. This contained data on hospitalisation rate and efficacy data for molnupiravir in preventing hospitalisation and death. Due to the confidential nature of these data the values and the results are provided in a confidential appendix for the Appraisal Committee.

In sensitivity analyses (see Section 3.4) the hospitalisation rate is changed from 2.79% to 1%, 5% and 10%. These ranges would allow decision makers to explore the cost-effectiveness of treatments in subgroups that are of greater, or lower, risk of hospitalisation. Stakeholders noted that some groups are at particularly high-risk, with one stakeholder reporting that from a survey 39 of 497 (7.8%) of blood cancer patients with a positive test for COVID-19 required hospitalisation and one stakeholder reported that the percentage of patients with primary immunodeficiency or secondary immunodeficiency who required hospitalisation were [redacted] and [redacted] respectively.

The proportion of hospitalised patients requiring supplemental oxygen was estimated from an ISARIC report[43] where the requiring oxygen of any level on admission was calculated at 81% (55% high flow oxygen, 16% non-invasive ventilation, and 10% invasive ventilation). These proportions were assumed to be independent of treatment (intervention or SoC) due to lack of data, and it is plausible that if a person requires hospitalisation, then the intervention has not worked. The EAG ran a sensitivity analysis assuming that the proportion requiring supplemental oxygen was reduced to 75% (with 60% on high-flow oxygen, 10% non-invasive ventilation and 5% invasive ventilation) for patients who have received an intervention.

The model applies an RR to account for other medical attended visits (MAVs) (i.e., visits other than hospital admission) compared to admissions. This RR was estimated from data in Nyberg *et al.*[39] and was equal to 1.37 (1.23% MAV rate divided by 0.9% hospitalisation rate). Only costs were considered for MAVs and incorporated a visit to an accident and emergency department.

Two key clinical outcomes were extracted from the living systematic reviews: RRs for hospitalisation or death, and RRs for day 28 all-cause mortality, which are shown in Figure 6 and Figure 7 respectively. The RR for hospitalisation or death was assumed to apply for hospitalisations only due to the relatively low mortality rate compared to the admission rate. A separate RR was calculated for each intervention for deaths within hospital such that the overall RR for death at 28 days was consistent with the published estimate reported in Table 4 and Table 5. This methodology assumes that there were no deaths amongst non-hospitalised patients in the first 28 days of the model. The EAG believes that this limitation would have a negligible impact on the ICER.

The EAG assumed that there would be no further active treatment in hospital for patients treated in the community, and thus patients receive SoC only. This decision was based on the following factors: that the RRs for mortality for some of the interventions used in the community were substantially lower than the HRs for those treatments used in hospital where the midpoint efficacy was beneficial. For example, the RR for death for nirmatrelvir/ritonavir was 0.04 whilst the midpoint HR for death for baricitinib was 0.61, indicating that the residual effect of nirmatrelvir/ritonavir was larger than the impact of baricitinib, which was the most efficacious hospital intervention based on midpoint values. Furthermore, there is no evidence for the synergistic effects (or not) of using multiple interventions.

In line with NICE's final scope the model does not consider the impact of treatment on the transmission of SARS-CoV-2.[6] The community model may also slightly overestimate the costs associated with people in hospital at the time of catching COVID-19 as hospitalisation costs may be double-counted, although the EAG believes this will be of limited importance.

The modelling did not assess the logistical aspects of treatment in the community, but the EAG notes that this could be a large factor in deciding which treatments could be preferred, as oral treatments could be more acceptable to patients and healthcare systems than treatments that are given intravenously or subcutaneously.

3.2 Clinical Parameters and Inputs Used in this Rapid Assessment

3.2.1 Baseline characteristics after discharge

The economic model uses age and gender distributions to estimate both the rate of mortality beyond the duration of clinical evidence and to estimate HRQoL values for patients discharged from hospital and patients at high-risk remaining in the community. The baseline mean age for the modelled hospitalised cohort was calculated from weekly Office for National Statistics (ONS) data[44] reported in the middle of May 2022. For patients with COVID-19, these data included rates of hospital admissions per 100,000 people and number of deaths, by age bands. These values were multiplied by population data obtained from the ONS[45] to estimate the absolute number of admissions and deaths by age band. The estimated number of discharged patients was calculated by subtracting the number of deaths from the number of admissions.

Table 8 presents the estimated numbers and percentages calculated for admission, death, and discharge conditional on age band.

Table 8: Hospital admission and death weekly numbers and percentages by age band compared to the whole population (mid May 2022)

Age band	Hospital Admission n(%)	Death n(%)	Discharge n(%)
0 to 14	196 (3.9%)	2 (0.3%)	194 (4.4%)
15 to 24	126 (2.5%)	0 (0.0%)	126 (2.9%)
25 to 44	478 (9.4%)	7 (1.0%)	471 (10.7%)
45 to 54	237 (4.7%)	6 (0.9%)	231 (5.3%)
55 to 64	545 (10.8%)	29 (4.3%)	516 (11.8%)
65 to 74	761 (15.0%)	97 (14.4%)	664 (15.1%)
75 to 84	983 (19.4%)	209 (31.0%)	774 (17.6%)
85+	1,737 (34.3%)	324 (48.1%)	1,413 (32.2%)
Overall	5,062 (100%)	674 (100%)	4,388 (100%)

If the midpoint of each age band represented the entire band, mean ages for admission, death and discharge are estimated at 70.6, 82.8 and 68.7 years, respectively. Without data to accurately estimate the age for people with COVID-19 at high-risk of hospitalisation who do not get hospitalised, the EAG assumed that this equalled the age of patients who had not been hospitalised in order to maintain the average starting age for all comparators, which was 55 years in the base case.

The distribution between sexes was taken from an Intensive Care National Audit & Research Centre report[46] which reported that 38.3% of patients admitted to hospital from May 2021, in a critically ill state due to confirmed COVID-19, were female.

3.2.2 Time to hospital death in patients initiating SoC (with or without corticosteroids)

The EAG used the following steps to estimate the survival of patients admitted to hospital due to COVID-19 and receiving SoC.

The Kaplan-Meier (KM) estimate for OS was taken from the control arm of the RECOVERY study,[38] and was digitised which allowed pseudo-IPD to be reconstructed based on the algorithm developed by Guyot et al (2012).[47] A spline model (hazard scale) with 3 knots was subsequently fitted to the pseudo-IPD using the R package flexsurv and employing a natural cubic spline function. This model was selected over standard parametric functions (such as the exponential, Weibull, Gompertz, Log-Normal, Log-Logistic, Gamma, Generalized Gamma) to increase the accuracy in the estimate and because parametric extrapolation beyond the observed period of the trial was limited to a maximum of 70 days. This distribution was then calibrated to the current data such that 73.5% of patients were alive for the

population in need of oxygen and 86.0% of patients were alive for the population admitted with no need of supplemental oxygen at 28 days. These values were taken from a NICE rapid guideline[12] assuming that the outcomes for patients without corticosteroid use were generalisable to patients requiring supplemental oxygen and the outcomes for those patients corticosteroids were generalisable to patients not requiring supplemental oxygen. This decision was made as corticosteroids were only seen to be efficacious in patients not requiring supplemental oxygen. For illustration, Figure 13 shows the OS curves used in the model for SoC and remdesivir by oxygen requirement at hospital admission; the remdesivir data was calculated applying the HR shown in Table 4.

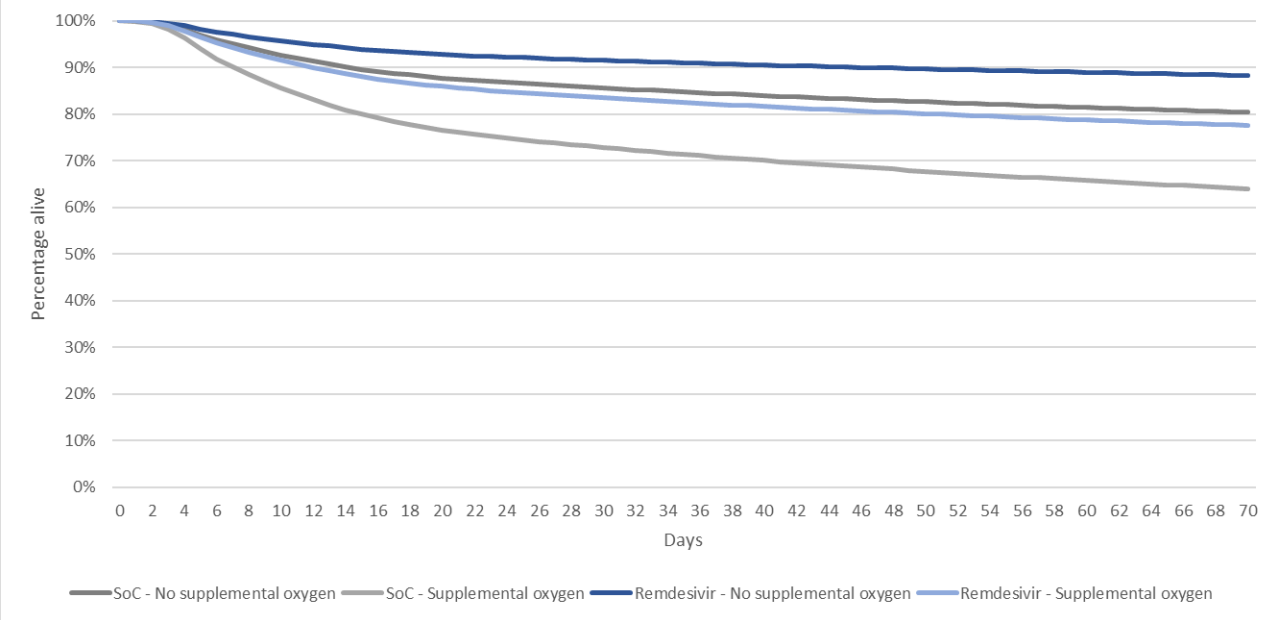

Figure 13: Illustration of OS curves used for the hospitalised cohort for SoC and remdesivir by oxygen requirement at entry

3.2.3 Time to discharge for patients initiating SoC

The methodology for calculating time to discharge for patients receiving SoC was similar to that for time to death (Section 3.2.2) with the following changes. The KM estimate for time to discharge was taken from the control arm of the RECOVERY study,[38] and a spline model (hazard scale) with 3 knots selected. This distribution was then calibrated to the current data such that 64.0% of patients for the population in need of supplemental oxygen and 80.4% of patients with no need of supplemental oxygen were discharged at 28 days. These values were taken from a NICE rapid guideline[12] assuming that the outcomes for patients without corticosteroid use were generalisable to patients requiring supplemental oxygen and the outcomes for patients using corticosteroids were generalisable to patients not requiring supplemental oxygen. For illustration, Figure 14 shows the time to discharge curves used in the model

for SoC and casirivimab/imdevimab by oxygen requirement at hospital admission; the data was calculated applying the HR shown in Table 4.

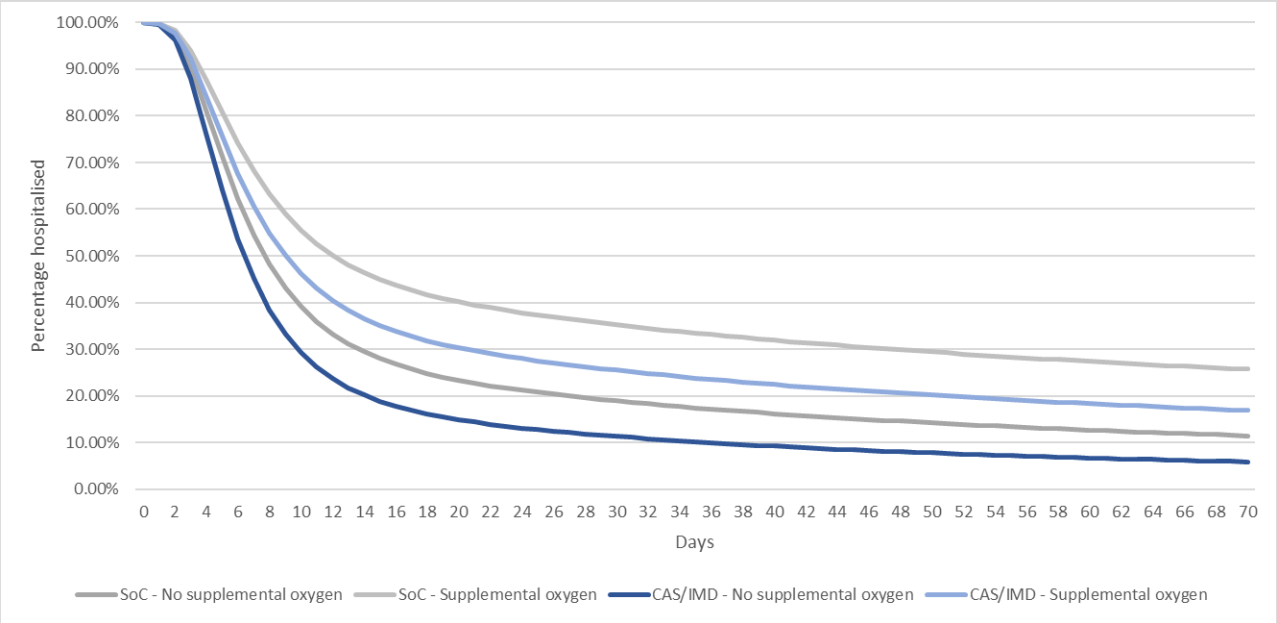

Figure 14: Illustration of time to discharge curves used for the hospitalised cohort for SoC and casirivimab/imdevimab by oxygen requirement at entry

3.2.4 Redistribution of patients according to supplemental oxygen/hospitalisation requirements

In order to estimate costs and QALYs during an average hospital stay, it was necessary to model how patients move between the 8-point ordinal scale as each scale has different consequences in terms of the costs of treatment and the HRQoL of the patient. Hospitalised patients with COVID-19 may receive supplemental oxygen, defined as LFO, HFO, and mechanical ventilation (MV). However, during their hospital stay, patients may require more or less intensive management. Hospitalised patients are divided into five states, which correspond to ordinal scales 3 to 7.

3.2.4.1 Assumed distribution of patients on the 8-point ordinal scale on hospital entry

By definition, all patients admitted to hospital due to COVID-19 without the need for supplemental oxygen are in ordinal stage 4. For patients requiring supplemental oxygen, data from ACTT-1[19] which reported the distribution of ordinal score by treatment for placebo on admission to hospital were used. These data however do not reflect the distribution of current admissions as the percentage requiring IMV or ECMO (ordinal stage 7) was 46%, however a recent value suggests that this was only 1%.[46] The distribution from ACTT-1 was adjusted such that only 1% of patients resided in ordinal stage 7

with those patients reallocated from ordinal stage 7 being redistributed between ordinal stages 5 and 6, according to their relative weight in the ACTT-1 study.

Table 9 and Table 10 show the proportions of patients across the ordinal health stages at baseline for those requiring supplemental oxygen and those not requiring supplemental oxygen, respectively. The EAG is aware that remdesivir should not be used at ordinal scale 7 but considers this to be a minor limitation given the small proportion of patients in this scale.

3.2.4.2 Distribution of hospitalised patients between the ordinal stages on SoC at day 14

Beigel *et al*. report data from the ACTT-1 study[19] for the placebo arm which detailed the ordinal stage distribution at baseline and 14 days later. Because of small numbers, which would have meant that movement between some stages was impossible, a continuity correction was added for all possible transitions, splitting 1 new observation at day 14 equally over the five ordinal scales.

However, ACTT-1 was an early study and there have been many changes such as the vaccination programme, increased use of corticosteroids and changes in SARS-CoV-2 variants. These changes have meant that the results from this study are no longer generalisable to the UK, particularly in terms of the proportion of patients who reach ordinal scale 7 and require IMV or ECMO. In ACTT-1, the EAG calculated that the percentage of patients' time spent in ordinal scale 7 was 48%, contrastingly, this value has been reported in May 2022 to be only 4.12%.[48] The ACTT-1 data was calibrated so that the percentage of time in ordinal stage 7 was equal to 4.12%, with the patients no longer allocated to ordinal scale 7 being allocated to ordinal stage 6 instead. The decision to allocate to ordinal stage 6 was to avoid a situation where the predicted outcomes for patients at stage 7 on hospital entry were better than those for patients admitted at ordinal stage 6. The estimated proportions of patients in hospital across the ordinal health stages at day 14 are shown in

Table **9** and Table 10 for patients not requiring supplemental oxygen and those requiring it respectively.

Table 9: The distribution of hospitalised patients not requiring supplemental oxygen on entry to hospital and at day 14

Ordinal Health Scale	Assumed proportion on entry to hospital (day 0)	Assumed proportion of patients alive at day 14
3	0%	21%
4	100%	36%
5	0%	26%
6	0%	14%

7	0%	3%

Table 10: The distribution of hospitalised patients requiring supplemental oxygen on entry to hospital and at day 14

Ordinal Health Scale	Assumed proportion on entry to hospital (day 0)	Assumed proportion of hospitalised patients at day 14
3	0%	4%
4	0%	15%
5	56%	28%
6	43%	46%
7	1%	7%

3.2.4.3 Movement between ordinal scales between day 0 and day 14

We assumed that the distribution of patients changes linearly from the distribution at baseline to the proportions assumed at day 14; for simplicity, these proportions were assumed to remain constant after day 14 until the end of hospitalisation (day 70). Figure 15 provides the assumed splits between ordinal scales over a 28-day period.

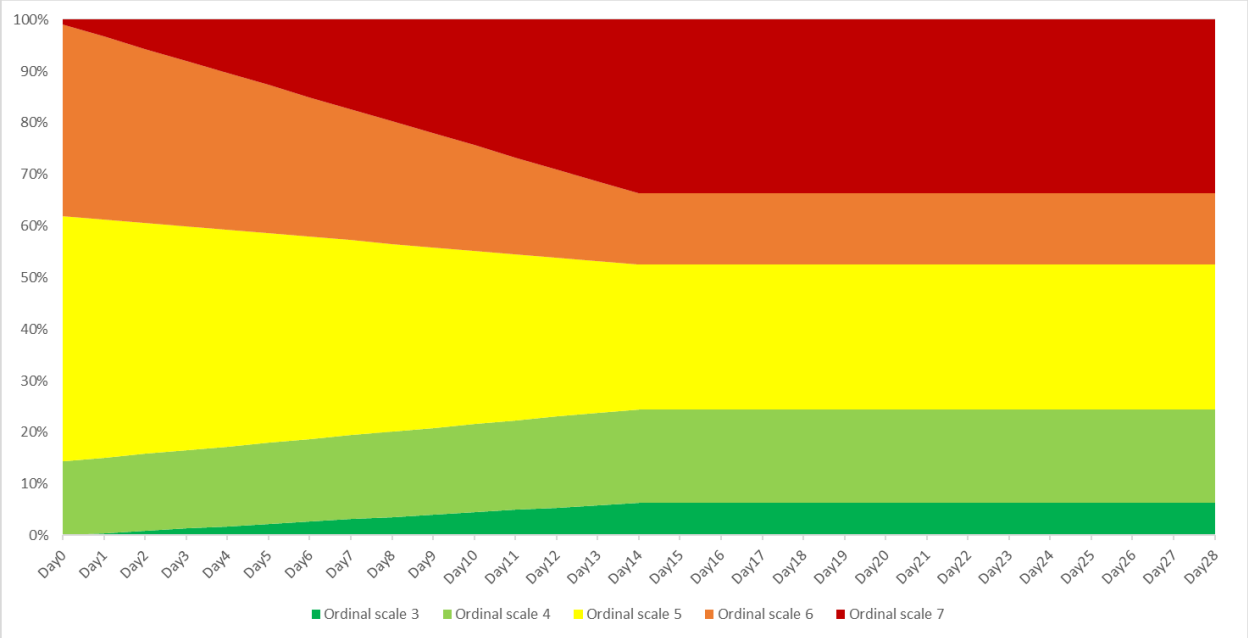

Figure 15: Linear assumptions for distribution across the five ordinal scales during hospital stay

3.2.5 Treatment effects for interventions compared with SoC

The treatment effects for interventions are summarised in Table 4 and Table 5. Where data were not available for clinical improvement or time to discharge a value of 1.0 was used as the model results were not sensitive to these values within the observed range associated with other interventions. A value of 1.0 indicates that the level of clinical improvement and time to discharge are the same for an intervention and for SoC.

3.2.6 Duration of treatment/number of doses

The dosage information data were taken from the NICE COVID-19 rapid guideline.[12] Where either the dosage or the duration of treatment was not available, this information was taken from alternative sources. Table 11 summarises the dosage information used in the model.

Table 11: Dosing information of the interventions included in the model

Intervention	Dosing	Source
Casirivimab/imdevimab	600 mg of both drugs administered together once	Marketing Authorisation
Molnupiravir	800 mg twice daily for 5 days	NICE guideline[12] and Marketing Authorisation
Tocilizumab	Single dose of 8 mg/kg with a maximum of 800 mg. Assumed 50% will receive the maximum dose with the rest getting 600 mg	NICE guideline, [12] Marketing Authorisation and an assumption
Nirmatrelvir/ritonavir	300 mg of nirmatrelvir and 100 mg of ritonavir twice daily for 5 days	NICE guideline[12] and Conditional Marketing Authorisation
Remdesivir	100 mg once daily for 5 days for the hospital setting, and 3 days for the community setting. A 200 mg loading dose on day 1 was used for both	NICE guideline[12]
Sotrovimab	500 mg single infusion	Conditional Marketing Authorisation
Tixagevimab/cilgavimab	600 mg of both drugs administered together once	Montgomery *et al.* 2022[49]
Baricitinib	4 mg once daily for 14 days or discharge whichever earlier	Recommended dose and COVID-NMA Initiative[10]

3.2.7 Mortality rate assumed post-hospitalisation and for those people who did not require hospital admission

The unadjusted rate of mortality for the general population is taken from the England and Wales life table 2018-2020.[50] After discharge, patients hospitalised with COVID-19 were assumed to be at an

elevated risk of death whilst they have long COVID. An SMR of 7.7 (7.2 – 8.3) was applied based on the RR reported by Ayoubkhani *et al*.[21] which was estimated from 47,780 patients treated for COVID-19 in NHS hospitals and discharged alive, using matched-controls and which had a median follow-up of 140 days. This SMR was also applied to patients at high-risk in the community for the period in which they were simulated to have long COVID.

3.2.8 Serious Adverse Events

Whilst the living systematic reviews allowed the relative risks related to SAEs to be extracted, on inspection the ERG identified that these were not events related to the unwanted impacts of the interventions but were conditions related to severe COVID-19. As such, many interventions were associated with less SAEs than SoC, which is generally atypical for efficacious pharmacological treatments. As the model was explicitly tracking the severity of patients using the 8-point ordinal scale the EAG decided to omit SAEs from the model. The degree to which this is favourable, or unfavourable to specific treatments is unknown.

3.2.9 Long COVID

To facilitate modelling, the authors have not strictly adhered to previously defined definitions of long COVID but have taken a simplistic approach with sensitivity analyses undertaken to assess the uncertainty of the impact of long COVID in the base case.

The prevalence of long COVID within the wider community has been taken from an ONS report dated the 6th May 2022,[51] which in supplementary tables reports adjusted model estimates for long COVID of any severity and at any point since the last vaccine of: 8.7% of double-vaccinated patients and 8.0% of triple-vaccinated patients, who had the Omicron BA 1 variant; and 15.9% of double-vaccinated patients and 8.6% of triple-vaccinated patients, who had the Delta variant. Having noted the relatively wide CIs for the ONS estimates, the difference depending on vaccination status (with no data reported for unvaccinated patients) and the method it proposes to use for estimating the duration of long COVID (described below), the EAG assumed that 10% of patients in the community who were at high-risk of severe COVID-19 but did not need hospitalisation would experience long COVID. The EAG was not aware of any evidence on the impact of community treatment on the incidence of long COVID and thus assumed that long COVID was independent of treatment. The degree to which this is favourable, or unfavourable to specific treatments is unknown.

The duration of long COVID-19 was estimated from an ONS publication dated the 1st of June 2022.[52] This stated that of people with self-reported long COVID, defined as "*symptoms continuing for more than four weeks after the first suspected coronavirus (COVID-19) infection that were not explained by*

something else" 72% of people had been first infected by COVID-19 (or suspected they had) at least 12 weeks earlier, 42% were infected at least one year previously, and 19% at least two years previously. This publication also reports that 22% of people had suspected they were infected by COVID-19 less than 12 weeks previously; it was not clear to the EAG why the addition of the proportion of patients less than 12 weeks, and 12 weeks or more, did not add up to 100%, but only 94%.

The EAG fitted simple parametric distributions to the three reported estimates of at least 12 weeks duration (72% with long COVID at 12 weeks, 42% at 1 year, and 22% at 2 years). A Gamma distribution (shape = 100.547, scale 0.644), a Weibull distribution (shape =0.749, scale 57.268) and a lognormal distribution (mean = 3.468, standard deviation 1.562 (on the log scale) were observed to fit the data well. The mean survival times from these distributions were 64.7 weeks (Gamma), 68.3 weeks (Weibull) and 108.6 weeks (lognormal). Figure 16 shows the Gamma and lognormal distributions, which had the lowest and highest mean survival times.

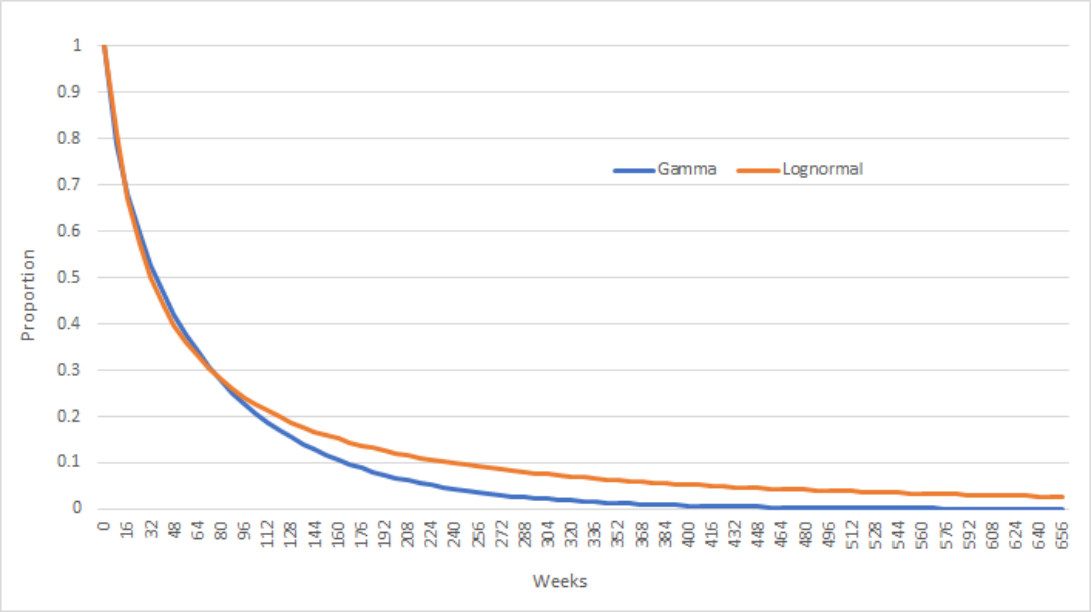

Figure 16: Assumed duration of long Covid

For its base case, the EAG assumed the lognormal distribution was most appropriate but undertook sensitivity analyses halving and doubling the mean duration, the range of which includes the mean from the Gamma distribution. The reason for this was that based on the previous ONS report, on which the EAG had conducted similar analyses, it was seen that the mean time with long COVID had increased, and the data is relatively immature and may be administratively censored. The EAG notes that its analyses are simplistic as formal survival analysis methods were not used, and that it does not assume

that all patients must have long COVID for at least 4 weeks, as used in some definitions but believes that the analyses undertaken are informative for decision making despite this limitation.

From Evans *et al*.[53] it is estimated that at approximately 6 months, 51.7% of patients with non-missing data (n=830) reported that they had not recovered from COVID-19; this value increases to 71.2% when patients stating they were not sure if they had recovered were included. The patients included in the study were hospitalised early in the pandemic (between March and November 2020) and it is unclear how generalisable this result is to patients hospitalised in 2022. The best-fitting gamma and log-normal distributions shown in Figure 16 estimate the proportions of patients not recovered from long COVID to be 57.8% and 55.3% at 26 weeks which is similar to the value reported in Evans *et al*.[53] Given the uncertainty in patients who stated they were not sure if they had recovered, a simplistic assumption was made that all patients hospitalised due to COVID-19 would suffer long COVID. The EAG was not aware of any evidence on the impact of hospital treatment on the incidence of long COVID and thus it was assumed that this is independent of treatment. The degree to which this is favourable, or unfavourable to specific treatments is unknown.

Whilst the simplistic approach used does not capture any potential differential severities of long-term effects based on initial severity of COVID-19[54], the impact of vaccination status, or the consequences of any organ damage caused by long COVID the authors believe that this method is still informative for decision making. A sensitivity analysis is conducted where the annual costs of long COVID are increased by approximately a factor of 2.5.

3.3 Costs and Health-Related Quality of Life

3.3.1 Drug acquisition costs

Whilst the EAG acknowledges that some stock may have already been acquired before this appraisal, recommendations are to inform future commissioning decisions and so the list price is used in this report. Drug acquisition costs, both list prices and prices with Patient Access Scheme (PAS) discounts applied were provided to the EAG by NICE. All analyses in this report have used list prices, with analyses using the PAS for tocilizumab and baricitinib included in a confidential appendix. Table 12 summarises the list prices used in the model. Three drugs had list prices which were not publicly available: casirivimab/imdevimab; molnupiravir; and tixagevimab/cilgavimab. No economic analyses are presented for these interventions in this report but will be contained in a confidential appendix. The type of commercial arrangements for the prices used in the confidential appendix are presented in Table 13. For corticosteroids, daily costs were assumed to be negligible compared to the in-hospital day cost and were not included for simplicity.

Table 12: List prices of interventions used in this report

Intervention	List price	Notes
Tocilizumab	£512.00 £256.00	Price for 1 vial of 400 mg tocilizumab Price for 1 vial of 200 mg tocilizumab
Nirmatrelvir/ritonavir	£829.00	Price for 20 nirmatrelvir tablets and 10 ritonavir tablets
Remdesivir	£340.00	Price for 1 vial of 100 mg remdesivir
Sotrovimab	£2209.00	Price for 1 vial of 500 mg sotrovimab
Baricitinib	£805.56	Price for a pack of 28 tablets, each contains 4 mg baricitinib
Baricitinib and remdesivir	As component interventions	As component interventions

Table 13: Source of the confidential prices used in the confidential appendix

Intervention	Type of commercial arrangement
Casirivimab/imdevimab	Confidential List Price
Molnupiravir	Confidential List Price
Tocilizumab	Simple PAS
Tixagevimab/cilgavimab	Confidential List Price
Baricitinib	Simple PAS
Baricitinib and remdesivir	Simple PAS for baricitinib

3.3.2 Administration costs

The EAG assumed that the costs associated with treatment administration whilst in hospital would be incorporated in the unit costs associated with hospitalisation (see Section 3.3.3). NICE provided the EAG with information from the COVID Medicines Delivery Units (CMDU) relating to how indicative local tariffs were calculated. The costs included elements for: staffing, administrative support, dispensing, clinical consumables, couriering medicines, travel, stationary, and hiring rooms, but excluded medical review to assess drug interactions and any changing in permanent staffing structures.

The costs associated with providing oral antivirals was estimated to be £410 per person, whereas the costs associated with IV infusions was estimated to be £820 per person. For simplicity, the costs associated with administering injections were assumed to be the same as oral antivirals. Within the

analyses it has been assumed that there is likely to be a delay in patients receiving intravenous casirivimab/imdevimab and that a subcutaneous version would be used instead.

Stakeholders commented that due to drug interactions, additional time related to medication reviews would be required for some interventions and that these costs should be incorporated in the model. The need for additional time and the costs associated with this time are both uncertain so have not been included in the model. However, the EAG comments that due to the NMB approach taken, any determined costs associated with additional medication review could be subtracted from the NMB values, allowing the NICE appraisal committee, and other stakeholders, to determine the relative cost-effectiveness of interventions.

3.3.3 Unit costs associated with hospitalisation

Following stakeholder comments some sources for costs have been updated and the latest version of the National Schedule of NHS costs (2020-2021) has been used.[55] A stakeholder suggested alternative sources for the costs associated with ordinal scales 3, 4 and 5 which were as follows: for ordinal scale 3, a weighted average of currency codes DZ11R to DZ11V (Lobar, Atypical or Viral Pneumonia, without Interventions); for ordinal scale 4, a weighted average of currency codes DZ11N to DZ11Q (Lobar, Atypical or Viral Pneumonia, with Single Interventions); and for ordinal scale 5 a weighted average of DZ11K to DZ11M (Lobar, Atypical or Viral Pneumonia, with Multiple Interventions). These appeared plausible and the EAG estimated the cost per bed-day by dividing the average costs per currency code by the average length of stay per currency code taken from the 2017/2018 National Schedule of NHS cost[56] as no later data on length of stay existed. However, the results lacked face validity as the estimated average cost per bed-day was less in ordinal scale 5 than in ordinal scales 3 and 4.

The EAG used an alternative approach which generated plausibly valid costs per bed-day for the ordinal scales. The NHS currency codes used are detailed in Table 14.These costs are larger than those in the report sent out for stakeholder consultation, apart from ordinal scale 3 which is lower.

Table 14: The bed day costs and utility values/decrement in HRQoL used in the economic model by ordinal scale

Ordinal scale	Clinical status	Unit cost	Source	Utility decrement (unless stated)	Source
3	hospitalised, no longer requiring ongoing medical care	£248	National Schedule of NHS costs 2020 – 2021[57] Using the weighted average of DZ11R to DZ11V (Lobar, Atypical or Viral Pneumonia, without Interventions) for a regular day or night admission	0.36	Wilcox et al (2017)[58]
4	hospitalised, not requiring supplemental oxygen	£563	National Schedule of NHS costs 2020 – 2021[57] Using the weighted average of DZ19H - DZ19N (Other Respiratory Disorders) for non-elective short stay		
5	hospitalised, LFO	£828	National Schedule of NHS costs 2020 – 2021[57] and National Schedule of NHS costs 2017 – 2018[56] Using the weighted average of DZ19H - DZ19N (Other Respiratory Disorders) for non-elective long stay having incorporated the average length of stay for each currency code	0.58	Hollmann et al (2013)[59]
6	hospitalised, HFO or NIV	£1977	National Schedule of NHS costs 2020 – 2021[57] Using XC07Z (Adult Critical Care, 0 Organs Supported)		
7	hospitalised, receiving IVM or ECMO	£2393	National Schedule of NHS costs 2020 – 2021[57] Using the weighted average of XC01Z, XC02Z, XC03Z, XC04Z, XC05Z, and XC06Z (Adult Critical care one or more organs supported)	Utility value of 0	assumption

HFO: high-flow oxygen; IVM: invasive mechanical ventilation; LFO: low-flow oxygen; NIV: non-invasive ventilation

3.3.4 Costs associated with COVID-19 for outpatients or following discharge

3.3.4.1 Monitoring costs

For simplicity, monitoring/follow-up was assumed to occur in the first year only. Following discharge, patients were assumed to undergo 2 chest X-rays and 6 GP e-consultations on average related to their COVID-19 as in Rafia *et al*.[16] A one-off cost of £384 was applied to all patients assuming the cost of a chest X-ray was £44 (taken from Stroke *et al*.[60] and inflated to 2019/2020 prices using NHSCII pay and prices indices[61]) and the cost associated with a GP e-consultation was £49.[61]

3.3.4.2 Costs associated with long COVID

The EAG assumed that management costs for long COVID were similar to the management of chronic fatigue syndrome. For time constraints, the EAG pragmatically searched for literature and found an economic evaluation study evaluating multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome in the Netherlands.[62] Healthcare resource use included GP care, mental healthcare specialist, paramedical care, medical specialist care, hospital care, medications, alternative healers, company physicians, and the evaluated interventions. The EAG substituted the company physician cost with GP care and noted the similarity in costs between arms when intervention costs were excluded. An average of the two costs was used, which resulted in an annual cost of €1195. After conversion using the average of the HMRC rates[63] published in January and December 2016, and inflation using NHS cost inflation index pay and prices indices,[61] an annual cost of £1013 was estimated for patients with long COVID. As long COVID can be associated with organ damage and may have additional consequences that would not be associated with chronic fatigue syndrome, a scenario analysis was performed assuming a cost of £2500 per year.

3.3.5 Health-related quality of life

NICE's preferred measurement of HRQoL is the EQ-5D[64] which asks participants to value 5 domains of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on either a 3-level scoring system (EQ-5D-3L) or a five-level scoring system (EQ-5D-5L). A value of 1.00 generated by this instrument indicates perfect health whereas a value of 0.00 indicates a state equivalent to death.

3.3.5.1 Unadjusted baseline utility value by age

Baseline utility values (prior to any decrements/adjustments) are taken from Ara and Brazier based on the age-sex utility values (EQ-5D-3L) in the UK.[65]

3.3.5.2 HRQoL during the hospitalisation episode

Due to the nature of this rapid assessment, no formal systematic review of the literature was conducted to identify the most appropriate utility values. Hence, utility values (or decrements) were sourced from Rafia *et al*.[16] which estimated the utility of patients not requiring supplemental oxygen using patients

with clostridium difficile infection as proxies and estimated the utility of patients requiring supplemental oxygen using patients with influenza (H1N1) as proxies. A stakeholder highlighted some systematic reviews of utility in COVID-19 patients, but all had limitations. Both Nobari *et al.*[66] and Hay *et al.*[67] focussed on general populations rather than those admitted to hospital whereas Walle-Hansen *et al.*[68] reported changes in the EQ-5D-Visual Analogue Scale, and in the change in each domain of the EQ-5D between scores before COVID-19 infection and six months after hospitalisation.

3.3.5.3 HRQoL for high-risk patients with COVID-19 in the community

People at high-risk of requiring hospital care with COVID-19 but who remain in the community without long COVID were assumed to have the same utility as the general age- and sex-matched population as detailed in Section 3.3.5.1. This is a simplification but one that the authors of the report believe would have limited impact due to the short duration of the COVID-19 episode.

3.3.5.4 HRQoL related to long COVID

A paper by Evans *et al.*[53] reported the impact on HRQoL following hospitalisation due to COVID-19. The EQ-5D 5 level (EQ-5D-5L) prior to hospitalisation was observed to be 0.84 but was 0.71 after hospitalisation, suggesting a utility impact of long COVID of 0.13. This value is not dissimilar to a reported utility loss in patients following severe sepsis.[69] It was assumed that this disutility would apply to all patients for their duration of long COVID. Whilst the data in Evans *et al.*[53] indicated that utility loss was correlated with WHO class, with more severe patients having more utility loss, the EAG's simplistic approach used the average value for all patients.

3.4 Analyses undertaken

Probabilistic sensitivity analysis (PSA) is the most appropriate method for providing the most accurate estimation of the ICER, however this could not be undertaken within the timescales of the project. This was because there was a need to use the SOLVER function within Excel to calculate the proportion of patients treated in the community who are admitted to hospital, and die within this episode, as the model assumed that deaths due to COVID-19 only occurred in the hospital (see Section 3.1.2). This calculation added considerable computational time for each new parameter set precluding PSA, although to approximate the results from a PSA, the mean values for clinical effectiveness were used rather than median values in a 'mean efficacy' scenario. Given the large uncertainty in the clinical effectiveness estimates, the approximation of PSA results by using the mean value was deemed a small limitation by the authors.

Three 'deterministic' analyses were run, which were i) using the mean value for clinical effectiveness data, ii) using the most favourable limit of the 95% CI for clinical effectiveness data, and iii) using the least favourable limit of the 95% CI for clinical effectiveness data. For each of the three, the median

(which is typically also the mean) value was used for all other parameters. For brevity, the analyses have been referred to as 'mean efficacy', 'high efficacy' and 'low efficacy' respectively. One exception was made in relation to the 'mean efficacy' which was for the use of remdesivir in a community setting. This was because there were no observed deaths in either arm and using a mean HR of 7.36 was assumed to be overly punitive and a value of 1.00 was used instead.

When operationalising these analyses, problems were encountered for the low efficacy values for four treatments for patients with COVID-19 at high-risk of hospitalisation in the community. This was because Excel generated a numerical error when the multiplier for RR of death for the intervention compared with hospitalised patients treated with SoC was greater than 121 as, due to the number of decimal places used in Excel, the package was attempting to calculate the natural log of zero. As such, the EAG assumed that the upper limit of the 95% CIs for the RR of mortality at 28 days were 1.82 for casirivimab/imdevimab, 3.07 for remdesivir, and 1.99 for sotrovimab, which were the values calculated when a multiplier of 121 was applied to the RR of death for interventions compared with hospitalised patients treated with SoC. These values were used in the 'low' efficacy scenario instead of the reported values in the studies. The EAG notes that for all analyses no attempts of incorporating prior beliefs have been conducted and a frequentist approach using distributions derived from the raw data is used. The EAG comments that it may be clinically implausible that treatments which have a statistically significant beneficial HR relating to hospitalisation or death would be associated with increased RR of death at 28 days, but this limitation could not be addressed in the timescales of the project.

These analyses were supplemented by sensitivity analyses and are believed to provide the NICE appraisal committee with pertinent information relating to the true uncertainty in the decision problem, which is believed by the authors to be much larger than any difference between the mean results from a PSA and from a deterministic analysis using the mean of the distribution. As the efficacy of treatments are assumed to be independent, then there is considerable uncertainty in the true treatment effect (see Figure 5 and Figure 9) and it is plausible that one intervention had its 'low efficacy' value whilst another had its 'high efficacy' value. In such scenarios the more cost-effective treatment can be ascertained by comparing the NMB for each intervention using the appropriate scenario.

Eight sensitivity analyses were performed, which explored the impact of changing: i) the duration of long COVID (ranging from half to double that of the base case); ii) changing the rate of hospital admission in the community with people being at 'high risk' of hospitalisation from a value of 2.79% to 1.00%, 5.00% and 10.00%; iii) changing the average age of patients at high-risk of hospitalisation in the community from 55 years to 50 and 60 years; iv) using a HR of unity for all interventions in relation to time to hospital discharge and time to clinical improvement; v) changing the baseline distribution of supplemental oxygen requirements from that associated with SoC (19% no supplemental oxygen, 55%

high flow oxygen, 16% non-invasive ventilation, and 10% invasive ventilation) to an arbitrarily less severe baseline distribution (25% no supplemental oxygen, 60% high flow oxygen, 10% non-invasive ventilation, and 5% invasive ventilation) for patients who have received an intervention in the community; vi) changing the cost per year associated with long COVID to £2500 per year rather than £1013 per year; vii) assuming a utility decrement of 0.02 per day for patients receiving IV treatment in the community; and viii) changing the SMR for people during the period of long COVID from 7.7 to 5.0 and 10.0.

The results presented provide the ICER, measured in terms of cost per QALY gained, for each intervention compared to SoC and the efficiency frontier, which contains all interventions that are not dominated or extendedly dominated. For the efficiency frontier, the willingness to pay (WTP) at which the preferred treatment changes, presented in terms of cost per QALY thresholds, is provided. A full incremental analysis is an appropriate method for comparing interventions when all treatments would be considered for use in patients and where there is confidence that the relative treatment effects are comparable in terms of key factors (such as the same SoC, the same vaccination levels, and the same SARS-CoV-2 variant). In this report there is considerable differences between studies in key factors which could invalidate incremental analyses. As such, the results from incremental analyses should be treated with considerable caution.

To allow a broader view of the cost-effectiveness, the EAG has provided the ICER for each treatment compared with SoC and used an NMB approach. Within this framework, the largest NMB is associated with the most cost-effective strategy at the stated cost-per-QALY threshold, and multiple strategies can be compared simultaneously, as the absolute difference in strategies in terms of cost, and monetarised health differences, can be easily determined. The formula for calculating NMB is the increase in QALYs associated with an intervention multiplied by a stated cost per QALY threshold minus the additional costs associated with the intervention compared with the costs associated with SoC. If NMB is positive the intervention is cost-effective compared with SoC at the selected threshold; if the NMB is negative, then the intervention is not cost-effective compared with SoC at the selected threshold. When multiple interventions are considered, the intervention with the greatest NMB would be interpreted as the most cost-effective intervention. The advantage of the NMB approach is twofold. First, that if an intervention is not appropriate for treating a group of patients, then this NMB can be ignored without affecting the other values. Second, interventions can be compared using different scenarios specific to an intervention, so for example, the NMBs could be compared between one intervention at high efficacy and one intervention at low efficacy, were this desired. NMB values have been presented using a threshold of £20,000 per QALY gained and a threshold of £30,000 per QALY gained.

For the sensitivity analysis, only NMB values were presented in order that many results can be shown simultaneously. For the sensitivity analyses presented in this report, cost per QALY thresholds of £20,000 per QALY and £30,000 per QALY have been used.

One limitation associated with the omission of PSA is that value of information analyses could not be conducted to assess the monetary implications of recommending an intervention that was not the most cost-effective and to put a ceiling on the expenditure of research addressing knowledge gaps. This is an area for future research.

3.5 The use of severity modifiers

From the 31st of January 2022, NICE Appraisal committees would consider the severity of a condition, defined as the future health lost by people with a condition receiving standard care[70] and that a greater weight can be applied to QALYs if a condition is deemed to be severe. The guidance from NICE is that if there is an absolute discounted QALY shortfall of less than 12 and that the proportional shortfall in discounted QALYs is less than 85% then no severity modifier should be applied in the decision problem, and that the ICER remains unchanged.

For patients admitted to hospital, the mean age was assumed to be 70.6 years and with 38.3% being female. Using these characteristics, the EAG calculated that the discounted QALYs associated with the general population would be approximately 8.68. Based on the results presented in Section 4, SoC is associated with estimated discounted QALYs of 4.66 for patients who require supplemental oxygen on admission and 5.85 for patients who do not require supplemental oxygen on admission. For those requiring supplemental oxygen, the absolute shortfall was 4.40 discounted QALYs and the proportional shortfall was 49%; these numbers are lower for those who do not require supplemental oxygen. As such, no severity modifier is applied for patients who are hospitalised due to COVID-19.

For patients at high-risk of hospitalisation in the community, the mean age in the base case was assumed to be 55 years. The 38.3% proportion of females used for hospitalised patients was assumed to be generalisable to patients at high-risk in the community. Using these characteristics, the EAG calculated that the discounted QALYs associated with the general population would be approximately 13.42. Based on the results presented in Section 4, the absolute shortfall in discounted QALYs for patients at high-risk of hospitalisation was less than 1, and the proportionate shortfall in discounted QALYs was 4%. Given these values, no severity modifier is applied for patients who are at high-risk of hospitalisation due to COVID-19.

3.6 Model validation

The EAG validated its model by using the same parameters and assumptions as Rafia *et al*.[16] and achieving similar results for remdesivir in terms of costs, QALYs, and the ICER. During the stakeholder consultation period one implementation error was identified. This related to the outpatient setting and was unfavourable to treatments. This error has been corrected with the updated model used to produce the results in this report.

4 COST-EFFECTIVENESS RESULTS

The cost-effectiveness results have been divided into three subsections. The first provides the results for hospitalised patients who require supplemental oxygen on admission, the second provides the results for hospitalised patients who do not require supplemental oxygen on admission with the third providing the results for patients at high-risk of hospitalisation in the community. Each of the three subsections are further divided to provide the results from the mean efficacy, high efficacy, and low efficacy scenarios due to considerable uncertainty in the observed efficacy within pivotal studies and changes since the study relating to: the evolving nature of SoC; the impact of vaccination; the impact of previous SARS-CoV-2 infection; and the predominant SARS-CoV-2 variant.

The EAG stresses that this report only uses publicly available list prices. The PASs for tocilizumab and baricitinib are not included which means that the results presented are not accurate representations of the true ICERs for these drugs. Furthermore, three drugs do not have publicly available list prices: casirivimab/imdevimab; molnupiravir; and tixagevimab/cilgavimab. Results incorporating PASs, and confidential list prices are contained in a confidential appendix that is seen by the NICE Appraisal Committee. This confidential appendix also includes confidential data from PANAROMIC which changes the ICER estimates for all drugs proposed for use in the community in high-risk patients.

The results need to be interpreted with caution and in the context of external information. For example, in September 2022, the WHO offered strong recommendations against the use of casirivimab/imdevimab in patients with COVID-19 and against the use of sotrovimab in patients with non-severe COVID-19. As such, the efficacy values associated with these two drugs are highly likely to be nearer the low efficacy values rather than the mean efficacy values, and there is considerable uncertainty in the efficacy of the remaining treatments.

Incremental analyses will be particularly uncertain but have been included for completeness. A NMB approach has been used to allow results to be compared when different assumptions are made for each intervention (for example, in relation to efficacy) or where some interventions are omitted as they would not be appropriate for a particular patient. Pairwise ICERs for the mean, high and low efficacy scenarios have been presented for each intervention compared with SoC in the non-confidential base case for each of the three populations.

4.1 Results for hospitalised patients who need supplemental oxygen on admission

4.1.1 Mean efficacy results for patients requiring supplemental oxygen on admission to hospital

The results of the mean efficacy analysis for patients requiring supplemental oxygen on admission to hospital are shown in Table 15. All interventions were estimated to have a cost per QALY gained compared to SoC below £11,000.

Table 15: Mean efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	18,408	4.66	-	-	-	-
Tocilizumab	21,347	5.15	5976	6896	11,814	5976
Remdesivir	23,643	5.14	10,996	4287	9048	Dominated
Baricitinib	25,601	5.52	8366	10,003	18,601	11,559
Baricitinib/remdesivir	26,137	5.38	10,706	6711	13.931	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained

QALY – quality-adjusted life years; SoC – standard of care

Discounted QALYs for casirivimab/imdevimab are 5.03

4.1.2 High efficacy results for patients requiring supplemental oxygen on admission to hospital

The results of the high efficacy analysis for patients requiring supplemental oxygen on admission to hospital are shown in.

Table 16. All interventions were estimated to have a cost per QALY gained compared to SoC below £11,000. The costs associated with tocilizumab are lower than for other drugs due to the assumed higher rate of discharge of patients as the remaining interventions do not have data and assumed to have the same discharge rate as SoC.

Table 16: High efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	18,408	4.66	-	-	-	-
Tocilizumab	19,345	5.44	1198	14,096	22,731	1198
Remdesivir	28,388	5.63	10,287	9,423	19,125	Ext Dom
Baricitinib	29,293	5.88	8902	13,718	25,946	Ext Dom
Baricitinib/remdesivir	33,385	6.09	10,450	13,835	28,167	21,577

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained

Ext Dom – Extendedly dominated; QALY – quality-adjusted life years; SoC – standard of care

Discounted QALYs for casirivimab/imdevimab are 5.74

4.1.3 Low efficacy results for patients requiring supplemental oxygen on admission to hospital

The results of the low efficacy analysis for patients requiring supplemental oxygen on admission to hospital are shown in Table 17. All interventions except for baricitinib and tocilizumab were dominated by SoC due to increased hazards of death associated with the upper limit of the 95% CI being above 1 (see Table 4). The ICER for baricitinib was below £10,000, that for tocilizumab was below £30,000.

Table 17: Low efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	18,408	4.66	-	-	-	-
Remdesivir	19,953	4.58	Dominated	-3175	-3989	Dominated
Baricitinib/remdesivir	19,668	4.48	Dominated	-4750	-6562	Dominated
Baricitinib	21,947	5.13	7466	6083	10,824	7466
Tocilizumab	23,691	4.84	28,548	-1389	461	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained

QALY – quality-adjusted life years; SoC – standard of care

Discounted QALYs for casirivimab/imdevimab are 4.21

4.2 Results for hospitalised patients who do not need supplemental oxygen on admission

4.2.1 Mean efficacy results for patients requiring no supplemental oxygen on admission to hospital

The results of the mean efficacy analysis for patients not requiring supplemental oxygen on admission to hospital are shown in Table 18. All interventions were estimated to have a cost per QALY gained compared to SoC below £11,000.

Table 18: Mean efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	9325	5.85	-	-	-	-
Baricitinib	11,535	6.36	4362	8054	13,122	4362
Remdesivir	12,216	6.14	10,114	2826	5685	Dominated
Baricitinib/remdesivir	13,072	6.28	8750	4947	9230	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab are 6.07

4.2.2 High efficacy results for patients requiring no supplemental oxygen on admission to hospital

The results of the high efficacy analysis for patients not requiring supplemental oxygen on admission to hospital are shown in Table 19. All interventions were estimated to have a cost per QALY gained compared to SoC below £15,000.

Table 19: High efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	9325	5.85	-	-	-	-
Baricitinib	12,704	6.56	4770	10,919	18,004	4770
Remdesivir	13,559	6.42	7443	7144	12,832	Dominated
Baricitinib/remdesivir	15,310	6.67	7279	10,591	18,814	22,888

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab are 6.48

4.2.3 Low efficacy results for patients requiring no supplemental oxygen on admission to hospital

The results of the low efficacy analysis for patients not requiring supplemental oxygen on admission to hospital are shown in Table 20. With the exception of baricitinib, all interventions were estimated to be dominated by SoC due to the 95% CI for these interventions being greater than 1 (see Table 4). Baricitinib had a cost per QALY below £5000.

Table 20: Low efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	9325	5.85	-	-	-	-
Baricitinib	10,400	6.13	3778	4619	7466	3778
Remdesivir	11,105	5.80	Dominated	-2787	-3291	Dominated
Baricitinib/remdesivir	11,049	5.74	Dominated	-3979	-5106	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab are 5.57

4.3 Results for patients at high-risk of hospitalisation treated in the community

4.3.1 Mean efficacy results for patients at high-risk of hospitalisation

The results of the mean efficacy analysis for patients at high-risk of hospitalisation are shown in Table 21. Nirmatrelvir/ritonavir was estimated to have a cost per QALY compared to SOC of below £10,000 with the remaining interventions having an ICER below £30,000.

Table 21: Mean efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	662	13.42	-	-	-	-
Nirmatrelvir/ritonavir	1600	13.56	6852	1800	3169	6852
Sotrovimab	3449	13.55	21,168	-154	1163	Dominated
Remdesivir	4317	13.54	29,269	-1157	91	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.54, 13.54 and 13.48 respectively

4.3.2 High efficacy results for patients at high-risk of hospitalisation

The results of the high efficacy analysis for patients at high-risk of hospitalisation are shown in Table 22. Nirmatrelvir/ritonavir was estimated to have a cost per QALY compared to SOC of below £10,000, remdesivir was estimated to have a cost per QALY compared to SOC of below £20,000, and sotrovimab was estimated to have a cost per QALY compared to SOC of below £30,000.

Table 22: High efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	662	13.42	-	-	-	-
Nirmatrelvir/ritonavir	1531	13.56	6264	1907	3295	6264
Sotrovimab	3315	13.56	19,302	96	1471	Dominated
Remdesivir	4120	13.56	25,476	-743	614	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.55, 13.54 and 13.52 respectively

4.3.3 Low efficacy results for patients at high-risk of hospitalisation

The results of the low efficacy analysis for patients at high-risk of hospitalisation are shown in Table 23. Nirmatrelvir/ritonavir was estimated to have a cost per QALY compared to SOC of below £10,000, whilst remdesivir and sotrovimab were estimated to have a cost per QALY compared to SOC of below £30,000 and £40,000 respectively.

Table 23: Low efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	662	13.42	-	-	-	-
Nirmatrelvir/ritonavir	1734	13.55	8043	1594	2926	8043
Sotrovimab	3693	13.54	25,014	-608	604	Dominated
Remdesivir	4694	13.52	38,793	-1953	-914	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.52, 13.53 and 13.43 respectively

4.4 Sensitivity Analysis Results

The eight sets of sensitivity analyses described in Section 3.4 were run. For reference, the NMBs of each intervention, using a threshold of £20,000 per QALY gained are shown in Figure 17, Figure 18 and Figure 19 for patients who are hospitalised and require supplemental oxygen, patients who are hospitalised but do not require supplemental oxygen, and patients with COVID-19 in the community who are at high-risk of hospitalisation respectively. Figure 20, Figure 21and Figure 22 provide the same analyses but using a threshold of £30,000 per QALY, respectively. The patterns of NMB are the same at both the £20,000 and £30,000 WTP values with few changes in the sign associated with the NMB. The sign of the NMB changed for.

- Tocilizumab at low efficacy in patients admitted to hospital who require supplemental oxygen which had a negative NMB at a WTP of £20,000 but a positive NMB at a WTP of £30,000.
- Remdesivir at mean and high efficacy in patients at high-risk in the community which had a negative NMB at a WTP of £20,000 but a positive NMB at a WTP of £30,000.
- Sotrovimab at mean and low efficacy in patients at high-risk in the community which had a negative NMB at a WTP of £20,000 but a positive NMB at a WTP of £30,000.

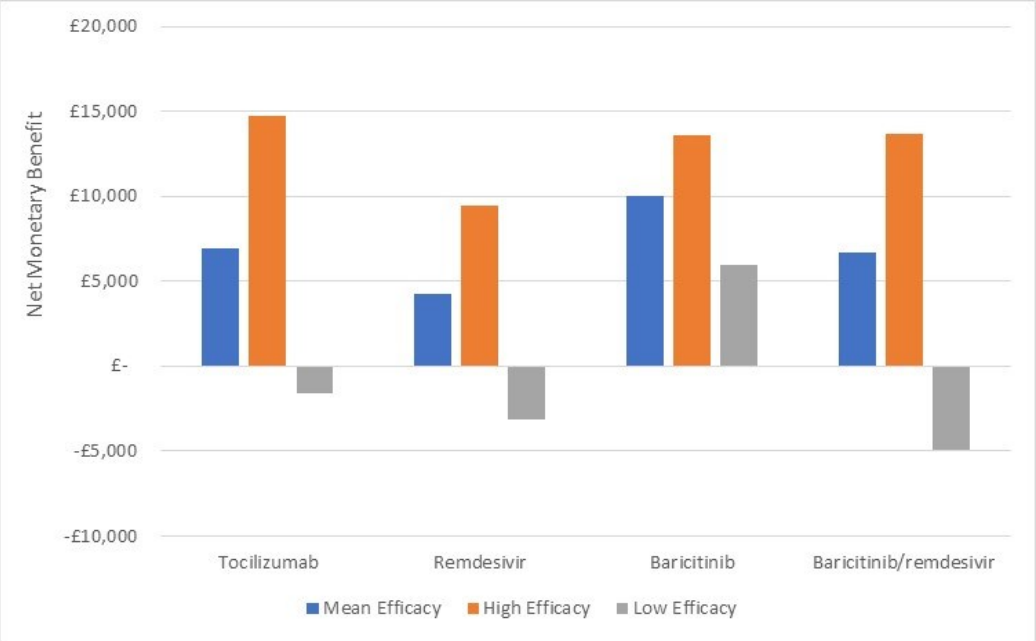

Figure 17: Base case net monetary benefits for patients admitted to hospital who require supplemental oxygen assuming a threshold of £20,000 per QALY gained

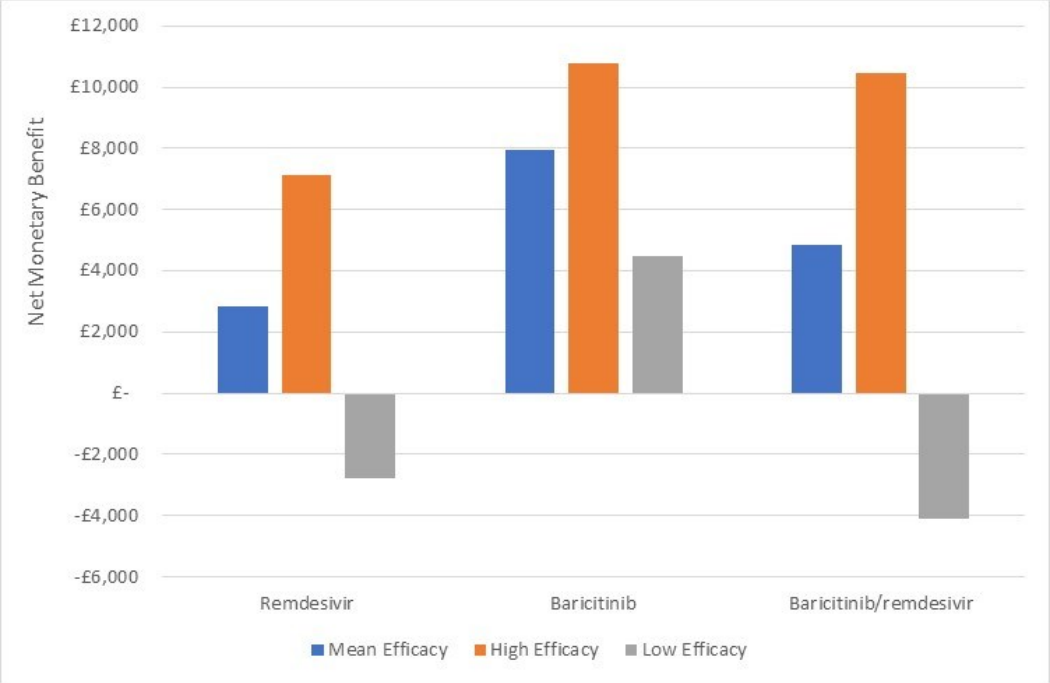

Figure 18: **Base case net monetary benefits for patients admitted to hospital who do not require supplemental oxygen assuming a threshold of £20,000 per QALY gained**

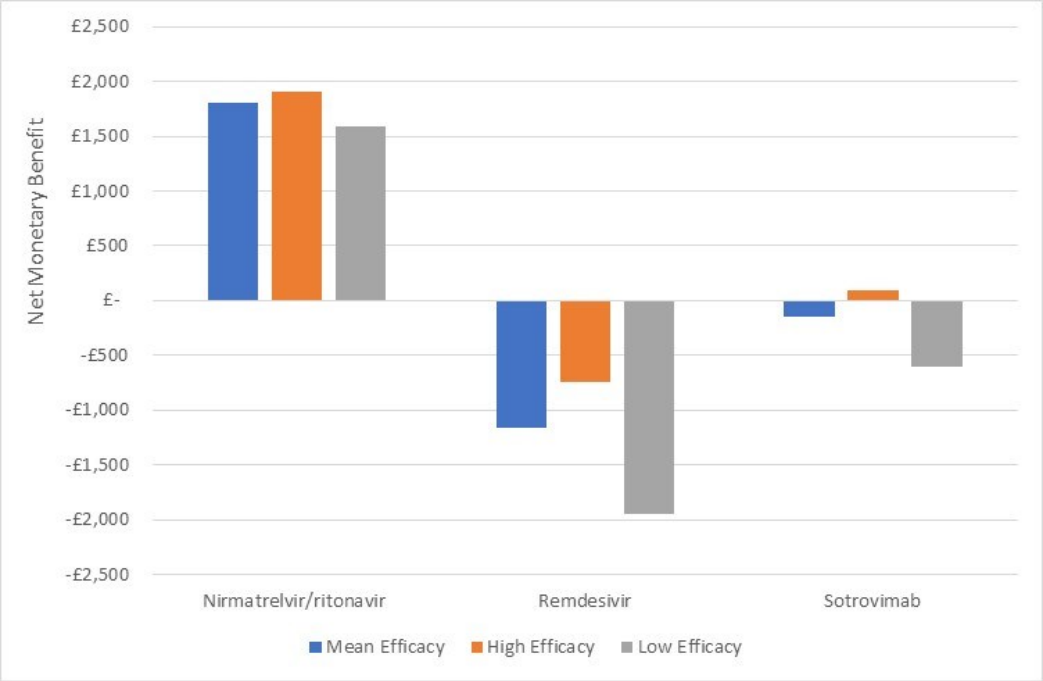

Figure 19: **Base case net monetary benefits for patients with COVID-19 in the community and high-risk of hospitalisation assuming a threshold of £20,000 per QALY gained**

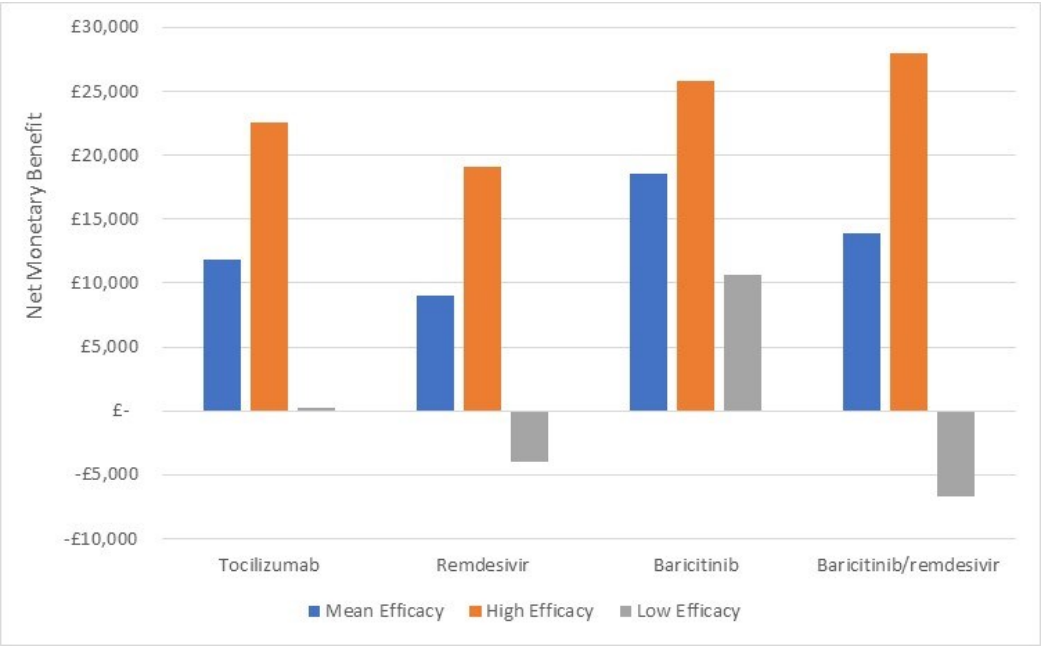

Figure 20: **Base case net monetary benefits for patients admitted to hospital who require supplemental oxygen assuming a threshold of £30,000 per QALY gained**

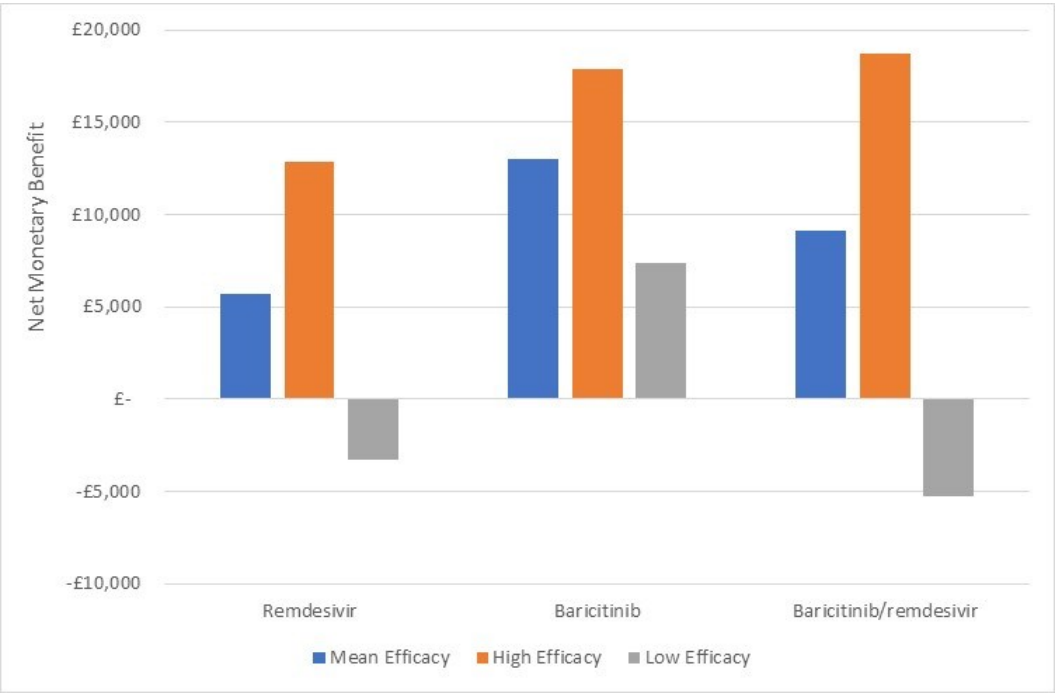

Figure 21: **Base case net monetary benefits for patients admitted to hospital who do not require supplemental oxygen assuming a threshold of £30,000 per QALY gained**

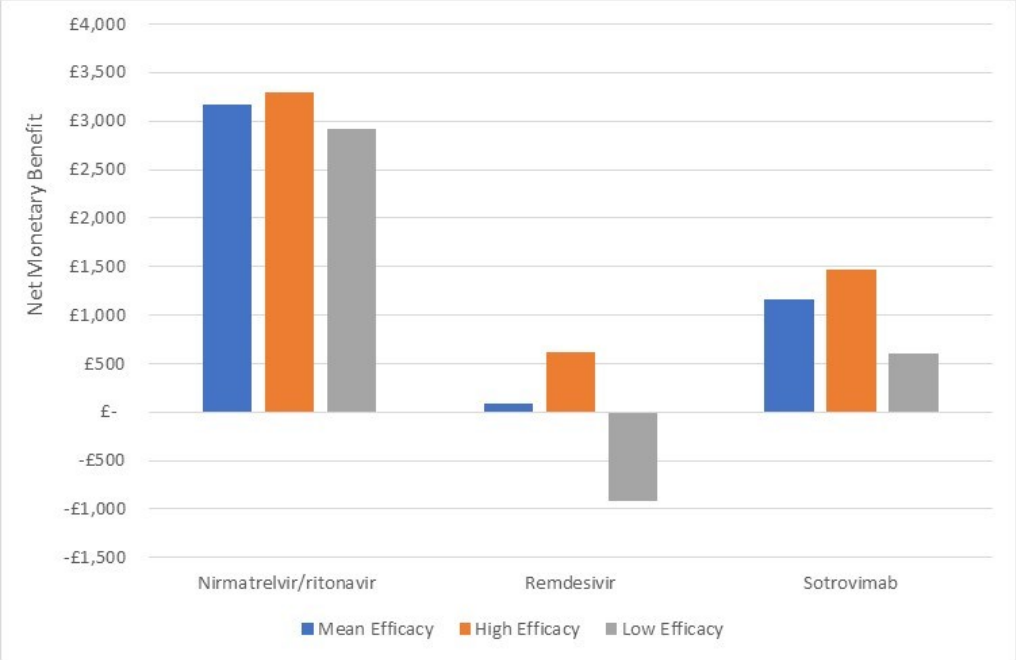

Figure 22: Base case net monetary benefits for patients with COVID-19 in the community and high-risk of hospitalisation assuming a threshold of £30,000 per QALY gained

4.4.1 Amending the duration of long COVID

The NMB results when the duration of long COVID is doubled (to 217.2 weeks) and halved (to 54.3 weeks) are shown in Figure 23, Figure 24 and Figure 25 for people admitted to hospital requiring supplemental oxygen, those admitted to hospital with no need for supplemental oxygen, and those treated in the community at high-risk of hospitalisation respectively, using a WTP of £20,000 per QALY. Corresponding data using a WTP of £30,000 per QALY are shown in Figure 26, Figure 27 and Figure 28.

For patients in hospital, longer durations of COVID reduced NMBs, as there were more survivors with long COVID when treatment was beneficial. In contrast, NMBs were increased in patients at high-risk in the community as treatments stopped patients being hospitalised and therefore reduced the numbers assumed to have long COVID. There was only one instance where the NMB had a different sign compared with the base case when the duration of COVID was changed. This was for sotrovimab in high-risk patients in the community at mean efficacy and assuming a WTP of £20,000 where NMB was negative in the base case but was positive when the duration of COVID was doubled. The change had a moderate impact on the ICERs, with changes being between +/- £2000 per QALY.

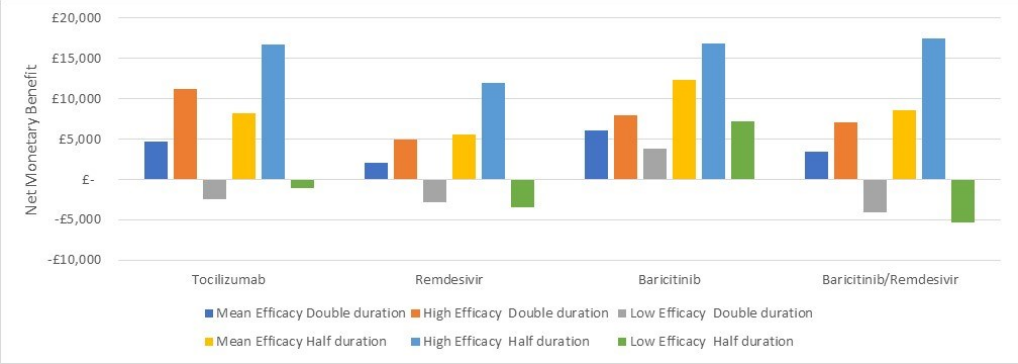

Figure 23: **The NMB results for patients admitted to hospital who require supplemental oxygen when the duration of long COVID is halved and doubled. Assuming a WTP of £20,000**

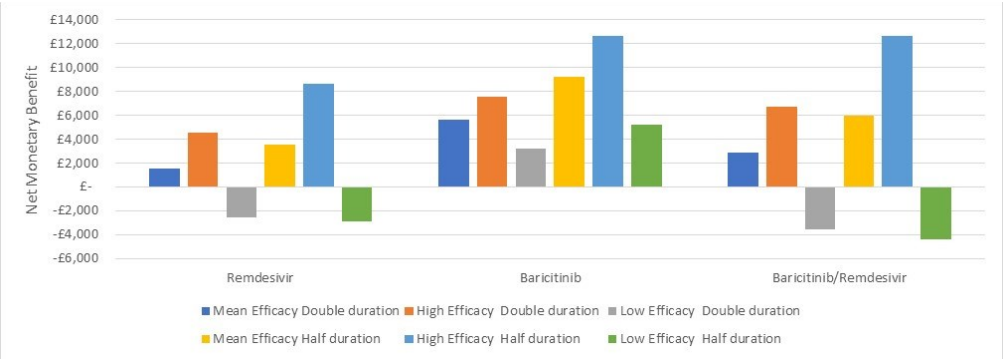

Figure 24: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the duration of long COVID is halved and doubled. Assuming a WTP of £20,000**

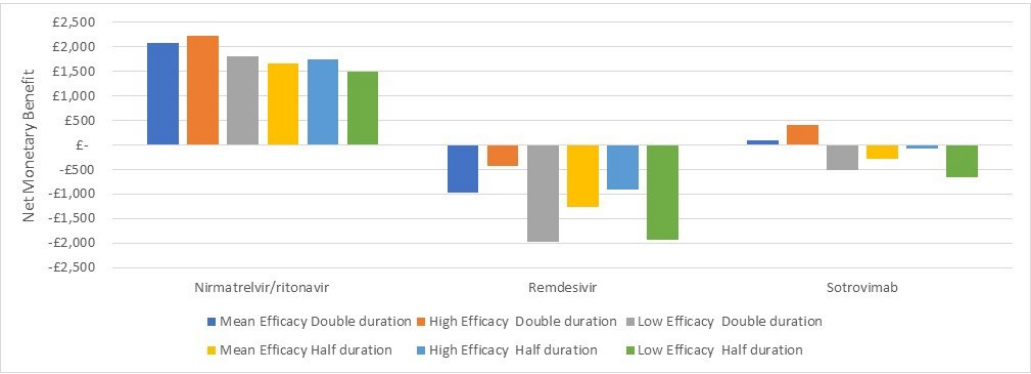

Figure 25: **The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the duration of long COVID is halved and doubled. Assuming a WTP of £20,000**

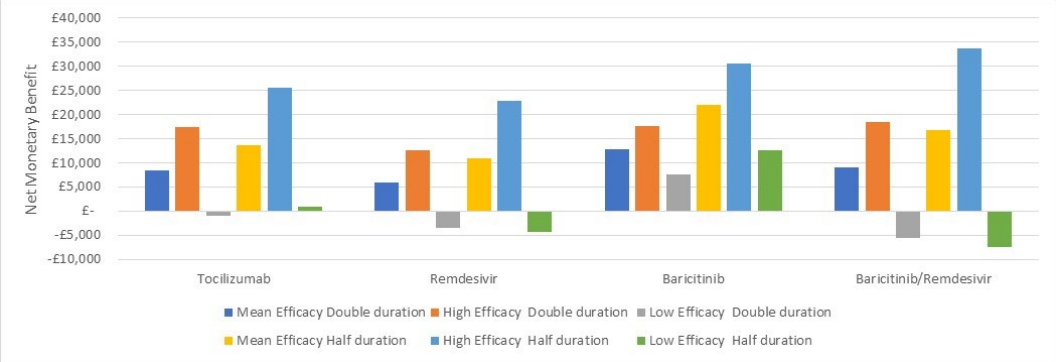

Figure 26: **The NMB results for patients admitted to hospital who require supplemental oxygen when the duration of long COVID is halved and doubled. Assuming a WTP of £30,000**

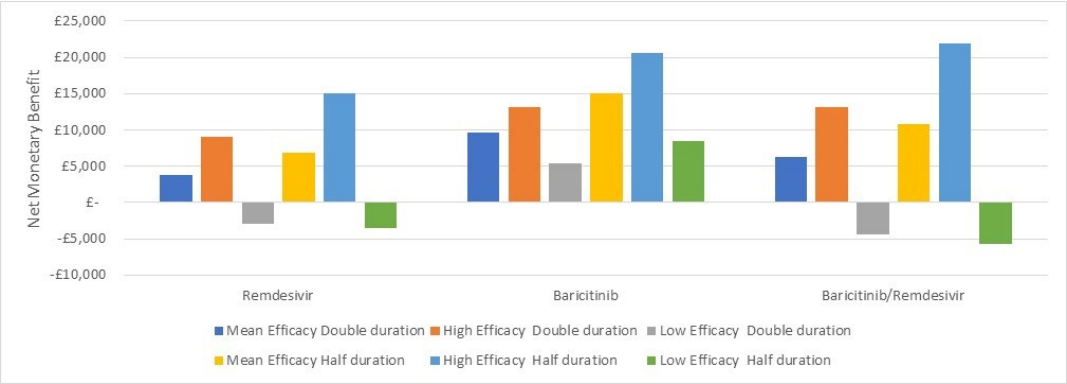

Figure 27: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the duration of long COVID is halved and doubled. Assuming a WTP of £30,000**

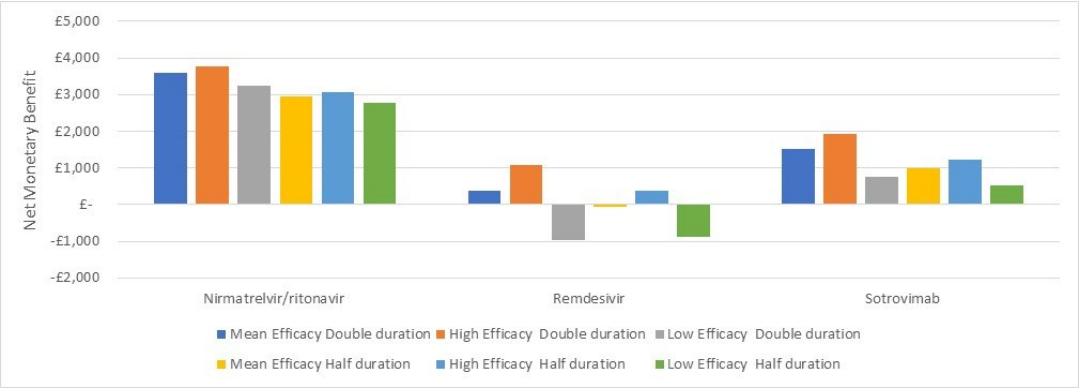

Figure 28: **The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the duration of long COVID is halved and doubled. Assuming a WTP of £30,000**

4.4.2 *Amending the hospital admission percentage for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC*

The NMB results when the hospitalisation admission percentage for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC was changed from 2.79% to 1%, 5%, and 10% are shown in Figure 29 assuming a WTP of £20,000 per QALY and Figure 30 assuming a WTP of £30,000 per QALY. The proportion of patients with COVID-19 at high-risk of being hospitalised being admitted to hospital makes a large difference to the NMB with values increasing as the admission proportion increases. All interventions had a positive NMB when the proportion of patients hospitalised was increased to 5.00% and the mean efficacy scenario was used independent of the WTP assumed. The ICERs changed considerably based on the proportion of high-risk patients hospitalised. The ranges for the drugs when assuming 1% and 10% and the mean efficacy were: nirmatrelvir/ritonavir (£23,189, £272) remdesivir (£84,027, 7213) and sotrovimab (£62,342, £4583)

Figure 29: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the hospital admission percentage was changed. Assuming a WTP of £20,000

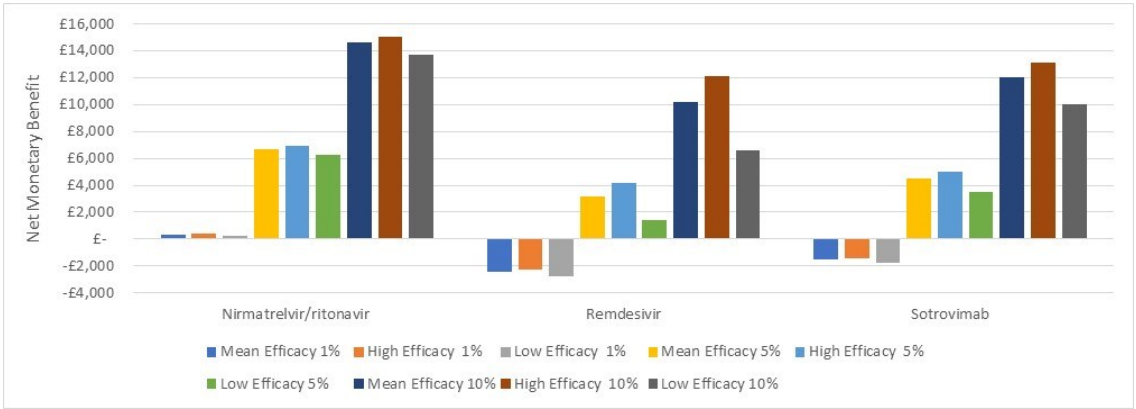

Figure 30: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the hospital admission percentage was changed. Assuming a WTP of £30,000

4.4.3 Amending the age of people with COVID-19 in the community at high-risk of hospitalisation treated with SoC

The NMB results when the age assumed for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC was changed from 55 years to 50 years and 60 years are shown in Figure 31, assuming a WTP of £20,000 per QALY, Figure 32 used a WTP of £30,000 per QALY. The NMBs decrease as the age of the patients increases because less QALYs are gained when a death is prevented. However, the EAG notes that there is no explicit link between risks of poor outcomes and age, and it is likely that all other things being equal, older patients are at a higher risk and that the results could be misleading.

Figure 31: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the age was changed from 55 years to 50 years and 60 years. Assuming a WTP of £20,000 per QALY

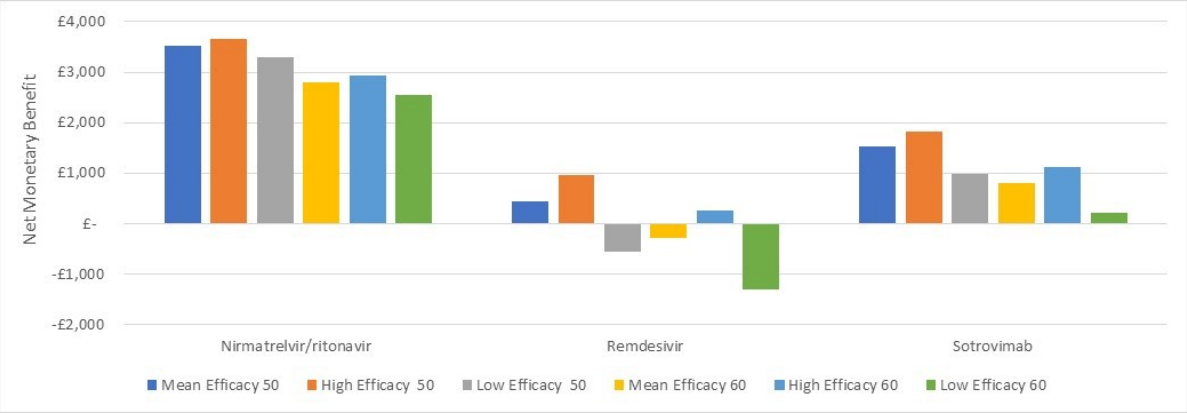

Figure 32: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the age was changed from 55 years to 50 years and 60 years. Assuming a WTP of £30,000 per QALY

4.4.4 *Using a HR of unity for all interventions in relation to time to hospital discharge and time to clinical improvement*

The NMB results when all interventions and SoC had the same impact on time to hospital discharge and time to clinical improvement are shown in Figure 33 for patients requiring supplemental oxygen and in Figure 34 for patients not requiring supplemental oxygen, assuming a WTP of £20,000 per QALY. Figure 35 assuming a WTP of £20,000 per QALY, used a WTP of £30,000 per QALY. This sensitivity analysis did not change the patterns or the sign of the NMBs. These parameters were not large drivers of the ICER.

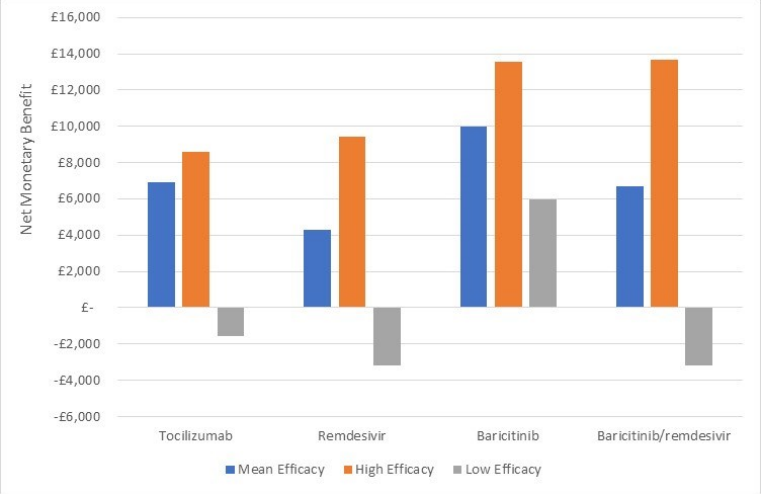

Figure 33: The NMB when a HR of unity was used for all interventions in relation to time to hospital discharge and time to clinical improvement for patients requiring supplemental oxygen. Assuming a WTP of £20,000 per QALY

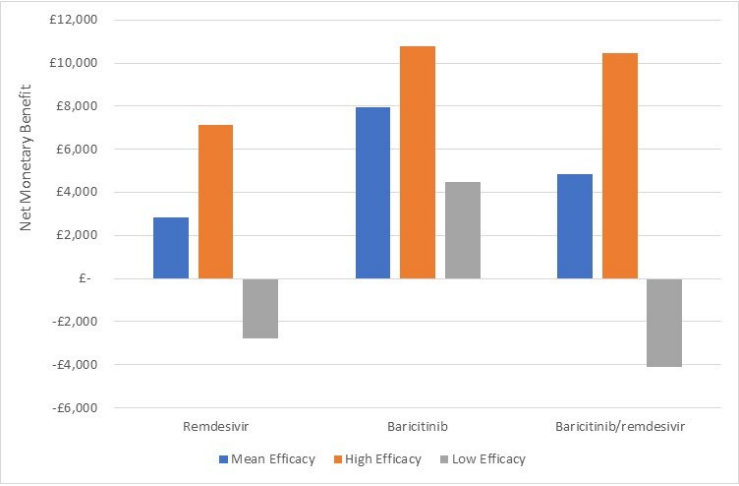

Figure 34: The NMB when a HR of unity was used for all interventions in relation to time to hospital discharge and time to clinical improvement for patients not requiring supplemental oxygen. Assuming a WTP of £20,000 per QALY

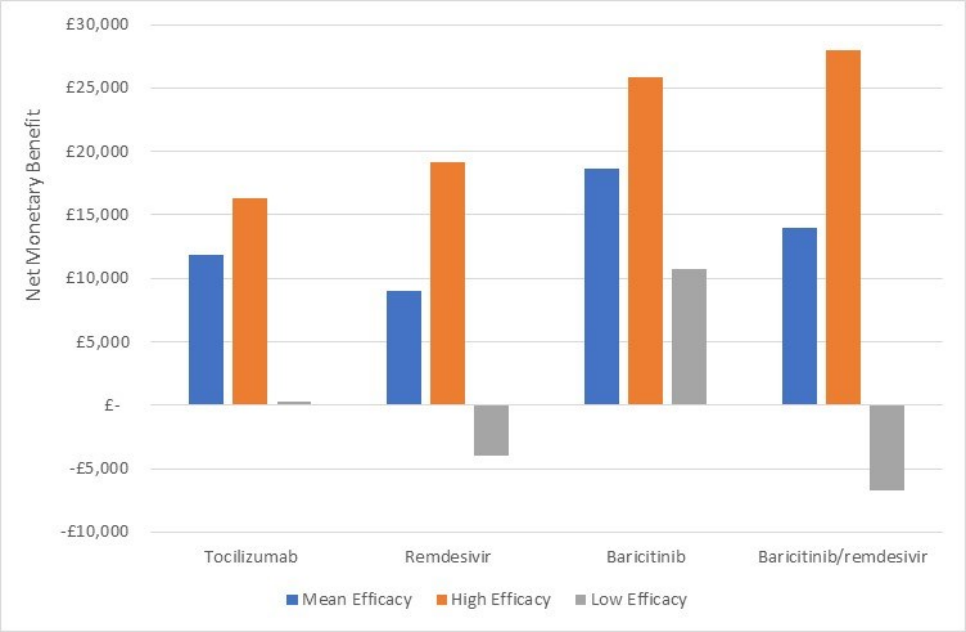

Figure 35: **The NMB when a HR of unity was used for all interventions in relation to time to hospital discharge and time to clinical improvement for patients requiring supplemental oxygen. Assuming a WTP of £30,000 per QALY**

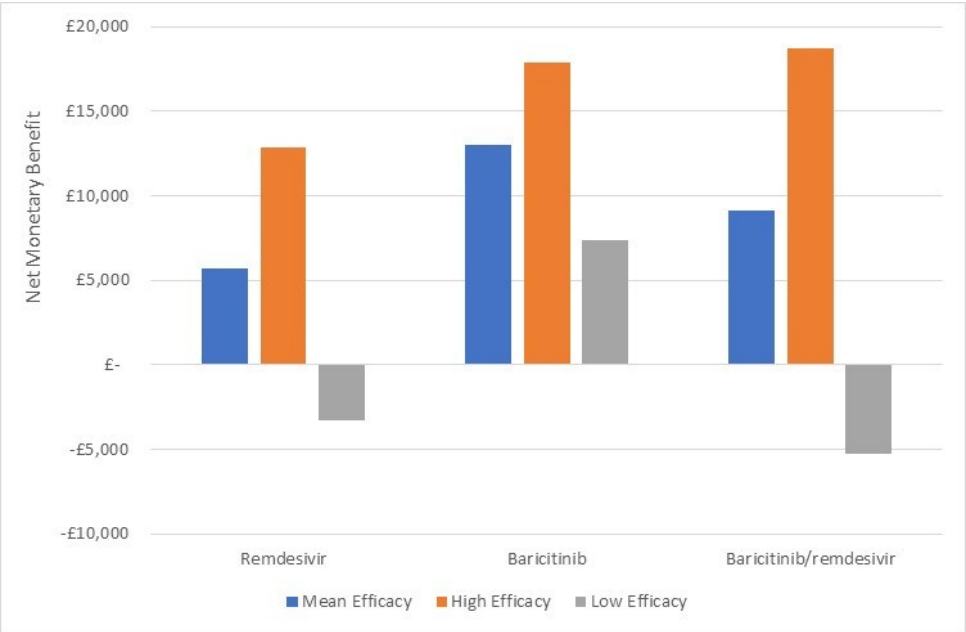

Figure 36: **The NMB when a HR of unity was used for all interventions in relation to time to hospital discharge and time to clinical improvement for patients not requiring supplemental oxygen. Assuming a WTP of £30,000 per QALY**

4.4.5 Changing the baseline distribution of supplemental oxygen requirements for interventions a HR of unity for all interventions in relation to time to hospital discharge and time to clinical improvement

The NMB results when the interventions were assumed to have a less severe distribution following treatment in the community are shown in Figure 37 assuming a WTP of £20,000 per QALY. Figure 38 provides NMBs assuming a WTP of £30,000 per QALY. This sensitivity analysis did not change the patterns, or the sign of the NMBs and had little impact on the ICERs.

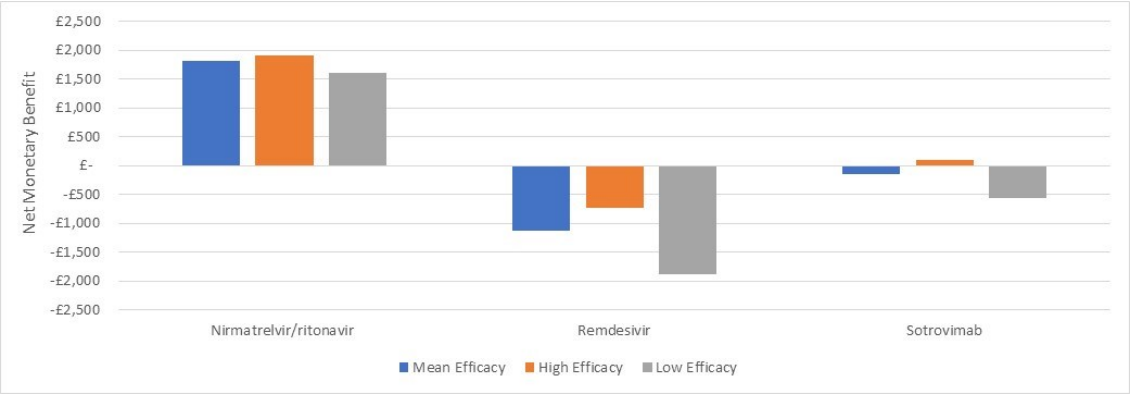

Figure 37: The NMB results when treatment in the community for high-risk patients was associated with less supplemental oxygen on admission to hospital. Assuming a WTP of £20,000 per QALY

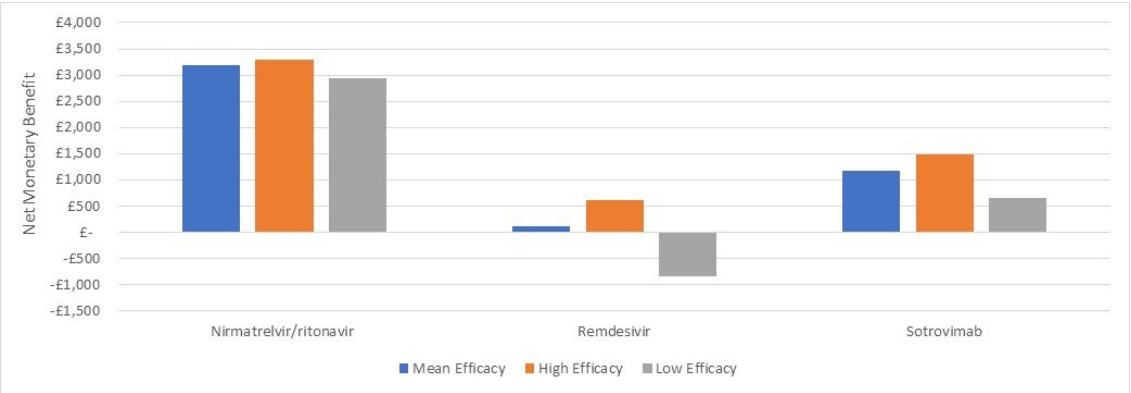

Figure 38: The NMB results when treatment in the community for high-risk patients was associated with less supplemental oxygen on admission to hospital. Assuming a WTP of £30,000 per QALY

4.4.6 Increasing the cost per year associated with long COVID

The NMB results when the costs associated with long COVID were assumed to be £2500 per year rather than £1013 are shown in Figure 39, Figure 40, and Figure 41assuming a WTP of £20,000 per QALY for the hospitalised requiring supplemental oxygen, hospitalised without the need for supplemental oxygen and high-risk in the community respectively. Figure 42, Figure 43, and Figure 44 show the corresponding NMBs assuming a WTP of £30,000 per QALY. The increased cost per year of long COVID did not change the patterns, or the sign of the NMBs and had little impact on the ICERs.

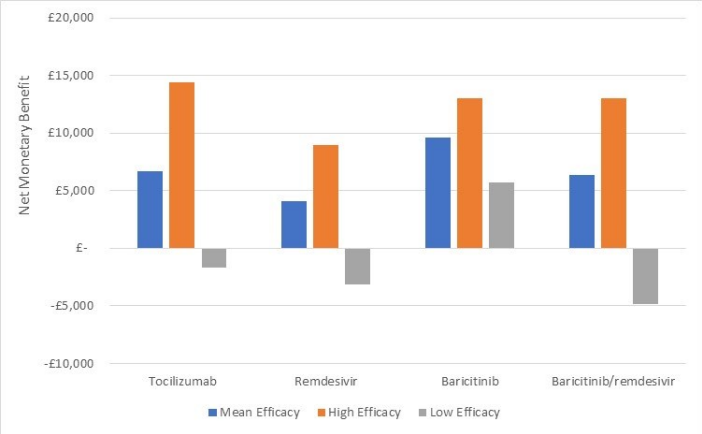

Figure 39: The NMB results for patients admitted to hospital who require supplemental oxygen when the annual cost of long COVID is assumed to be £2500. Assuming a WTP of £20,000 per QALY

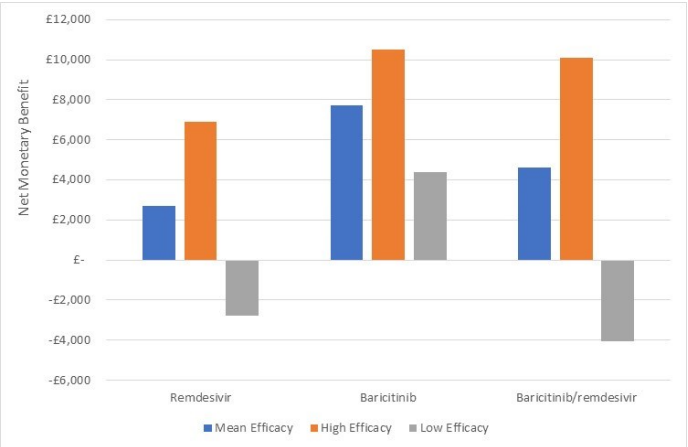

Figure 40: The NMB results for patients admitted to hospital who do not require supplemental oxygen when the annual cost of long COVID is assumed to be £2500. Assuming a WTP of £20,000 per QALY

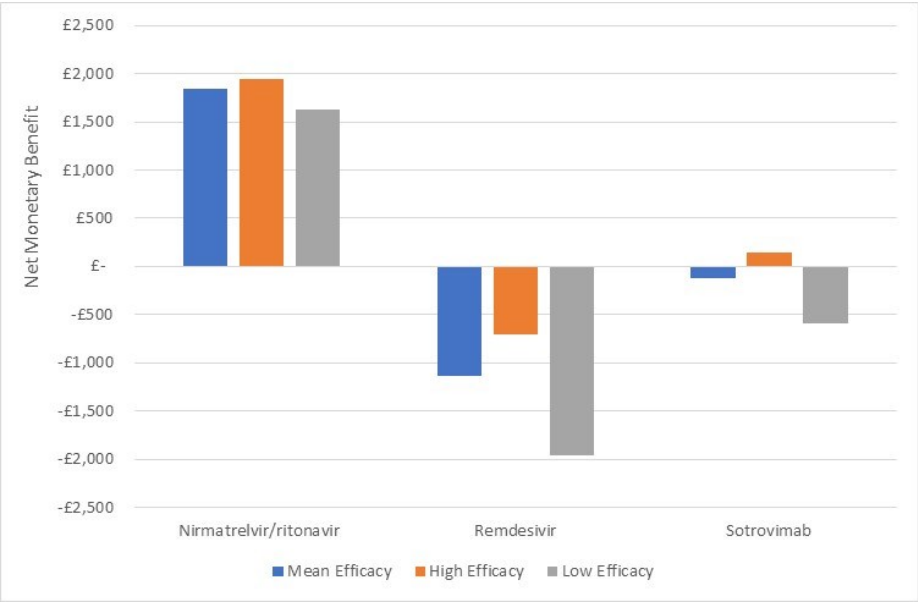

Figure 41: The NMB results for high-risk patients in the community when the annual cost of long COVID is assumed to be £2500. Assuming a WTP of £20,000 per QALY

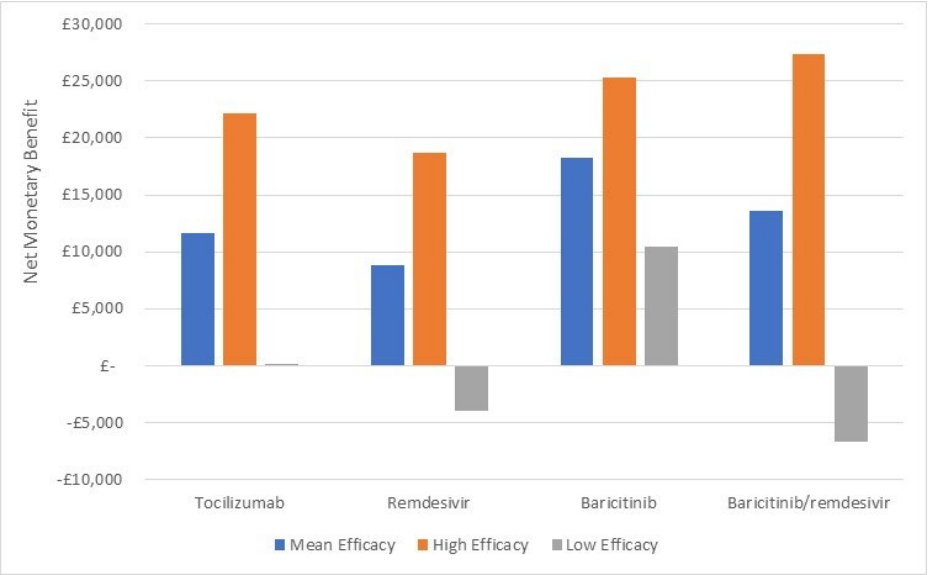

Figure 42: The NMB results for patients admitted to hospital who require supplemental oxygen when the annual cost of long COVID is assumed to be £2500. Assuming a WTP of £30,000 per QALY

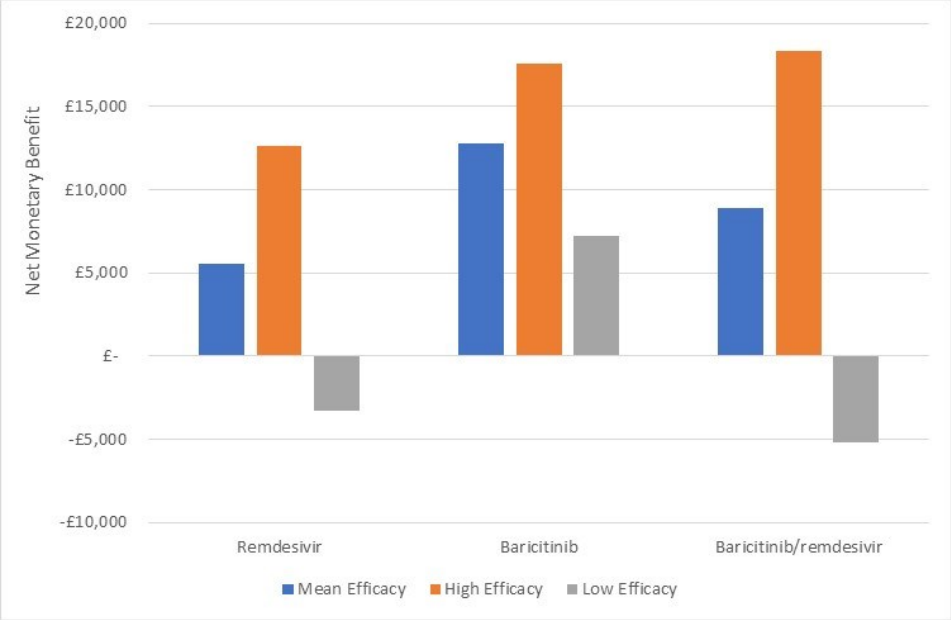

Figure 43: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the annual cost of long COVID is assumed to be £2500. Assuming a WTP of £30,000 per QALY**

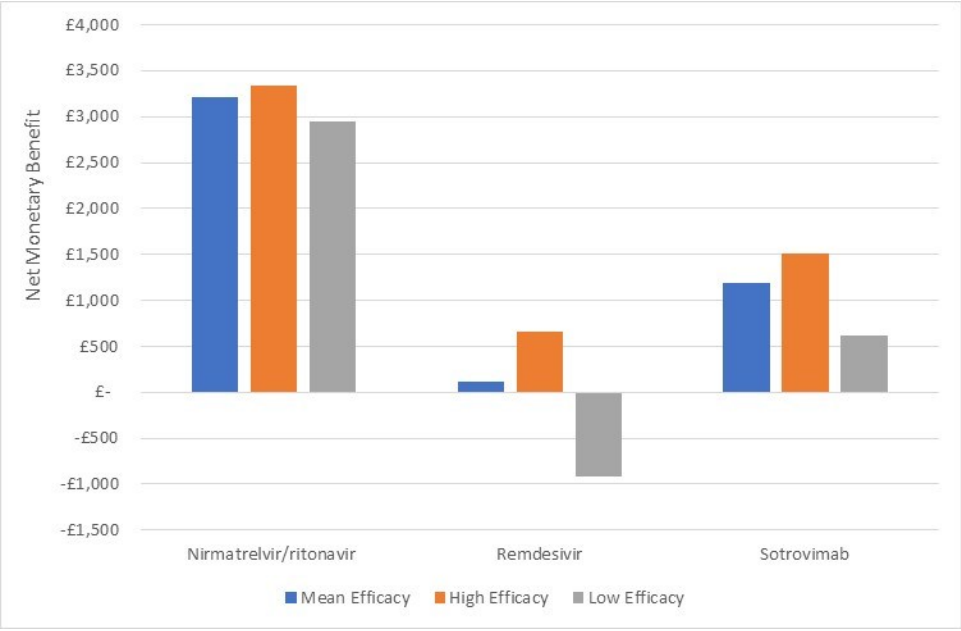

Figure 44: **The NMB results for high-risk patients in the community when the annual cost of long COVID is assumed to be £2500. Assuming a WTP of £30,000 per QALY**

4.4.7 Applying a utility decrement of 0.02 per day for people in the community receiving IV treatment

The NMB results when a disutility of 0.02 per day for those receiving IV treatment in the community are shown in Figure 45 assuming a WTP of £20,000 per QALY and in Figure 46 assuming a WTP of £30,000. This sensitivity analysis made no discernible change to the NMBs or ICERs.

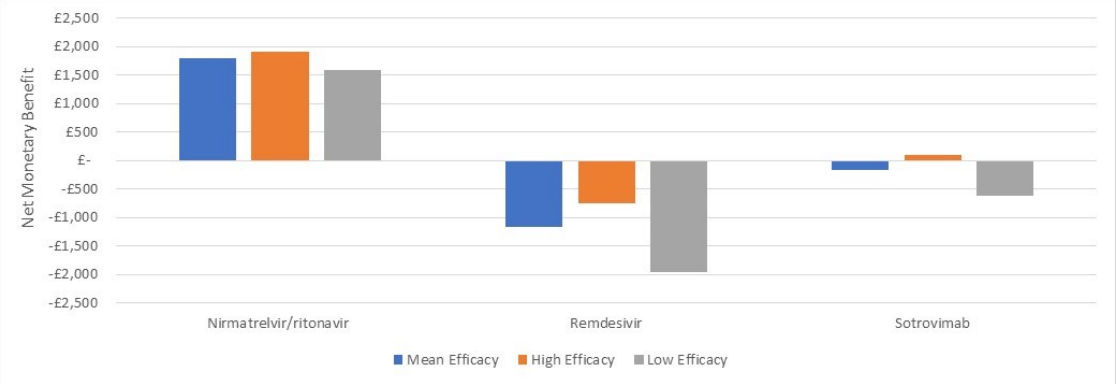

Figure 45: The NMB results when a disutility of 0.02 per day is assumed for patients receiving IV treatment in the community. Assuming a WTP of £20,000 per QALY

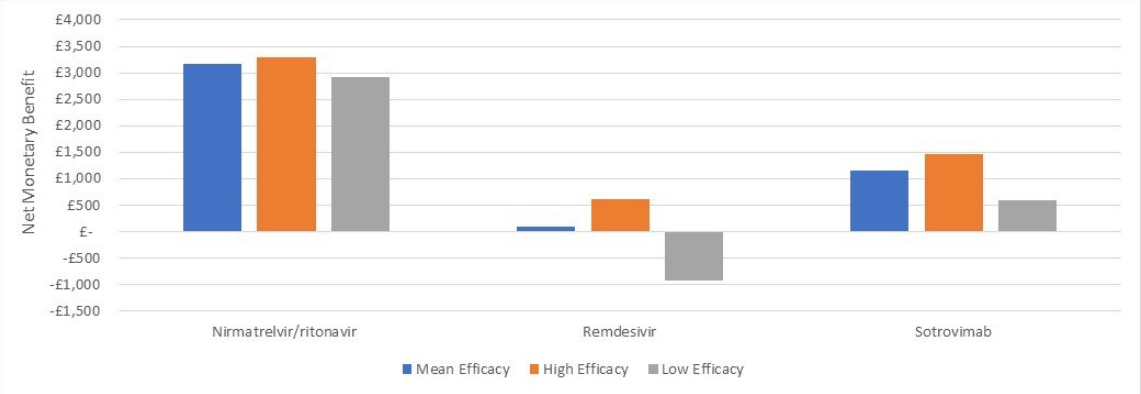

Figure 46: The NMB results when a disutility of 0.02 per day is assumed for patients receiving IV treatment in the community. Assuming a WTP of £30,000 per QALY

4.4.8 Changing the SMR for people with long COVID

The NMB results when the SMR associated with long COVID is changed from 7.7 to 5.0 and 10.0 are shown in assuming a WTP of £20,000 per QALY. provide these data assuming a WTP of £30,000 per QALY. The change in the SMR for people with long COVID did not change the patterns, or the sign of the NMBs and had little impact on the ICERs.

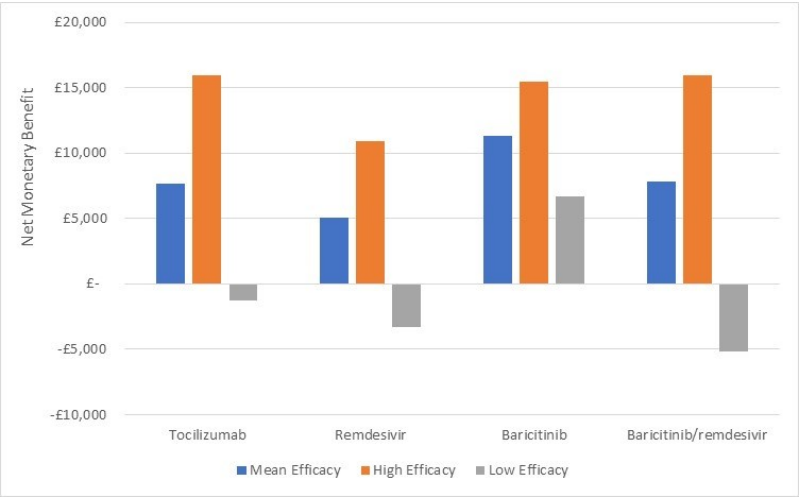

Figure 47: **The NMB results for patients admitted to hospital who require supplemental oxygen when the SMR associated with long COVID is changed. Assuming a WTP of £20,000 per QALY**

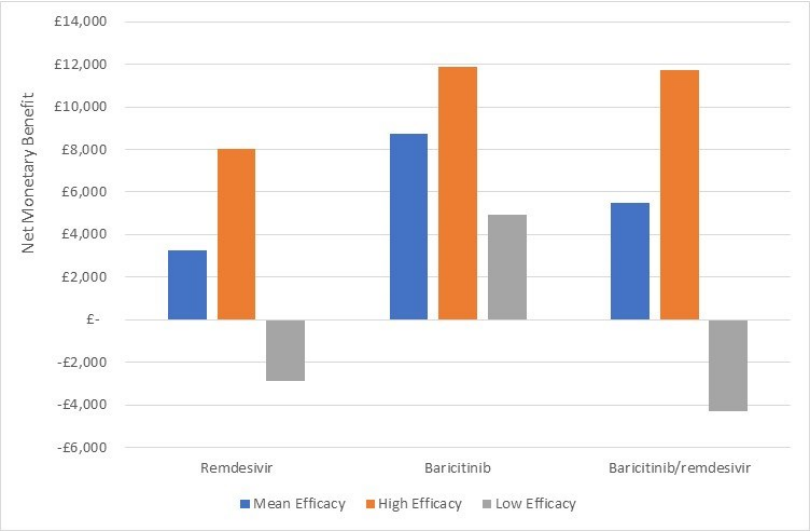

Figure 48: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the SMR associated with long COVID is changed. Assuming a WTP of £20,000 per QALY**

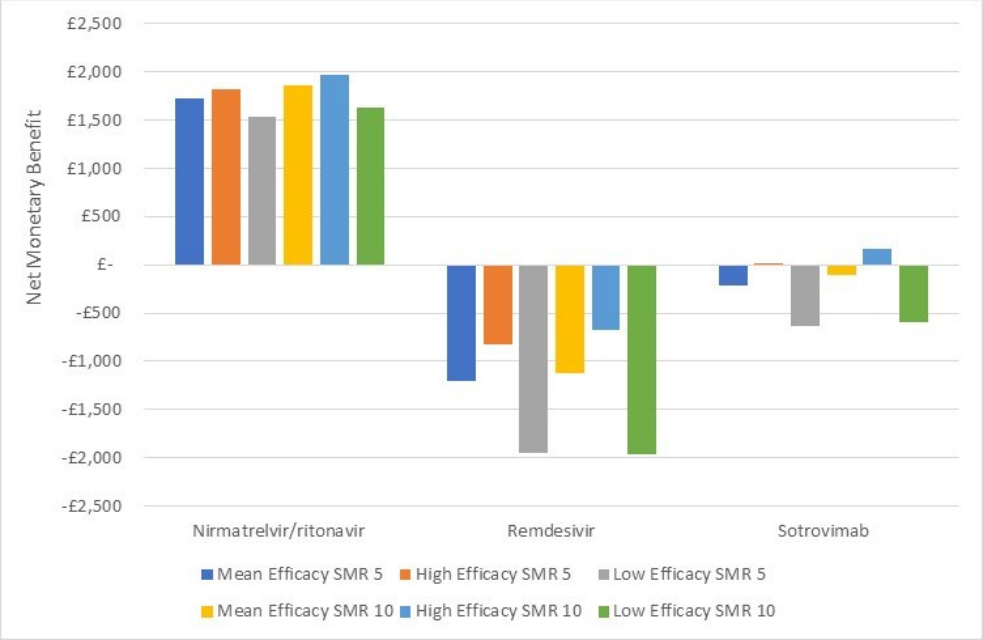

Figure 49: **The NMB results for high-risk patients in the community when the SMR associated with long COVID is changed. Assuming a WTP of £20,000 per QALY**

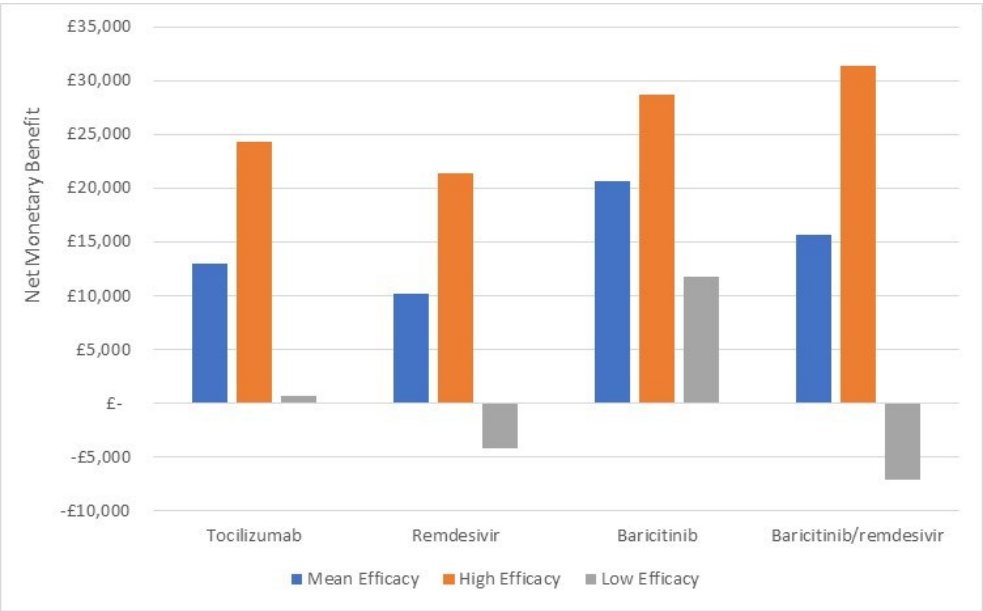

Figure 50: **The NMB results for patients admitted to hospital who require supplemental oxygen when the SMR associated with long COVID is changed. Assuming a WTP of £30,000 per QALY**

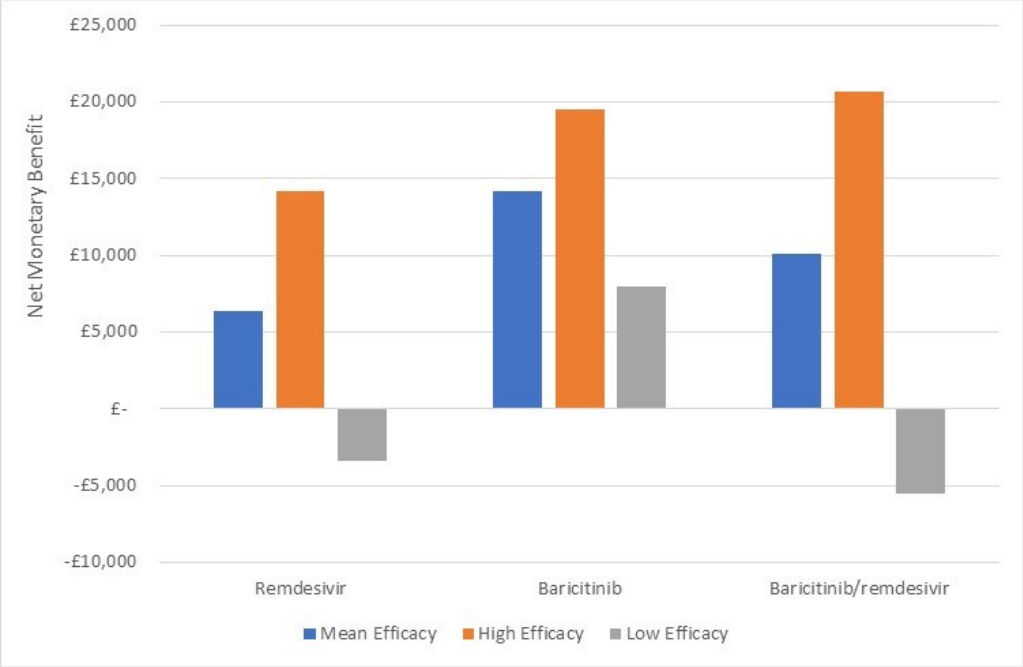

Figure 51: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the SMR associated with long COVID is changed. Assuming a WTP of £30,000 per QALY**

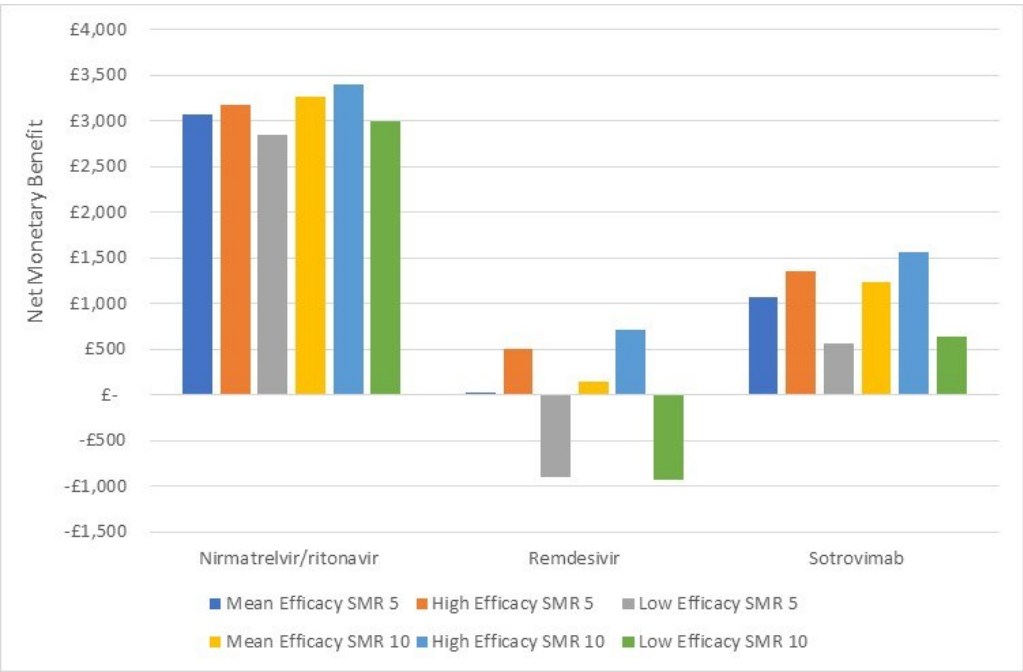

Figure 52: **The NMB results for high-risk patients in the community when the SMR associated with long COVID is changed. Assuming a WTP of £30,000 per QALY**

4.5 Summary of cost-effectiveness analyses.

The results provided in this report provide an indication of plausible ICERs for each intervention although the results for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab could not be presented due to confidential list prices, and the PAS prices for baricitinib and tocilizumab could not be incorporated in this report. There were two key drivers of the ICERs: these were the efficacy of intervention and the proportion of high-risk patients in the community that needed hospitalisation. Other variables impacted on the ICERs to much less degrees.

The ICERs were more favourable to treatments when efficacy was assumed to be high, with ICERs routinely below £30,000 in interventions used in hospital, however, ICERs were much higher where efficacy was assumed to be low, with some interventions dominated. In the community, a similar pattern was seen, although no drug was dominated at low efficacy. For the drugs used in the community, the proportion of high-risk patients in the community that needed hospitalisation greatly changed the ICER with large differences between those generated using a 1% proportion and those generated using 10%. The confidential appendix provides the proportion of high-risk patients who were hospitalised in the PANORAMIC study, although the EAG highlights the difference in the definition of high-risk in the PANORAMIC study and that used by GSK in its interim analysis which was used in this report.

Whilst the EAG provided analyses using mean, high and low efficacy, the results from the pivotal trials may no longer be generalisable given change in the SARS-CoV-2 variant, the current SoC and the change in vaccination status of the population. This is demonstrated by sotrovimab having favourable median and mean efficacies in prevention hospitalisation, but this drug is not authorised in the USA, as it is unlikely to be effective against the Omicron BA.2 subvariant, Further the WHO has made strong recommendations against the use of sotrovimab. Given potential further changes in the variant, the results presented in this report, and within the confidential appendix, should be treated with caution.

5 DISCUSSION AND CONCLUSIONS

5.1 Summary Of Clinical-Effectiveness data

For time reasons, the EAG used data from two living systematic reviews and had to assume that the reported efficacy of treatments was generalisable to other settings. This assumption may not be correct due to: the evolving nature of SoC; the impact of vaccination; the impact of previous SARS-CoV-2 infection; and the predominant SARS-CoV-2 variant. In addition, patient age, ethnicity, sex, and immune system competence may be treatment effect modifiers. This point is proven in the case of casirivimab/imdevimab which had beneficial mean efficacy values but where guidance from the USA Food & Drug Administration that '*sotrovimab is not authorized in any US state or territory at this time*' (the 5th April 2022) as it is unlikely to be effective against the Omicron BA.2 sub-variant.[14]

All treatments were associated with a midpoint beneficial effect on preventing mortality, except for remdesivir for patients at high-risk in the community where there were no deaths in either arm. Noting the caveats associated with assuming transportability of treatment effects and the relatively wide CIs associated with preventing mortality, the EAG did not feel confident that it could robustly identify a treatment that was more efficacious than others or, potentially, SoC.

The interventions should be reviewed for activity against current and future variants. If it is shown that these confer more or less protection than against the predominant variant in the key clinical studies, then decision makers may choose to select the 'high' or 'low' efficacy results to guide estimates of cost-effectiveness.

5.2 Summary of Cost-Effectiveness analyses

For patients who have been hospitalised due to COVID-19, all treatments had scenarios where the ICER was below £20,000 compared with SoC, however, in the low efficacy scenario only baricitinib and tocilizumab had ICERs under £30,000 compared with SoC. For patients with COVID-19 in the community at high-risk of hospitalisation, nirmatrelvir/ritonavir was estimated to have an ICER below £10,000 compared with SoC, with sotrovimab and remdesivir having ICERs below £30,000. However, in the low efficacy scenario, the ICER for sotrovimab is greater than £30,000. The EAG stresses that, for all interventions in all settings, if the drug does not work well against current or future variants the ICER could be markedly higher than that estimated in the low efficacy scenario.

The analyses in this report are more favourable to remdesivir treatment in hospital than previous estimates reported by Rafia *et al*.[16] The primary reasons for this are differing assumptions in the models. In Rafia *et al*.[16] remdesivir was associated with an odds ratio for clinical improvement that indicated that remdesivir was harmful, compared with SoC. to a patient who did not die in hospital and the

proportion of patients in ordinal scale 7 receiving SoC was large (22% at day 14). In our analyses, remdesivir is now associated with improved outcomes for patients who do not die in hospital but also the proportion of patients in ordinal scale 7 who receive SoC was significantly reduced (9% at day 14). These changes result in a considerable saving in hospital costs, which results in a lower ICER in our work.

The analyses did not look at the logistical aspects of providing treatment. For patients in hospital this is unlikely to be a significant issue, however it could be for patients in the community. Local decision makers would need to ascertain whether IV treatment for patients with COVID-19, if that were the patient's preference, is possible. The analysis did also not consider the impact of patient preference of route of administration on utility.

5.2.1 Strengths of the economic analysis include:

- The use of effectiveness data from living systematic reviews
- An attempt by the EAG to align the results of SoC produced by the model with data observed in mid-2022
- Uncertainty in the model inputs and assumptions has been explored in sensitivity analyses
- The modelling attempts to capture movement between the 8-point ordinal scale to consider the costs and consequences of patient improvement and patient decline
- The modelling explicitly attempts to take the impact of the longer-term implications of COVID-19 into consideration
- The development of the model allows for a relatively quick evaluation of the treatments should more contemporary data become available.

5.2.2 Limitations of the analysis include:

- The characteristics of the decision problem may have changed considerably since the pivotal trials for each intervention was conducted. Such changes include the emergence of new SARS-CoV-2 variants, the introduction of a vaccination programme, proportion of people with a history of prior SARS-CoV-2 infection and the widespread use of corticosteroids in SoC. The EAG assumed that none of these were treatment effect modifiers and that the treatment effects were generalisable which is likely to be incorrect for a proportion of interventions.
- No recent studies were identified using the Omicron BA5 most prevalent in England in the Summer of 2022

- No head-to-head studies of interventions were identified that could be used in the modelling and the uncertainty regarding the most efficacious treatment is large.
- List prices are used for all interventions; results including PASs could not be provided in a publicly available document
- For some interventions list prices were not publicly available. As such, no ICERs have been presented for these drugs
- Uncertainty remains in the underlying rates of hospitalisation in patients with COVID-19 at high-risk of hospitalisation under SoC
- Uncertainty remains in the underlying rates of death in patients hospitalised due to COVID-19 who receive SoC
- All deaths associated with people at high-risk in the community are assumed to occur in hospital
- SoC only was assumed to be provided to patients in hospital if they had been treated with an intervention in the community as the residual effects of some treatments used in the hospital were larger than treatments used in hospital.
- Treatments used in hospital were not assumed to affect the proportion of discharged people with long COVID and that treatments used in the community were not assumed to affect the proportion of people not admitted to hospital with long COVID
- All patients were assumed to be discharged from hospital at day 70, which could favour the more efficacious treatments in reducing hospital costs
- No prior beliefs were incorporated relating to the clinical efficacy of the interventions. It may be clinically implausible that treatments which have a statistically significant beneficial HR relating to hospitalisation or death would be associated with increased RR of death at 28 days.
- The model did not consider secondary infections, which is likely to be unfavourable to the interventions
- The model did not consider reinfections. It is unknown if this is favourable or unfavourable to the interventions
- The model did not consider enablement benefits such as maintaining the capacity for operations or in avoiding delays in patients' treatment that could arise due to either a reduced number of patients in hospital with COVID-19, or reduced staff absence due to COVID-19
- No value of information analysis was conducted. This would allow funders to estimate the relative benefits of investing in future research

- No analysis was conducted on whether it is logistically possible to treat patients in the community with COVID-19 and a high-risk of hospitalisation with IV drugs

5.2.3 Areas of future research.

There is considerable uncertainty related to many aspects of this evaluation which hinders forming an accurate estimate of the ICER. A key uncertainty is the clinical effectiveness of interventions in conditions that do not replicate those in the pivotal studies. Contemporary research assessing the relative clinical effectiveness of interventions (and SoC) within head-to-head studies at current levels of vaccination, against the current predominant SARS-CoV-2 variant would be beneficial if the results could be obtained in a timely manner. Further data related to the probability of hospital admission and death for patients at high-risk in the community would also improve the precision of the estimated ICERs as would ascertaining the average age of this population. If possible, analysing efficacy data by previously specified risk groups, such as age band, and underlying risk category, may allow more granular results to be obtained. The impacts of long COVID in terms of morbidity and mortality is currently uncertain and further research is required in this area. Value of information analyses could be undertaken to efficiently direct future research although it is clear that the efficacy of the interventions will be a key driver of any cost-effectiveness results.

Given current knowledge the EAG is happy that the results produced using relatively simplistic techniques supported with sensitivity analyses are informative to decision makers. If data become available that show that the sum of the consequences for a cohort of homogenous people is not equal to the sum from a same-sized cohort of heterogeneous people then more complex modelling techniques, such as individual patient models may be required. More complex modelling could explore the benefits associated with the possibility of secondary infection and reinfection, and with wider aspects such as enablement benefit.

5.3 The use of patient and public involvement

There was no patient and public involvement in producing this report. This was not considered possible within the timescales of the project. However, the EAG is aware that at the NICE Technology Appraisal Committee that will discuss this topic, there will be patient and public involvement and representation, and this may result in the EAG changing model parameters and generating revised results.

5.4 Equality, Diversity, and Inclusion

As this report is secondary research, no patient participation was involved and the EAG did not need to consider the equality, diversity, and inclusion of participants. The primary research team was part of the ScHARR Technology Assessment Group contracted by the Department of Health, and this team is

a diverse group representing a wide range of protected characteristics, consisting of seniority, ages, ethnicity, and religious beliefs, and including both males and females. The clinical team represent experts within their field who have successfully worked with the ScHARR Technology Assessment Group on previous projects. The lead author is not the most senior member of the team.

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All authors commented on the final monograph.

Ethics statement

No ethical approval was needed as all included data were from secondary published sources.

Data sharing statement

All data requests should be submitted to the corresponding author for consideration.

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7 APPENDICES

Appendix 1: Summary of clinical studies used to inform the economic model

Table 24: Summary of study and patient characteristics of included studies with relevant outcomes to inform the economic model (all data extracted from https://covid-nma.com/,[10] unless specified otherwise)

Author, year	Design	Population	Severity	Sample size (n)	Intervention	Comparator	Follow-up	Funding	Overall risk of bias
Baricitinib									
Marconi et al. 2021[71] (status: published) COV-BARRIER (NCT04421027)	RCT, single blind	Patients with confirmed COVID-19 admitted to 101 centres in Argentina, Brazil, Germany, India, Italy, Japan, Mexico, Russia, South Korea, Spain, UK, and the USA (including Puerto Rico)	Mild to severe Mean age: NR but includes adults aged ≥18 years	1525	Baricitinib, 4 mg/day (n=764) (delivered orally)	Placebo (n=761)	60 days	Private	Some concerns
Horby et al 2022[72] (status: preprint) RECOVERY (NCT04381936)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 159 centres in the UK.	Mild to critical Mean age: NR but includes adults aged ≥2 years	8156	Baricitinib, 4 mg/day (n=4148) (delivered orally)	Standard care (n=4008)	28 days	Public/ non-profit	Some concerns

Ely et al. 2022[73] (status: published) COV-BARRIER (NCT04421027)	RCT, double blind	Patients with confirmed COVID-19 admitted to 18 centres in Argentina, Brazil, Mexico, and the USA.	Critical Mean age: NR but includes adults aged ≥18 years	101	Baricitinib, 4 mg/day (n=51) (delivered by nasogastric tube or orally)	Placebo (n=50)	60 days	Private	Low RoB
Kalil et al. 2020[74] (status: published) ACTT-2 (NCT04401579)	RCT, double blind	Patients with confirmed COVID-19 admitted to 67 centres in Denmark, Japan, Mexico, Singapore, South Korea, Spain, UK, and the USA.	Mild to critical Mean age: NR but includes adults aged ≥18 years	1033	Baricitinib, 4mg/day plus Remdesivir, 100 mg/day[a] (n=515) (baricitinib delivered by nasogastric tube or orally; remdesivir delivered intravenously)	Placebo plus Remdesivir, 100 mg/day[a] (n=518) (remdesivir delivered intravenously)	29 days	Public/ non-profit	Low RoB
Casirivimab/imdevimab									
Horby et al. 2022[75] (status: published) RECOVERY-REGEN (NCT04381936)	RCT, unblinded	Hospitalised patients with suspected or confirmed COVID-19 at 127 centres in the UK	Mild to critical Mean age: NR but includes patients ≥12 years	9785	REGN-COV2, 8g (n=4839) (casirivimab, 4g and imdevimab 4g delivered intravenously)	Standard care (n=4946)	28 days	Mixed (Public/ Private)	Some concerns

Somersan-Karakaya et al., 2022[76] (status: published) (NCT04426695)	RCT, double blind	Hospitalised patients with confirmed COVID-19 at 103 centres across USA, Brazil, Chile, Mexico, Moldova, and Romania	Mild to moderate Mean age: NR but includes adults aged ≥18 years	1364 (3-arm trial)	REGN-COV2, 8g (n=455) (casirivimab, 4g and imdevimab 4g delivered intravenously)	Placebo (n=452)	56 days	Mixed (Public/ Private)	Some concerns
O'Brien et al. 2022[77] (status: published) (NCT04452318)	RCT, double blind	Outpatients with confirmed COVID-19 (asymptomatic) treated at 112 centres in Moldova, Romania, and the USA.	Mild outpatients Mean age: NR but includes adults aged ≥18 years and adolescents aged ≥12 to <18 years	314	REGN-COV2, 1200 mg (n=156) (delivered subcutaneously once-off)	Placebo (n=158)	226 days	Mixed (Public/ Private)	Some concerns
Weinreich et al. 2021[78] (status: published) (NCT04425629)	RCT, double blind	Outpatients with COVID-19 (mild) treated at 82 centres in Mexico and the USA	Mild outpatients Mean age: NR but includes adults aged ≥18 years	1678 (Amended phase 3 portion only of trial)	REGN-COV2, 1200 mg (n=838) (delivered intravenously once-off)	Placebo (n=840)	28 days	Mixed (Public/ Private)	Some concerns
				3029	REGN-COV2, 2400 mg (n=1529)	Placebo (n=1500)			

				(Original and amended phase 3 portion of trial)	(delivered intravenously once-off)				
Molnupiravir									
Caraco et al. 2021[79] (status : published) MOVe-OUT (NCT04575597)	RCT, double blind	Outpatients with confirmed COVID-19 (asymptomatic, mild) treated by 82 centres in 14 countries	Mild outpatients Mean age: NR (no further details provided)	302 (4 arm trial)	Molnupiravir, 1600 mg/day (n=76) (delivery method NR)	Placebo (n=74)	210 days	Private	Low RoB
Fischer et al. 2021[80] (status: published) (NCT04405570)	RCT, double blind	Outpatients with confirmed COVID-19 (mild) treated by 10 centres in the USA	Mild outpatients Mean age: NR but includes adults aged ≥18 years	202 (4 arm trial)	Molnupiravir, 1600 mg/day (n=55) (delivered orally)	Placebo (n=62)	28 days	Mixed (Public/ Private)	High RoB
Jayk Bernal et al. 2021[81] (status: published)	RCT, double blind	Outpatients with confirmed COVID-19 (mild-moderate) treated by 107 sites in 20 countries	Mild-moderate outpatients	1433	Molnupiravir, 1600 mg/day (n=716) (delivered orally)	Placebo (n=717)	28 days	Private	Low RoB

			Mean age: NR (no further details provided)						
Koudinya Tippabhotla et al. 2022[82] (status: preprint) (CTRI/2021/07 /034588)	RCT, unblinded	Outpatients with confirmed COVID-19 (mild) treated at 16 centres in India	Mild outpatients Mean age: NR but includes adults aged ≥18 years and ≤60 years	1220	Molnupiravir, 1600 mg/day (n=610) (delivered orally)	Standard care (n=610)	28 days	Private	Some concerns
Nirmatrelvir/ritonavir									
Hammond et al. 2022[83] (status: published) EPIC-HR (NCT04960202)	RCT, double blind	Outpatients with confirmed COVID-19 (mild) treated by 343 centres in 21 countries	Mild outpatients Mean age: NR but includes adults aged ≥18 years	2246	Nirmatrelvir, 600 mg/day plus ritonavir, 200 mg/day (n=1120) (delivered orally)	Placebo (n=1126)	34 days	Private	Some concerns
Remdesivir									
Ader et al. 2022[84] (status: published) DisCoVeRy (NCT04315948)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 48 centres in France, Belgium, Portugal, Austria, and Luxembourg	Mild to critical Mean age: NR but includes adults aged ≥18 years	857	Remdesivir 100 mg/day[a] (n=429) (delivered intravenously)	Standard care (n=428)	90 days	Public/ non-profit	Some concerns

Biegel et al. 2020[19] (status: published) (NCT04280705)	RCT, double blind	Patients with confirmed COVID-19 admitted to 60 centres in 10 countries	Mild to critical Mean age: NR (no further details provided)	1062	Remdesivir 100 mg/day[a] (n=541) (delivered intravenously)	Placebo (n=521)	28 days	Public/ non-profit	Some concerns
Mahajan et al. 2021[85] (status: published) (NR)	RCT, unblinded	Patients with confirmed COVID-19 admitted to a single centre in India	Moderate to severe Mean age: NR but includes adults aged between 18 and 60 years	82	Remdesivir 100 mg/day[a] (n=41) (delivered intravenously)	Standard care (n=41)	24 days	None	High RoB
Spinner et al. 2020[86] (status: published) (NCT04292730)	RCT, unblinded	Patients with COVID-19 admitted to 105 centres in the USA, Europe, and Asia	Mild to severe Mean age: NR but includes patients ≥12 years	596	Remdesivir 100 mg/day [a] (5 & 10 arms days merged) (n=396) (delivered intravenously)	Standard care (n=200)	28 days	Private	Some concerns
Wang et al. 2020[87] (status: published) (NCT04257656)	RCT, double blind	Patients with confirmed COVID-19 admitted to 10 centres in China	Severe Mean age: NR but includes	237	Remdesivir 100 mg/day [a] (n=158) (delivered intravenously)	Placebo (n=79)	28 days	Mixed (Public/ Private)	Some concerns

			adults aged ≥18 years						
Gottlieb et al. 2021[88] (status: published) PINETREE (NCT04501952)	RCT, double blind	Outpatients with confirmed COVID-19 (mild) treated at 64 centres in Denmark, Spain, UK, and USA.	Mild outpatients Mean age: NR but includes patients ≥12 years	584	Remdesivir 100 mg/day [a] (n=292) (delivered intravenously)	Placebo (n=292)	28 days	Private	Some concerns
Sotrovimab									
Gupta et al. 2022[89] (status: published) COMET-ICE (NCT04545060)	RCT, double blind	Outpatients with confirmed COVID-19 (mild) and at high risk for Covid-19 progression, treated at 57 centres in the USA, Canada, Brazil, Spain, and Peru.	Mild outpatients Mean age: NR but includes adults aged ≥18 years	1057	Sotrovimab, 500 mg once-off (n=528) (delivered intravenously)	Placebo (n=529)	168 days	Private	Some concerns
Tixagevimab/cilgavimab									
Montgomery et al. 2022 (status: published)[49] TACKLE (NCT04723394)	RCT, triple blind	Outpatients with confirmed COVID-19 (mild) treated at 95 centres in Argentina, Brazil, Czech Republic, Germany, Italy, Japan, Mexico, Poland, Spain,	Mild to moderate Mean age: NR but includes adults aged ≥18 years	910	Tixagevimab, 300 mg plus cilgavimab, 300 mg intramuscular injection (n=456)	Placebo (n=454)	28 days	Private	Some concerns

		Russian Federation, UK, Ukraine, and the USA							
Tocilizumab									
ARCHITECTS, 2021 (status: unpublished) (NCT04412772)	RCT, double blind	Patients with confirmed COVID-19 admitted to a single centre in the USA	Critical Mean age: NR (no further details provided)	21	Tocilizumab 8 mg/kg once-off (n=10) (delivered intravenously)	Placebo (n=11)	90 days	Public/ non-profit	Low RoB
Broman et al. 2022[90] (status: published) COVIDSTORM (NCT04577534)	RCT, unblinded	Patients with confirmed COVID-19 admitted to a single centre in Finland.	Moderate to-severe Mean age: NR but includes adults aged ≥18 years	88	Tocilizumab 400 to 800 mg once-off, depending on weight (n=59) (delivered intravenously)	Standard care (n=29)	90 days	No specific funding	Some concerns
COVIDOSE-2, 2021 (status: unpublished) (NCT04479358)	RCT, unblinded	Patients with confirmed COVID-19 admitted to multiple centres in the USA	Moderate to severe Mean age: NR but includes adults aged ≥18 years	28	Tocilizumab 40 mg or 120 mg once-off (n=20) (delivery method NR)	Standard care (n=8)	28 days	Public/ non-profit	Low RoB

Declercq et al. 2021[91] (status: published) COV-AID, 2021 (NCT04330638)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 16 centres in Belgium	Moderate to critical Mean age: NR but includes adults aged >18 years	342 (multi-arm trial)	Tocilizumab 8 mg/kg once-off (n=82) (delivered intravenously)	Standard care (n=72)	90 days	Public/ non-profit	Some concerns
Derde et al. 2021[92] (status: preprint) REMAP-CAP (NCT02735707)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 133 centres in 9 countries (UK, Netherlands, Ireland, Australia, New Zealand, Canada, Finland, Italy, Saudi-Arabia)	Severe to critical Mean age: NR but includes adults aged >18 years	2253 (multi-arm trial)	Tocilizumab, 8 mg/kg once-off (n=972) (delivered intravenously)	Standard care (n=418)	90 days	Mixed	Some concerns
Hermine et al. 2020[93] (status: published) CORIMUNO-TOCI 1 (NCT04331808)	RCT, unblinded	Patients with COVID-19 admitted to 9 centres in France	Moderate to severe Mean age: NR (no further details provided)	131	Tocilizumab 8 mg/kg (n=64) (delivered intravenously)	Standard care (n=67)	60 days	Public/ non-profit	Some concerns
Hermine et al. 2022[94] (status: published)	RCT, unblinded	Patients with suspected or confirmed COVID-	Severe to critical Mean age:	97	Tocilizumab 8 mg/kg once-off (n=51)	Standard care (n=46)	90 days	Public/ non-profit	Some concerns

CORIMUNO-TOCI-2 (NCT04331808)		19 admitted to 12 centres in France.	NR (no further details provided)		(delivery method NR)				
HMO-0224-20, 2021 (status: unpublished)	RCT, unblinded	Patients with confirmed COVID-19 admitted to multiple centres in Israel.	Severe-critical Mean age: NR but includes adults aged ≥18 years	54	Tocilizumab 8 mg/kg once-off (n=37) (delivered intravenously)	Placebo (n=17)	90 days	Public/ non-profit	High RoB
Horby et al. 2021[95] (status: published) RECOVERY (TCZ) (NCT04381936)	RCT, unblinded	Patients with suspected or confirmed COVID-19 admitted to 131 centres in the UK	Moderate to critical Mean age: NR (no further details provided)	4116	Tocilizumab 400 to 800 mg, depending on weight (n=2022) (delivered intravenously)	Standard care (n=2094)	28 days	Public/ non-profit	Some concerns
IMMCOVA, 2021 (status: unpublished) (NCT04412291)	RCT, unblinded	Patients with confirmed COVID-19 admitted to multiple centres in Sweden	Moderate to severe Mean age: NR but includes adults aged ≥18 years	49	Tocilizumab, 8 mg/kg once-off (n=22) (delivered intravenously)	Standard care (n=27)	28 days	Public/ non-profit	Low RoB

Rosas et al. 2022[96] (status: published) COVACTA (NCT04320615)	RCT, double blind	Patients with confirmed COVID-19 admitted to multiple centres across 9 countries (Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA)	Mild to critical Mean age: NR but includes adults aged ≥18 years	452	Tocilizumab, 8 mg/kg (n=301) (delivered intravenously)	Placebo (n=151)	60 days	Mixed	Some concerns
Rosas et al. 2021[97] (status: published) REMDACTA (NCT04409262) [b]	RCT, double blind	Patients with confirmed COVID-19 admitted to multiple centres in Spain, USA, Brazil, and Russia	Severe to critical Mean age: NR (no further details provided)	649	Tocilizumab 8 mg/kg once-off or twice (n=434) (delivery method NR)	Placebo (n=215)	60 days	Private	Some concerns
Rutgers et al. 2021[98] (status: preprint) (Trial NL8504)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 11 centres in the Netherlands.	Moderate to critical Mean age: NR but includes adults aged ≥18 years	354	Tocilizumab, 8 mg/kg once-off (n=174) (delivered intravenously)	Standard care (n=180)	90 days	Mixed	Some concerns
Salama et al. 2020[99] (status: published) EMPACTA	RCT, double blind	Patients with confirmed COVID-19 admitted to 65 centres in Brazil, Kenya, Mexico, Peru, South Africa, and USA	Mild to severe Mean age:	388	Tocilizumab, 8 mg/kg (n=259) (delivered intravenously)	Placebo (n=129)	60 days	Private	Some concerns

(NCT04372186)			NR but includes adults aged ≥18 years						
Salvarani et al. 2020[100] (status: published) (NCT04346355)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 24 centres in Italy	Severe Mean age: NR but includes adults aged ≥18 years	126	Tocilizumab, 8 mg/kg (n=60) (delivered intravenously)	Standard care (n=66)	30 days	Mixed	Some concerns
Stone et al. 2020[101] (status: published) (NCT04356937)	RCT, double blind	Patients with COVID-19 admitted to 7 centres in the USA	Mild to severe Mean age: NR but includes adults aged 19 to 85 years	243	Tocilizumab, 8 mg/kg once-off (n=161) (delivered intravenously)	Placebo (n=82)	28 days	Private	Low RoB
Talaschian et al. 2021[102] (status: preprint) IRCT200810 27001411N4	RCT, double blind	Patients with confirmed COVID-19 admitted to a single centre in Iran	Moderate to severe Mean age: NR (no further details provided)	40	Tocilizumab, 8 mg/kg (n=20) (delivered intravenously)	Standard care (n=20)	28 days	Public/ non-profit	High RoB
Veiga et al. 2021[103] (status: published)	RCT, unblinded	Patients with confirmed COVID-19 admitted to 9 centres in Brazil	Moderate to critical	129	Tocilizumab, 8 mg/kg once off (n=65)	Standard care (n=64)	29 days	Mixed	Some concerns

TOCIBRAS (NCT04403685)			Mean age: NR but includes adults aged ≥18 years		(delivered intravenously)				

NR, not reported; RCT, randomised controlled trial; RoB, risk of bias

[a] Different remdesivir loading dose

[b] Data extracted from http://www.metaevidence.org/covid19.aspx[11]

Therapeutics for people with COVID-19. An economic evaluation - ERRATUM

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	25/10/2022

1) Reason for this erratum

Following the NICE Appraisal Committee on the 18th November 2022 two errors were identified in the External Assessment Group's (EAG) model. These were:

1) In the community setting the relative risk of death for each drug was erroneously always set to the 'high efficacy' scenario. As such, the results for the 'mean efficacy' scenario and the 'low efficacy' scenarios had not used the correct relative risk for death and the incremental cost-effectiveness ratios (ICERs) were more favourable to the interventions.
2) The administration costs associated with oral treatments in the community had been erroneously set to £420 rather than £410.

These errors have been corrected and new results generated. These are provided in Section 2 as just the updated tables and figures as agreed with NICE.

2) Revised results

This section provides the updated results. The table and figure numbers have been set to those used in the EAG report seen by the committee with the section of the report also listed

Section 4.3.1 Mean efficacy results for patients at high-risk of hospitalisation

Table 21: Mean efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	662	13.42	-	-	-	-
Nirmatrelvir/ritonavir	1509	13.54	7058	1553	2754	7058
Sotrovimab	3288	13.49	37,143	-1212	-505	Dominated
Remdesivir	4095	13.46	96,485	-2722	-2366	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.48, 13.51 and 13.42 respectively

Section 4.3.2 High efficacy results for patients at high-risk of hospitalisation

Table 22: High efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	662	13.42	-	-	-	-
Nirmatrelvir/ritonavir	1521	13.56	6192	1917	3305	6192
Sotrovimab	3315	13.56	19,302	96	1471	Dominated
Remdesivir	4120	13.56	25,476	-743	614	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.55, 13.54 and 13.52 respectively

Section 4.3.3 Low efficacy results for patients at high-risk of hospitalisation

Table 23: Low efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	662	13.42	-	-	-	-
Nirmatrelvir/ritonavir	1519	13.49	12,612	502	1182	12,612
Sotrovimab	3278	13.38	Dominated	-3433	-3841	Dominated
Remdesivir	4089	13.28	Dominated	-6211	-7603	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.39, 13.44 and 13.26 respectively

Section 4.4 Sensitivity Analysis Results

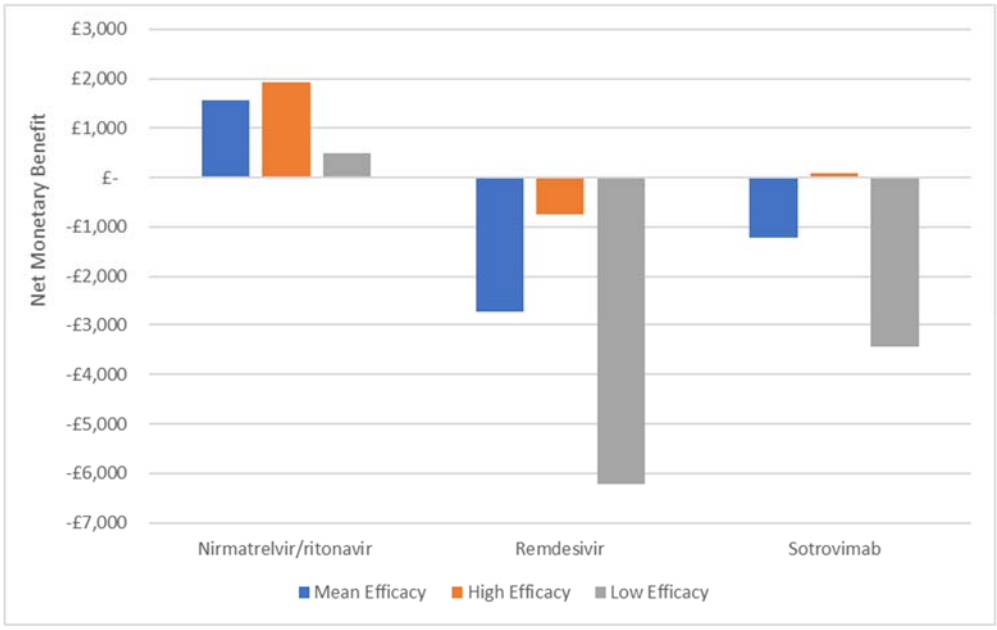

Figure 19: Base case net monetary benefits for patients with COVID-19 in the community and high-risk of hospitalisation assuming a threshold of £20,000 per QALY gained

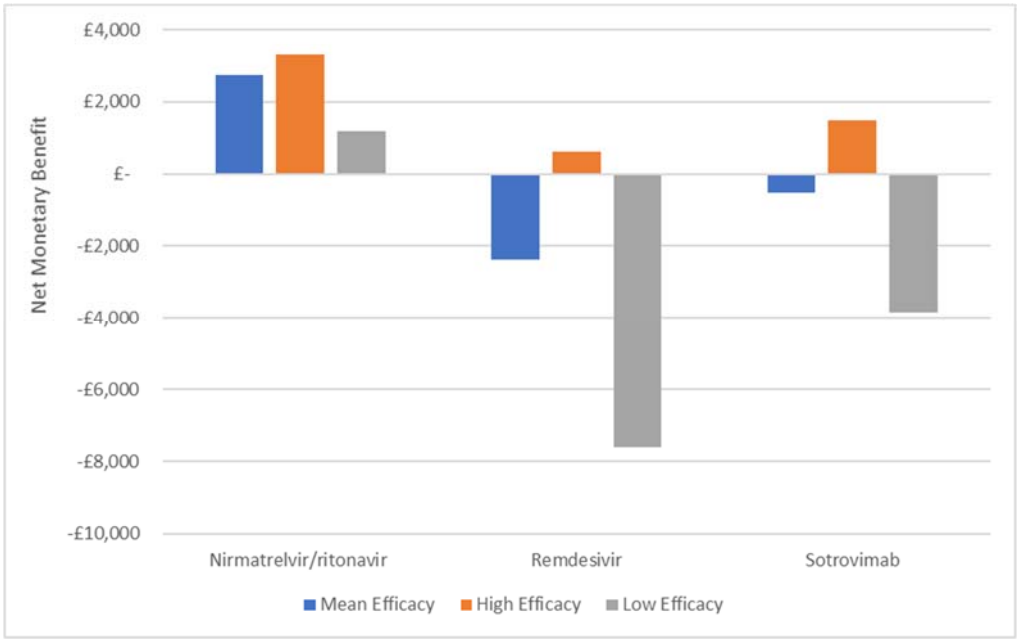

Figure 22: Base case net monetary benefits for patients with COVID-19 in the community and high-risk of hospitalisation assuming a threshold of £30,000 per QALY gained

Section 4.4.1 Amending the duration of long COVID

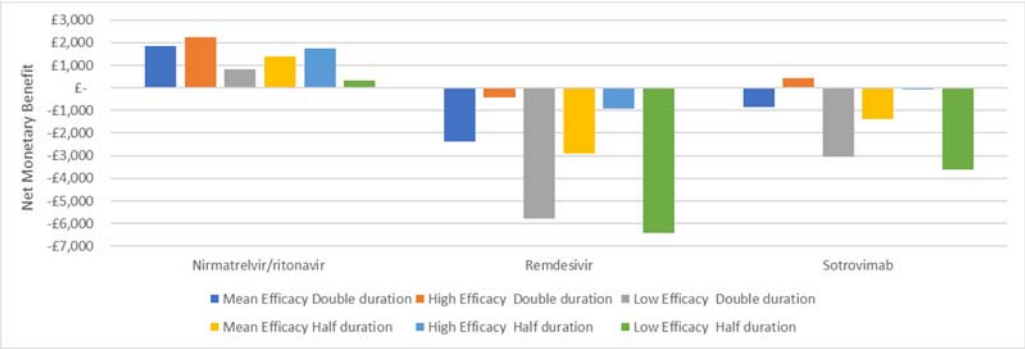

Figure 25: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the duration of long COVID is halved and doubled. Assuming a WTP of £20,000

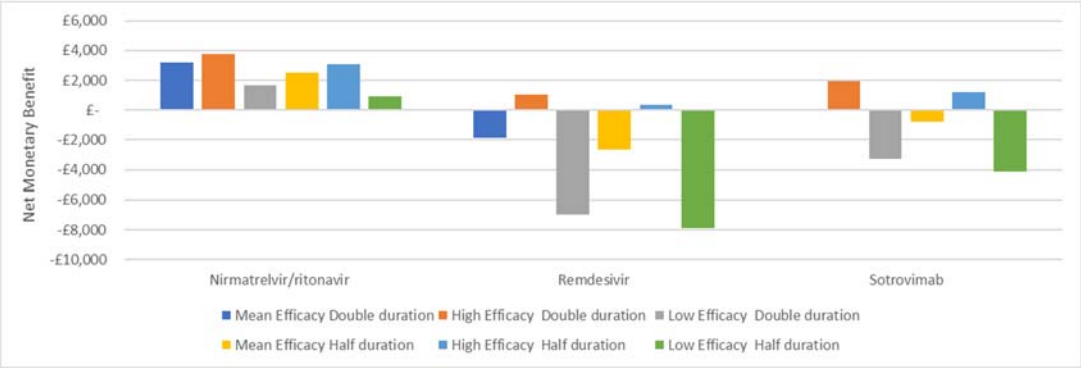

Figure 28: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the duration of long COVID is halved and doubled. Assuming a WTP of £30,000

Section 4.4.2 Amending the hospital admission percentage for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC

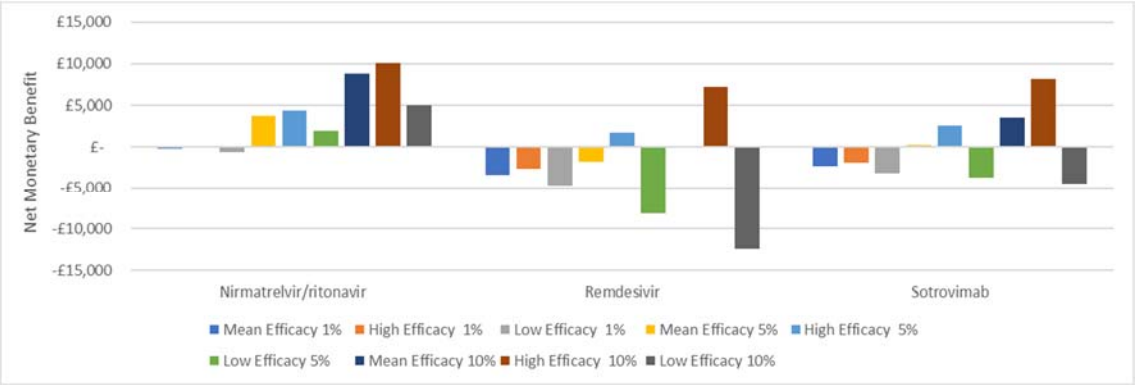

Figure 29: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the hospital admission percentage was changed. Assuming a WTP of £20,000

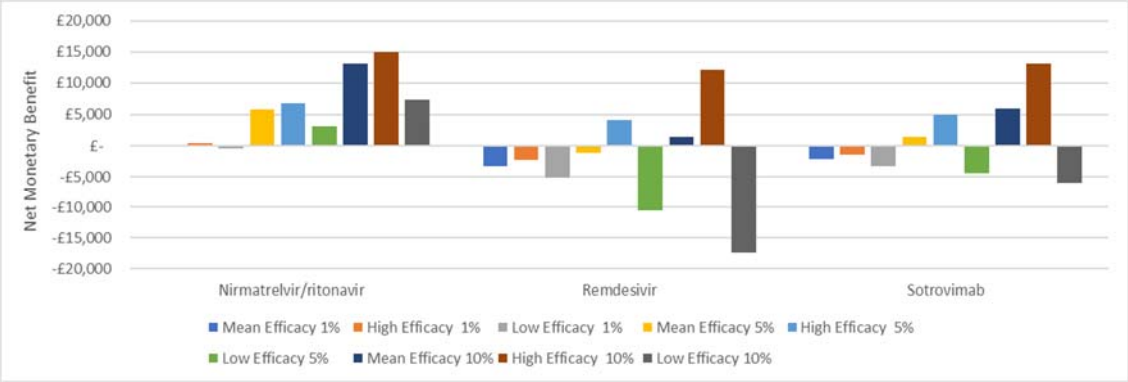

Figure 30: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the hospital admission percentage was changed. Assuming a WTP of £30,000

Section 4.4.3 Amending the age of people with COVID-19 in the community at high-risk of hospitalisation treated with SoC

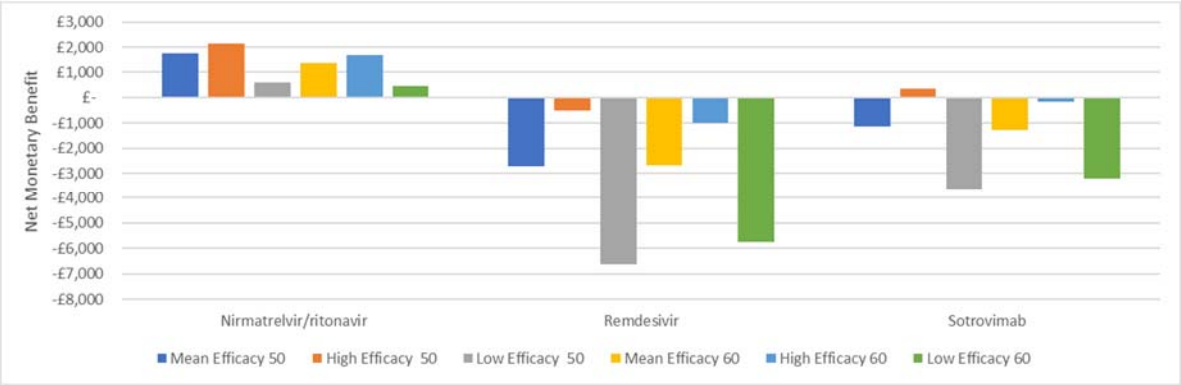

Figure 31: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the age was changed from 55 years to 50 years and 60 years. Assuming a WTP of £20,000 per QALY

Figure 32: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the age was changed from 55 years to 50 years and 60 years. Assuming a WTP of £30,000 per QALY

Section 4.4.5 Changing the baseline distribution of supplemental oxygen requirements for people with COVID-19 in the community upon hospitalisation

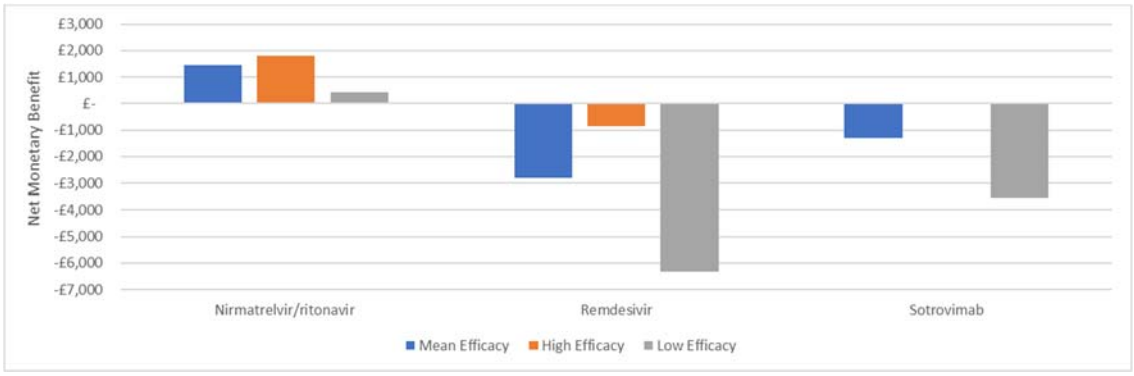

Figure 37: The NMB results when treatment in the community for high-risk patients was associated with less supplemental oxygen on admission to hospital. Assuming a WTP of £20,000 per QALY

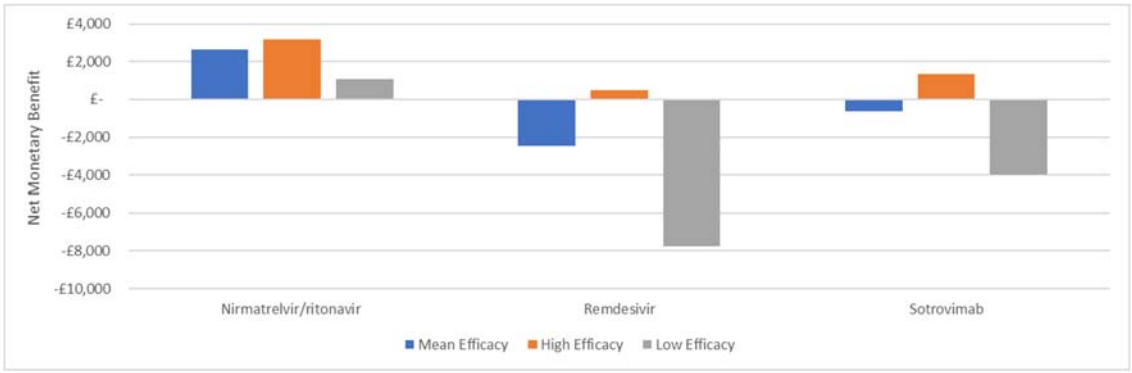

Figure 38: The NMB results when treatment in the community for high-risk patients was associated with less supplemental oxygen on admission to hospital. Assuming a WTP of £30,000 per QALY

Section 4.4.6 Increasing the cost per year associated with long COVID

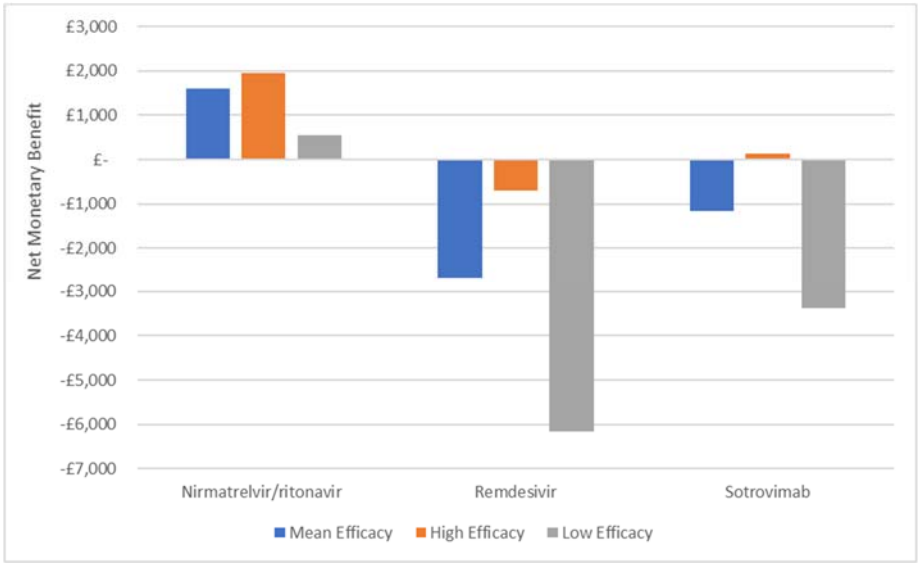

Figure 41: The NMB results for high-risk patients in the community when the annual cost of long COVID is assumed to be £2500. Assuming a WTP of £20,000 per QALY

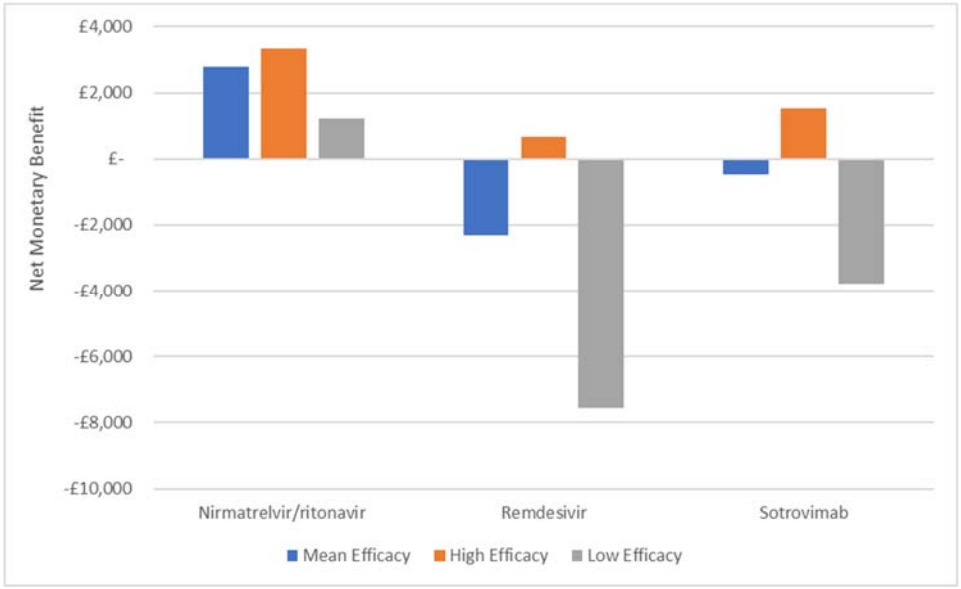

Figure 44: The NMB results for high-risk patients in the community when the annual cost of long COVID is assumed to be £2500. Assuming a WTP of £30,000 per QALY

Section 4.4.7 Applying a utility decrement of 0.02 per day for people in the community receiving IV treatment

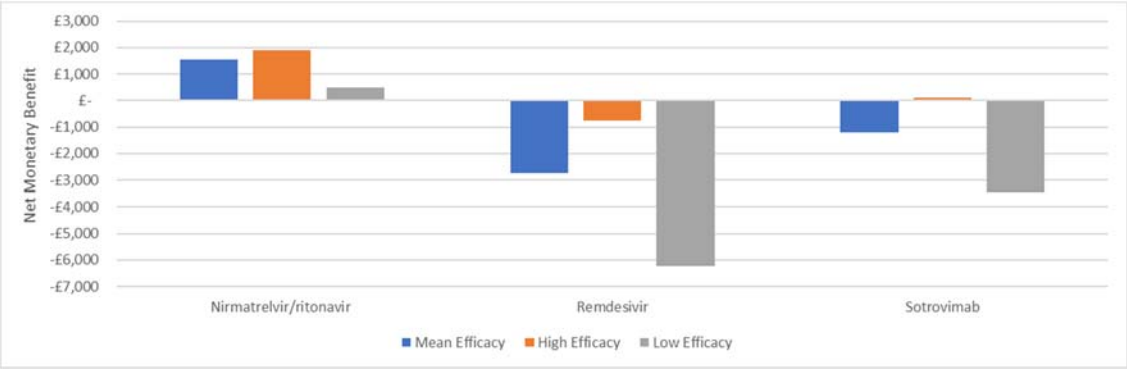

Figure 45: The NMB results when a disutility of 0.02 per day is assumed for patients receiving IV treatment in the community. Assuming a WTP of £20,000 per QALY

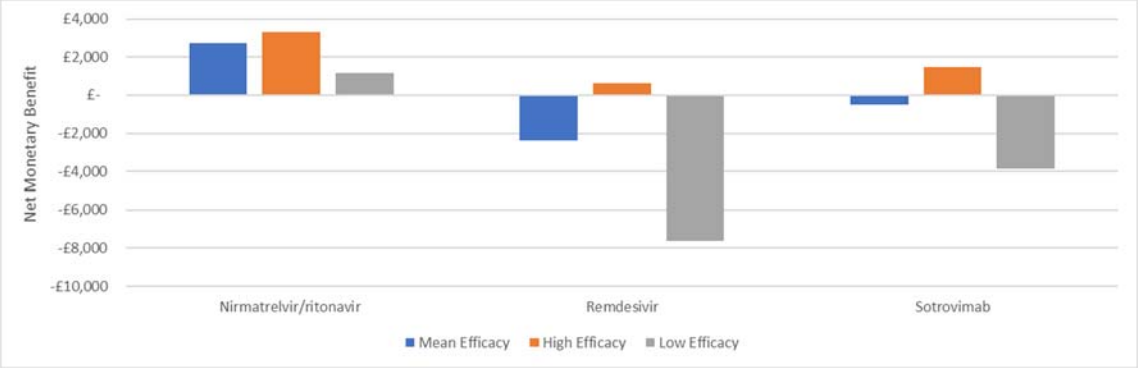

Figure 46: The NMB results when a disutility of 0.02 per day is assumed for patients receiving IV treatment in the community. Assuming a WTP of £30,000 per QALY

Section 4.4.8 Changing the SMR for people with long COVID

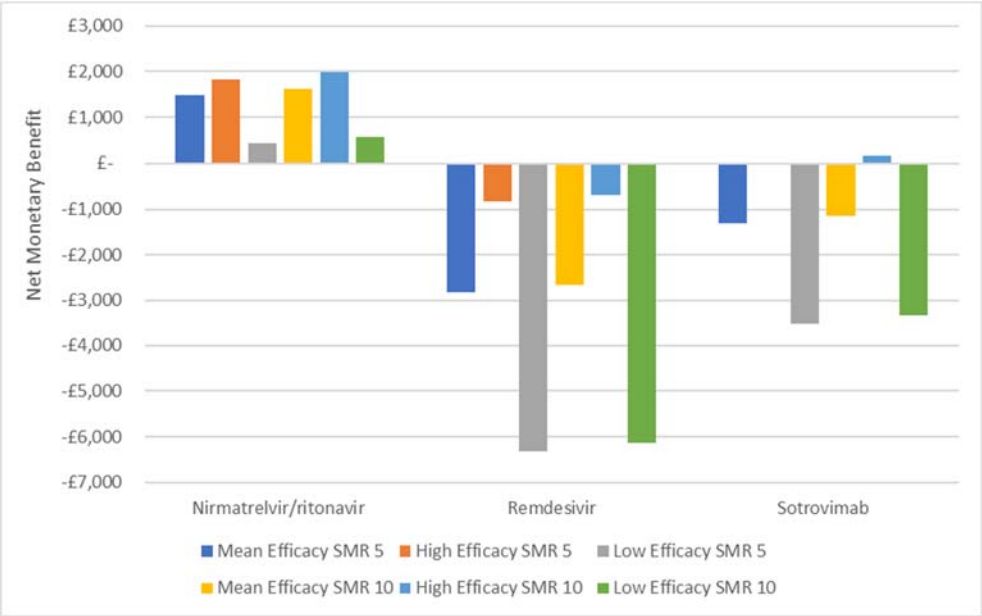

Figure 49: The NMB results for high-risk patients in the community when the SMR associated with long COVID is changed. Assuming a WTP of £20,000 per QALY

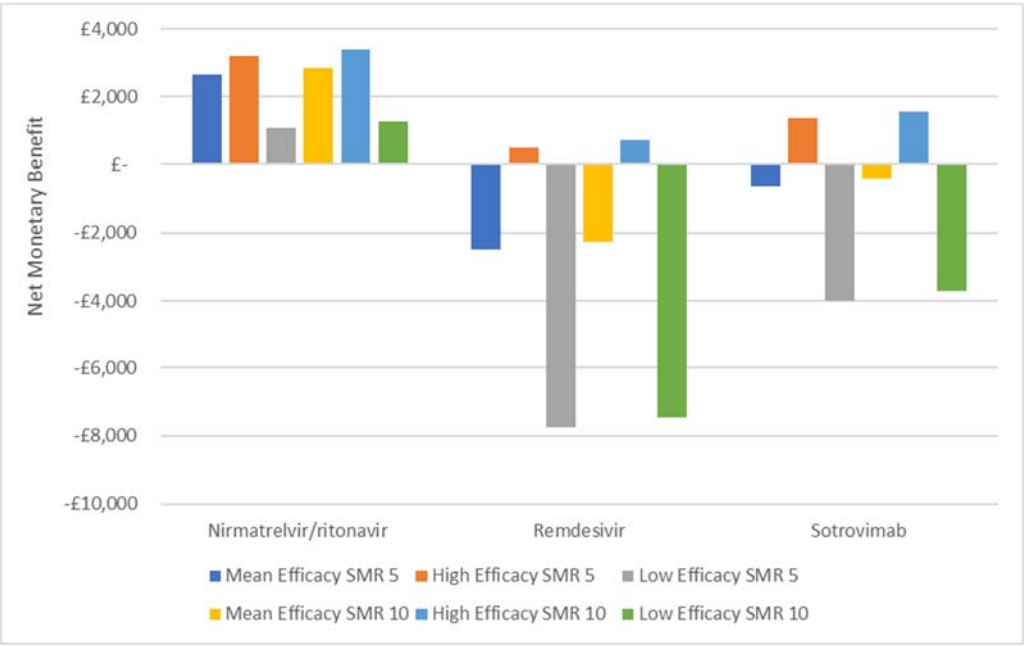

Figure 52: The NMB results for high-risk patients in the community when the SMR associated with long COVID is changed. Assuming a WTP of £30,000 per QALY

Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): preliminary analysis from the United Kingdom randomised, controlled open-label, platform adaptive trial

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Abstract

Background The safety, effectiveness and cost-effectiveness of molnupiravir, an oral antiviral medication for SARS-CoV-2, in patients in the community who are multiply-vaccinated and at increased risk of morbidity and mortality from COVID-19, has not been established. We aimed to determine whether molnupiravir added to usual care reduced hospital admissions/deaths among people at higher risk from COVID-19, and here report our preliminary analyses.

Methods Participants in this UK multicentre, open-label, adaptive, multi-arm, platform, randomised controlled trial were aged ≥50, or ≥18 years with comorbidities, and unwell ≤5 days with confirmed COVID-19 in the community, and were randomised to usual care or usual care plus molnupiravir (800mg twice daily for 5 days). The primary outcome measure was all-cause hospitalisation/death within 28 days, analysed using Bayesian models. The main secondary outcome measure was time to first self-reported recovery. A sub-set of participants in each group were assessed for the virology primary outcome measure of day seven SARS-CoV-2 viral load. Trial registration: ISRCTN30448031

Findings Between December 8, 2021 and April 27, 2022, 25783 participants were randomised to molnupiravir plus usual care (n=12821) or usual care alone (n=12962). Mean (range) age of participants was 56·6 years (18 to 99), 58·6% were female, and 99% had at least one dose of a SARS-CoV-2 vaccine. The median duration of symptoms prior to randomisation was two days (IQR 1 – 3), the median number of days from symptom onset to starting to take the medication was three days (IQR 3 – 4), 87% (11109/11997) received their medication within five days of symptom onset, and 95·4% (n=11857) of participants randomised to molnupiravir reported

taking molnupiravir for five days. Primary outcome measure data were available in 25000 (97%) participants and included in this analysis. 103/12516 (0·8%) hospitalisations/deaths occurred in the molnupiravir group versus 96/12484 (0·8%) in usual care alone with a posterior probability of superiority of 0·34 (adjusted odds ratio 1·061 (95% Bayesian credible interval [BCI]) 0·80 to 1·40). Estimates were similar for all subgroups. The observed median (IQR) time-to-first-recovery from randomisation was 9 (5–23) days in molnupiravir and 15 (7–not reached) days in usual care. There was an estimated benefit of 4·2 (95% BCI: 3·8 – 4·6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0·999 (estimated median TTR 10·3 [10·2 – 10·6] days vs 14·5 [14·2 – 14·9] days respectively; hazard ratio [95% BCI], 1·36 [1·3–1·4] days), which met the pre-specified superiority threshold. On day 7, SARS-CoV-2 virus was below detection levels in 7/34 (21%) of the molnupiravir group, versus 1/39 (3%) in the usual care group (p=0.039), and mean viral load was lower in the molnupiravir group compared with those receiving usual care [(SD) of $\log_{10}$(viral load) 3·82 (1·40) in the molnupiravir group and 4.93 (1·38) in the usual care group, (P<0·001)]. 59 (0·4%) participants experienced serious adverse events in the molnupiravir group and 52 (0·4%) in usual care.

Interpretation In this preliminary analysis, we found that molnupiravir did not reduce already low hospitalisations/deaths among higher risk, vaccinated adults with COVID-19 in the community, but resulted in faster time to recovery, and reduced viral detection and load.

Funding: This project is funded by the NIHR (NIHR135366). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Research in context (box)

Evidence before this study

A search of PubMed on 5 September 2022 with no date or language restrictions using the following search terms (randomised OR trial) AND (molnupiravir) AND (COVID* OR SARS-CoV-2 OR SARS-CoV) AND (systematic review) identified ten results. The two most comprehensive reviews were living reviews synthesising the findings of six trials of molnupiravir compared with either standard of care or placebo. The reviews suggest that molnupiravir reduces hospital admissions in patients with mild-moderate COVID-19, with the World Health Organisation (WHO) living guideline recommending use of molnupiravir in outpatients with mild-moderate COVID-19 at the highest risk of hospital admission. The largest randomised clinical trial identified by the evidence syntheses was the randomised, placebo-controlled, phase 3 MOVe-OUT trial. In this trial of 1433 unvaccinated COVID-19 outpatients, there was a relative reduction in the primary outcome measure of hospitalisations and deaths of approximately 30% up to day 29 post randomisation in people receiving molnupiravir, versus placebo. Of note, this reduction was closer to 50% with molnupiravir compared with placebo when the MOVe-OUT trial published their interim results, after recruiting 762 participants. The reason for this difference is unclear. A number of trials of molnupiravir have been conducted in India; to date, the full peer-reviewed findings have not been made publicly available. The ACE2 trial among 180 participants (both vaccinated and unvaccinated) demonstrated faster time to a negative PCR test with molnupiravir compared with placebo (8 days versus 11 days).

Added value of this study

In this preliminary analysis, we found that molnupiravir did not reduce hospitalisations/deaths among a multiply-vaccinated adult population with COVID-19 in the

community at higher risk of an adverse outcome, with similar estimates for all subgroups, during a time when the proportion of people with COVID-19 requiring hospital admission was low. However, molnupiravir resulted in earlier recovery across a wide range of measures including: time to recovery; sustained recovery overall as well as for key individual symptoms; reduced health care seeking in primary care in some services; and, reduced viral detection and load in a sub-group on Day 7. Molnupiravir was safe, but adverse effects were cited as a reason for withdrawing from the study drug in 1·1% (142/12821) randomised to receive it. Trials of molnupiravir have, thus far, been conducted in largely unvaccinated participants and prior to the emergence of the omicron SARS-CoV-2 variant. PANORAMIC provides an estimate of the effectiveness of molnupiravir in a multiply-vaccinated population whilst the omicron SARS-CoV-2 strain is dominant. The large sample size of PANORAMIC (>25,000 participants) allows for more precision around subgroup analyses estimates, to help determine the populations that may, or may not, derive benefit from molnupiravir. PANORAMIC additionally incorporates virological and cost-effectiveness analyses; such analyses have not been published (in detail) in other trials of molnupiravir.

Implications of all the available evidence

This preliminary analysis involving people vaccinated against SARS-CoV-2 infection at increased risk of an adverse outcome in the community and unwell with COVID-19 found that molnupiravir did not reduce already low hospital admission, but that molnupiravir resulted in faster time to recovery, earlier sustained recovery, reduced contact with GP services, and reduced viral detection and viral load.

INTRODUCTION

Early treatment of COVID-19 with directly acting antiviral drugs in the community may: prevent deterioration; speed recovery; reduce healthcare utilisation in the community; reduce viral shedding; and, reduce the need for hospital admission.

Molnupiravir is an oral antiviral that was initially developed for treatment of influenza,[1] but has subsequently been evaluated for treatment of COVID-19.[2] It is a prodrug; the ribonucleoside analogue β-d-N4 -hydroxycytidine (NHC) is metabolised to NHC-triphosphate in cells, which competes with naturally occurring nucleotides, especially cytidine triphosphate.[3] Once incorporated into viral RNA, the errant nucleotide induces 'viral error catastrophe,' impeding viral fitness and inhibiting replication.[3] Molnupiravir has demonstrated anti-SARS-CoV-2 activity in animal models,[4-6] and has been found to be safe and well tolerated at doses of 800mg twice daily in phase 1 trials [7,8] and phase 2/3 outpatient trials.[2,9,10]

The largest trial of molnupiravir to date has been the MOVe-OUT trial, a phase 3 industry-funded trial among unvaccinated, non-hospitalized patients at high risk of adverse outcomes.[10] Interim results after recruiting 762 participants showed a nearly 50% decrease in hospitalisations and deaths with molnupiravir compared to placebo, resulting in molnupiravir authorisation for use by several regulatory bodies.[11,12] However, the final results demonstrated a smaller effect (30% reduction in hospitalisations and deaths).[10] The reason for this difference has been debated.[13] Several Phase 3 trials have been conducted in India among non-hospitalized patients with reportedly mixed findings,[14] but to date the full peer-reviewed results have not been published. The AGILE CST-2 trial conducted in 180 vaccinated and

unvaccinated participants showed that molnupiravir resulted in a faster time to a negative PCR test compared with placebo (8 days versus 11 days).[15]

The effectiveness of molnupiravir in patients in the community who are multiply-vaccinated and at increased risk of morbidity and mortality from COVID-19 has not yet been established. We therefore aimed to determine the effectiveness of molnupiravir in reducing all-cause, non-elective hospital admissions and/or death within 28 days of randomisation in test-positive COVID-19 outpatients at higher risk of an adverse outcome in a UK population with high levels of SARS-CoV-2 vaccination. Ahead of a possible increase in COVID-19 incidence over the coming winter months, important decisions need to be taken urgently about possible deployment of antiviral drugs, and awareness of the scope of forthcoming analyses and inviting early scrutiny and discussion may be helpful. We therefore report a preliminary analysis here; outstanding data linkage and site queries are ongoing pending data lock and final analysis.

METHODS

Study design and oversight

We assessed the effectiveness of molnupiravir in the UK national, multi-centre, primary care, open-label, multi-arm, prospective, Platform Adaptive trial of NOvel antiviRals for eArly treatMent of covid-19 In the Community (PANORAMIC), which opened on December 8, 2021, and is ongoing. The protocol is available on the trial website (https://www.panoramictrial.org). A "platform trial" allows multiple treatments for the same disease to be tested simultaneously. A master protocol defines prospective decision criteria for

stopping randomisation to interventions for futility, declaring interventions superior, or adding new interventions.[16] Interventions evaluated in PANORAMIC include molnupiravir and nirmatrelvir/ritonavir.

The UK Medicines and Healthcare products Regulatory Agency and the South Central-Berkshire Research Ethics Committee approved the trial protocol. Online informed consent is obtained from all participants. The authors vouch for the accuracy and completeness of the data and for fidelity to the protocol. An independent Trial Steering Committee (TSC), and Data and Safety Monitoring Committee (DSMC) provide trial oversight.

Participants

People in the community were eligible if they were aged ≥50 years, or ≥18 years with comorbidities (supplementary appendix 1), had ongoing symptoms from COVID-19 that had started within the previous five days, and a positive polymerase chain reaction (PCR) or rapid antigen SARS-CoV-2 test within the past seven days. People were ineligible to be randomised to molnupiravir if they were pregnant or breastfeeding, were of childbearing potential and unwilling to use effective contraception, were already taking molnupiravir, or were allergic to molnupiravir. Patients at the highest risk of adverse outcomes with COVID in the UK have been advised to seek medical advice from special regional COVID specialist clinics to provide access to COVID antivirals or monoclonal antibodies, and were not the target population for PANORAMIC, although they were eligible. Potentially eligible people were screened, recruited, and enrolled in participating general practices, or online and telephonically with central trial teams across the UK.

Randomisation and masking

Eligible, consenting participants were randomised by a suitably qualified and trained medical or research professional in equal allocation between molnupiravir and usual care using a secure, web-based randomisation system (Spinnaker). Randomisation was stratified by age (</≥ 50 years) and vaccination status (yes/no). Participants and members of the trial team responsible for recruitment/follow-up/monitoring of participants were aware of group assignment. The trial investigators and recruiting clinicians were kept blind to emerging results, with only unblinded statisticians and the independent members of the DSMC granted access to unblinded results until the decision was made to close recruitment to molnupiravir.

Procedures

Participants received usual care plus molnupiravir 800mg twice daily for 5 days, or usual care alone. Participants randomised to molnupiravir were urgently couriered a participant pack containing molnupiravir, dosing and safety information, and a pregnancy test (only for use by participants of child-bearing potential). Usual care participants were emailed/posted a trial information booklet. Usual care in the UK National Health Service for COVID-19 in the community is largely focused on managing symptoms with antipyretics.[17] However, patients at very highest risk (very impaired immunity or extremely clinically vulnerable) are eligible for monoclonal antibodies (sotrovimab), intravenous antivirals (remdesivir), or oral antivirals (molnupiravir or nirmatrelvir/ritonavir) through the NHS.[18] Prescriptions of monoclonal antibodies and antiviral agents other than a study drug in the course of usual care was permitted, and monoclonal antibody use was recorded in an online diary. Participants randomised to molnupiravir would not have received additional molnupiravir through the NHS; however, those randomised to usual care may have received molnupiravir through the NHS and this was recorded in the online diary.

Participants were followed up through an online, daily diary for 28 days after randomisation, supplemented with telephone calls to non-responders on days 7, 14 and 28. Participants were asked: to rate a variety of symptoms (e.g. fever, cough and breathlessness) on an ordinal scale ('no problem,' 'mild problem,' 'moderate problem' or 'major problem'); whether they had been hospitalised or required contact with health and social services; how they were feeling on a scale of zero to ten (zero being the worst one can imagine, and ten being the best one can imagine); whether they felt fully recovered; whether they were taking over-the-counter medication; whether the number of people in the household with COVID-19 had changed; to confirm whether they had taken the antiviral agent (if applicable); and, at fortnightly intervals the EQ-5D-5L to assess their health-related quality of life. Participants could nominate a trial partner to help provide follow up data. We obtained consent to ascertain healthcare use outcome measure data from general practice and hospital records. Additional questions regarding longer term symptoms and healthcare use are asked at three and six months after randomisation; these results are not reported in this manuscript.

Virology sub-study

Between March 23, 2022 and April 27, 2022, enrolling participants were offered participation in an intensively and non-intensively sampled virology cohort. Those who took part were couriered European In-Vitro Diagnostic Devices Directive (CE-IVD) approved sampling kits and instructions for nasopharyngeal and dried blood spot self-sampling, with pre-paid postage and packaging, to post samples to the virology processing site. In the intensive sampling cohort, participants were asked to provide daily nasopharyngeal swabs for the first seven days, and on day fourteen (+/- 1 day). In the non-intensive sampling cohort, participants were asked to provide nasopharyngeal swabs on days one, five (+/- 1 day) and fourteen (+/- 1 day). Participants were asked to take the first sample on the day following randomization (usual care

group) or before the first dose of molnupiravir (molnupiravir group). All virology sampling participants were asked to take three finger-prick dried blood spot samples on days one, five (+/- 1 day) and fourteen (+/- 1 day).

Outcomes

The primary outcome measure was all-cause, non-elective hospital admission and/or death within 28 days of randomisation. Hospital admission was defined as at least one overnight stay in hospital, or at least one night in a 'Hospital at Home' programme after hospital assessment. Spending time during the course of a day in a hospital accident and emergency (A&E) unit that did not extend overnight was classified as an A&E attendance. An overnight stay in A&E was counted as an admission. Hospitalisation for a pre-existing condition, including elective procedures planned prior to trial entry, which had not worsened, did not contribute to our primary outcome measure.

Secondary outcome measures included: time to self-reported recovery (TTR) defined as the first instance that a participant reported feeling fully recovered from the illness; time to early sustained recovery (recovered by day 14 and remained recovered until day 28); time to sustained recovery (date participant first reported recovery and subsequently remained well until 28 days); rating from 0-10 of how well participants felt; time to initial alleviation of symptoms (date symptoms first reported as minor or none); time to sustained alleviation of symptoms (date symptoms first reported as minor or none and subsequently remained minor or none until 28 days); time to initial reduction of severity of symptoms; contacts with health and social services; hospital assessment without admission; oxygen administration; new household COVID-19 infections; and, safety outcome measures.

Statistical analysis

The sample size calculation and statistical analysis are detailed in the Adaptive Design Report and the Master Statistical Analysis Plan. The sample size was initially calculated based on a 3% event rate in usual care and an intervention was expected to lower the hospitalization/death rate to 2% (i.e., 33% relative reduction); 5300 participants per group would be required with 5% level of significance and 90% power. However, the proportion of participants admitted to hospital was lower than anticipated so the sample size calculation was revised to 16578 per group (90% power) and 12534 per group (80% power), assuming event rates of 1% and 0·67% in the usual care and treatment groups, respectively.

The primary analysis population was defined as all eligible participants concurrently randomised to the intervention and usual care, according to the group they were allocated to regardless of deviation from the protocol.

The primary outcome measure was analysed using a Bayesian logistic regression model, with weakly-informative Cauchy priors, regressed on treatment group, comorbidity, and stratification covariates (age, vaccination status). The success thresholds at final and interim analysis were pre-specified in the Adaptive Design Report and were dependent on the number of interims performed, which was a function of the speed of enrolment. If no interim analyses are performed (in the case of very fast enrolment) the success threshold at the final analysis is 0.975.

The sample size for the virology sub-study was based on simulations from a viral dynamic model from early 2020,[19] which suggested that 30 patients per arm would detect a 2·5-fold increase in viral clearance (undetectable viral load at day seven, the primary outcome measure

for this sub-study) in patients who started therapy within five days of symptom onset (90% power; alpha 0·05). Clinical improvement may be associated with smaller decreases in viral load, and viral dynamic modelling leveraging time series viral load data can detect much smaller drug effect sizes.[20] 300 patients would provide a 95% probability of seeing at least one example of a SARS-CoV-2 mutation occurring in at least 1% of participants.

Secondary time to event outcome measures were modelled using a Bayesian piecewise exponential model with weakly-informative normal priors and four time segments to estimate the hazard ratio for a treatment arm versus control, adjusting for age, vaccination status, and comorbidity status. For binary outcome measures with a low event rate, results were reported descriptively by treatment group and a Chi-square test or Fisher's exact test used. Early sustained recovery was analysed using a Bayesian logistic regression model, with randomised group, age, vaccination status, and comorbidity status included as covariates.

Missing data of primary outcome measure was 3%, which was less than 5%, therefore no pre-specified imputation of missing data was carried out.

Given that this is a pragmatic trial of a licensed medicine in its licensed population, we adopted a pharmacovigilance strategy and standard adverse event data were not routinely captured. Our strategy was to comprehensively capture safety data on serious adverse events and adverse events for which there is currently limited information (e.g., pregnancy). There was, however, a robust mechanism in place for participants to seek advice on the management of troublesome adverse events.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Population

The first participant was randomised on December 8, 2021, and randomization to molnupiravir was completed on April 27, 2022, by which time 25783 participants had been enrolled. 12821 were allocated to molnupiravir plus usual care, and 12962 to usual care alone (Figure 1). Data were extracted on August 17 2022 and the 504 randomised nirmatrelvir/ritonavir plus usual care and usual care alone are not included in the analyses presented here.

The mean age (range) of participants was 56·6 (18 to 99) years, and 17759/25783 (68·9%) had co-morbidities. 98·9% had at least one dose of a SARS-CoV-2 vaccine, and 94·4% had received at least three doses. Baseline characteristics were similar between groups (Table 1).

Of 12432 participants randomised to molnupiravir who provided medication use information, 95·4% (n=11857) reported taking molnupiravir for 5 days. 0·001% (n=19/12962) of usual care participants recorded receiving monoclonal antibody treatment out with PANORAMIC.

The median duration of symptoms prior to randomisation was 2 days (IQR 1 – 3), the median number of days from symptom onset to starting to take the medication was 3 days (IQR 3 – 4), and 87% (11109/11997) received their medication within first 5 days from start of symptoms.

Primary Outcomes

The proportion experiencing primary outcome measure events was less than 1% overall, and there was no evidence of a beneficial difference in hospitalisation/death between the groups (Table 2). There were 103/12516 (0·8%) hospitalisations/deaths in the molnupiravir group versus 96/12484 (0·8%) in usual care [adjusted odds ratio 1·06; 95% Bayesian credible interval (BCI) 0·80 – 1·40, probability of superiority 0·336]. Estimates were similar for all subgroups.

Secondary outcomes

The observed median (IQR) time-to-first-recovery from randomisation was 9 (5–23) days in molnupiravir and 15 (7–not reached) days in usual care. There was an estimated benefit of 4·2 (95% BCI: 3·8 – 4·6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0.999 (estimated median TTR (10·3 [10·2 – 10·6] days vs 14·5 [14·2 – 14·9] days respectively; hazard ratio [95% BCI], 1·36 [1·3–1·4] days), which met the pre-specified superiority threshold (Table 2). Subgroup analysis demonstrated that this benefit was consistent across all studied groups.

Compared to the usual care group, participants receiving molnupiravir more often reported: early sustained recovery (31·8% vs 22·6%; adjusted odds ratio 1·62 [95% BCI: 1·53 – 1·72]); higher self-rating of wellness on a score of 0 to 10 at days 7, 14 and 28; reduced time to sustained recovery; reduced time to sustained alleviation of all symptoms; reduced time to reduction of symptom severity; fewer moderate or severe symptoms at day 7, 14 and 28 (e.g. cough, shortness of breath, loss of smell/taste and fatigue); and, there was generally less health care seeking in primary care in the molnupiravir group (e.g., any contact with GP services: 19·6% vs 23·7%, respectively), although A&E attendances were similar (Table 2).

The number of new infections over 28 days in the households of participants was similar in both groups (35·9% for molnupiravir, 36·7% for usual care).

In the intensively sampled virology cohort, on Day 7, the SARS-CoV-2 virus was below detection levels in 7/34 (21%) in the molnupiravir group, and in 1/39 (3%) in the usual care group (p=0·039), and mean (SD) of $\log_{10}$(Viral load) was 3·82 (1·40) in the molnupiravir group and 4·93 (1·38) in the usual are group (p<0·001). This was similar in the less intensively sampled virology cohort at Day 7, but the viral loads detected at Day 14, although low in both groups, were on average slightly higher in the molnupiravir group.

Regarding safety, 59 (0·4%) participants experienced serious adverse events in the molnupiravir group and 52 (0·4%) in usual care, with no serious adverse event definitely related to the intervention. 142 (1.1%) participants in the molnupiravir group withdrew due to adverse effects attributed to the medication. There were no adverse events of special interest.

DISCUSSION

This analysis from the largest randomised trial involving people vaccinated against SARS-CoV-2 infection at increased risk of an adverse outcome in the community and unwell with COVID-19 found that molnupiravir did not reduce already low hospital admissions, but that participants provided with molnupiravir recovered by a median of six days sooner. Molnupiravir resulted in an improvement in early sustained recovery in about one in ten participants and reduced GP consultations. Faster patient reported recovery was consistent with a reduction in detectable virus and viral load in the studied subgroup on day seven among those who received molnupiravir.

Two living reviews of treatments for COVID-19; a World Health organisation (WHO) living guideline[21] and a living review and network analysis that informs the WHO on drug treatments;[22] identified six trials of molnupiravir. Of these trials, one was phase 1,[7] another was phase 2a,[2] one was the phase 3 MOVe-Out trial, [10] and three trials disclosed their data to the WHO (data were accessible to the review authors) but have not made their full findings publicly available. Concern has been raised regarding the lack of public sharing or formal publication of the findings of these three trials, along with nine others, all of which were conducted in India.[23] The reviews found that molnupiravir probably reduces: hospitalisation (odds ratio 0·54; 95% CI: 0·30 to 0·90; n=5 trials); and, time to symptom resolution (-3·3 days; 95% CI: - 4·8 days to -1·6 days; n=3 trials). The WHO therefore advises that molnupiravir may be of benefit in outpatients with mild-moderate COVID-19 at the highest risk of an adverse outcome. [21]

Prior to PANORAMIC, MOVe-OUT was the largest randomised trial of molnupiravir.[10] MOVe-OUT recruited 1,433 COVID-19 outpatients in over 20 countries to molnupiravir or placebo, with a primary outcome measure of all-cause hospitalisation or death within 29 days of enrolment.[10] The median age of participants was 43 years (range 18-90 years), which is younger than the average of 56·6 years for participants in PANORAMIC. Similar to PANORAMIC, all participants had at least one risk factor for progression to serious illness (obesity – 73·7%, age > 60 years – 17·2%, Diabetes – 15·9%), and the same dose and duration of molnupiravir was used. However, participants in MOVe-OUT were unvaccinated, whilst most UK adults are now multiply-vaccinated (primary course plus one or two boosters).[24] Furthermore, Delta, Gamma and Mu SARS-CoV-2 variants were most commonly seen in the MOVe-OUT trial,[25] whereas the predominant variant in circulation in

the UK has been Omicron since recruitment to PANORAMIC commenced in December 2021. [26]

In contrast to PANORAMIC, the MOVe-OUT trial investigators found that molnupiravir statistically significantly reduced the risk of hospitalisation or death compared with placebo (risk difference, −3·0 %; 95% CI: −5·9 % to −0·1%).[10] Of note, the observed benefit on hospitalisations/deaths in MOVe-OUT was reduced in the analysis from full trial dataset compared with the initial interim results, and analysis of the post-interim data in isolation did not suggest a beneficial impact of molnupiravir on this outcome measure.[13] The MOVe-Out investigators have considered many possible explanations, including: changes in the prevailing pandemic conditions and circulating SARS-CoV-2 variants; recruitment from sites in new regions with different hospitalisation policies; and, recruitment of participants with less severe illness. [10]

In the placebo-controlled MOVe-OUT trial, molnupiravir statistically significantly increased sustained recovery from anosmia (hazard ratio 1·20; 95% CI: 1·01 to 1·43) and fatigue (hazard ratio 1·15; 95% CI: 1·01 to 1·31), but not other symptoms.[10] In PANORAMIC, molnupiravir helped alleviate all of symptoms measured, including fever, cough, fatigue, muscle ache, diarrhoea, headache, loss of taste and smell, dizziness and feeling generally unwell, and shortened the time to self-reported. Molnupiravir may have shortened the time to resumption of normal activities, since the time that normal activities are affected is closely related to the duration of feeling unwell, but we did not measure this outcome directly.[27,28] Differences in recovery outcomes between MOVe-OUT and PANORAMIC may have arisen from the open design of PANORAMIC. The proportion experiencing adverse events was similar in PANORAMIC and MOVe-OUT.

Exploratory analyses from MOVe-OUT found that molnupiravir was associated with a greater reduction in mean viral load from baseline to days three, five and ten, compared with placebo. Furthermore, the AGILE CST 2 placebo-controlled trial of 180 participants (both vaccinated and unvaccinated) demonstrated a faster time to a negative PCR test (8 days versus 11 days) with molnupiravir.[15] These findings are consistent with the findings from PANORAMIC of a reduction in viral detection and load in a subgroup of the trial cohort with molnupiravir compared with usual care at day 7.

PANORAMIC is the largest randomised trial of novel antiviral agents to date, recruiting over 26,000 participants by 4 October 2022 with test-positive SARS-CoV-2 early on in their illness. We achieved ascertainment of 97% for the primary outcome measure. Due to the large sample size, we have been able to conduct subgroup analyses with good precision around effect size estimates to determine populations in which molnupiravir is most likely to have benefit. Participants were randomised a mean of 2 days after symptom onset, and nearly 90% reported beginning their treatment course within 5 days of symptoms onset.

While it is critical to ensure that patients who are likely to benefit receive treatment with antiviral agents, using these precious medicines for patients who are unlikely to benefit carries the risk of driving resistance, wasting resources, and exposing people unnecessarily to harm. Due to the potential mutagenic properties of molnupiravir, there is a theoretical risk that administering this drug on a large scale could lead to new SARS-CoV-2 variants. This is being evaluated through the PANORAMIC trial's virology sub-study. However, animal studies suggest that viral mutations induced by molnupiravir are likely to lead to reduced viral viability, and that there is low susceptibility to development of resistance.[29,30] Analysis

of mutation frequency and the infectivity of persisting strains after molnupiravir use is ongoing and will be reported separately.

Theoretical risks have been raised regarding the potential for molnupiravir to cause mutagenesis in human cells.[31] Evidence of bone and cartilage toxicity was found in an animal study in which molnupiravir was administered for three months and at five times the dose; however, this effect was not replicated in other animal studies in which molnupiravir was administered at even higher doses (up to 19 times the normal human dose) for up to a month.[32] No impairment of fertility was identified when molnupiravir was administered to rats at up to six times the usual dose that would be given to humans.[32] On the basis of all available evidence, the risk of human genotoxicity was deemed low by the Medicines and Healthcare products Regulatory Agency (MHRA).[33] Nonetheless, we incorporated safety measures in the trial, including: inclusion of adult participants only; exclusion of breastfeeding patients and those with known/suspected pregnancy; exclusion of participants of childbearing potential who were not willing to use effective contraception for the following 28 days; a pregnancy test to confirm non-pregnancy of participants of child-bearing potential; and, confirmation of a negative pregnancy through a safety call to the participant shortly after enrolment. We additionally would have recorded pregnancies occurring within 28 days of enrolment as adverse events of special interest with any such participants followed up until the outcome of their pregnancy was known. The numbers citing drug side effects as a reason for discontinuation was recorded; a small proportion stopped the drug and an even smaller proportion (just over 1%) did so because of side effects. We found few serious adverse events, with none definitely related to molnupiravir.

Molnupiravir is an orally administered drug with no known important drug interactions, and therefore, if effective, has potential for widespread distribution and use. Patients with COVID-19 who were extremely clinically vulnerable, whilst eligible for participation in PANORAMIC, were able to access monoclonal antibody and antiviral treatment directly from the NHS: our findings may therefore be less applicable to patients in this highest risk category. Our health economics analysis is ongoing, and we are continuing to evaluate the longer-term economic implications of molnupiravir administration through collection of outcome measure data at three and six months.

We are also studying the effect of COVID-19 on longer-term symptoms, namely long COVID. Long COVID syndrome may affect up to 43% of people who experience acute COVID-19,[34] and typically causes a range of physical and psychological symptoms.[35] There is limited research evaluating the effect of treatments given during acute COVID-19 illness on longer term outcomes,[36] and to date, no published data on the effect of molnupiravir administration on long-term outcomes. Given the demonstrated improvement in time to recovery of all symptoms, we await with interest the analysis of long COVID comparing those treated with molnupiravir and usual care.

The design of PANORAMIC breaks with the traditional trial paradigm in which the "participant comes to the research." The molnupiravir comparison in PANORAMIC allowed "research to be taken to the patient," with remote recruitment of participants possible from all four UK nations, irrespective of where people live or receive their healthcare. This is important, as research suggests that the low representation of people from diverse and ethnic minority backgrounds is because their access to research is more difficult.[37] The ability of participants to be recruited, enrolled and followed up without having to leave their homes

reduces the burden of trial procedures on participants and reduces spread. PANORAMIC strives to be a 'democratic' trial, with a proactive outreach strategy, led by the trial's national pharmacy, and inclusion and diversity lead, with the support of UK-wide pharmacy networks, to actively promote the trial UK-wide and to people from all backgrounds. This includes people from ethnic minority background and people residing in areas of higher deprivation, who may be disproportionately affected by COVID-19, yet also traditionally poorly represented in clinical trials. Participants living in areas with the most deprived quintile of the Index of Multiple Deprivation was around 10%, and about 30% lived the least deprived areas; this may be explained by large numbers being recruited after self-screening and follow up online. The proportion of participants from ethnic minority origin was nearly 6%; the mean age of our participants was 56.6 years and as there are proportionally fewer people of ethnic minority origin in older age groups in the UK, [38] this is largely representative of the general population.

The open-label design means that we cannot estimate the proportion of the positive effect of molnupiravir on symptoms resulting from any placebo effect. However, the objective primary outcome measure in PANORAMIC (non-elective hospitalisation and/or death) is unlikely to be affected by a placebo effect. Furthermore, the virology sub-study found reduced duration of viral RNA detection in nasal swabs with molnupiravir at day 7, which is in line with self-reported reduction in illness duration. In keeping with pragmatic trial design, PANORAMIC is designed to be more closely reflective of real-world practice; [39] our results are more likely to reflect what would happen if molnupiravir were introduced into routine clinical practice [39] and facilitate a more realistic cost-effectiveness and cost utility assessment. Of note, findings from our open label PRINCIPLE trial of repurposed drugs for community treatment of COVID-19 has found no difference in outcome measures relying on participants' self-reported recovery for several treatments. [40-42]

This preliminary analysis involving people vaccinated against SARS-CoV-2 infection at increased risk of an adverse outcome in the community and unwell with COVID-19 found that molnupiravir did not reduce already low hospital admission, but that molnupiravir resulted in faster time to recovery, earlier sustained recovery, reduced contact with GP services, and reduced viral detection and viral load. These benefits need to be considered in the context of the prevailing disease, burden on healthcare services, social circumstances, cost-effectiveness, and opportunity costs.

Contributors

Declaration of interests

JSN-V-T was seconded to the Department of Health and Social Care, England (DHSC) from October 2017 to March 2022. The views expressed in this paper are those of its authors and not necessarily those of DHSC. Berry statisticians are paid by the University of Oxford for their statistical work on the unblinded analyses for PANORAMIC, but their compensation is not dependent on the outcomes of arms in the study. SK has received research support from ViiV, Merck, Ridgeback, GSK and Vir and honoraria from Pfizer unrelated to this work. UW has received speaker/advisory board fees from AZ, Gilead, GSK/ViiV and MSD/Merck.

Data sharing

Data can be shared with qualifying researchers who submit a proposal with a valuable research question as assessed by a committee formed from the trial management group, including senior statistical and clinical representation. A contract should be signed.

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Recruiting sites

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Authors' contributions

CCB and JSN-V-T conceived the study. CCB is the Chief Investigator. PL, FDRH are co-Chief Investigators. CCB, PL, and FDRH decided to publish the paper. BRS, L-MY, JH, MD, CCB, FDRH, PL, GH, OAG, JD, NMR, DBR, SP, DML, JFS, KH, PE, OvH and ML provided input to the trial design. EO, JA, PE, LL, EH, LC, MB, MC, SB, CB, JCD, IR-W, AC-S and DB are responsible for study implementation and acquisition of data. CCB, OAG, L-MY, PL, FDRH, GH, NMR, DBR, MGP, DML, JFS, PE, JB, JD, SP, JSN-V-T and SK drafted the manuscript. HR leads the clinical team. L-MY, BRS, JH, VH, UG, JM, MAD, CTS, MF and NSB contribute to statistical analysis. SK, DBR, GH, NMR and MD provide input to safety evaluations, monitoring, and drug interactions. MGP is the National Pharmacy, and Inclusion and Diversity Lead for the trial. SP and MEP run the economic evaluation. JFS, DML and JB lead the virology sub-study. GH leads on patient and public

involvement. JC leads on the information systems. MB leads data management. CCB, PL, OAG, NMR, SP, DBR, KH, MGP, BRS, EO, JD, DML, SK, NF, NPBT, PE, JFS, JB, JA, MD, T-AM, MEP, GH, ML, BJ, NDH, JC, EH, LC, MB, MA, OvH, AU, L-MY and FDRH are members of the Trial Management Group supporting site recruitment, activity and delivery. OAG and CCB produced the first draft of the manuscript. All authors critically revised the manuscript. All authors are contributing to the conduct of the trial.

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Figure 1 Participant flow diagram

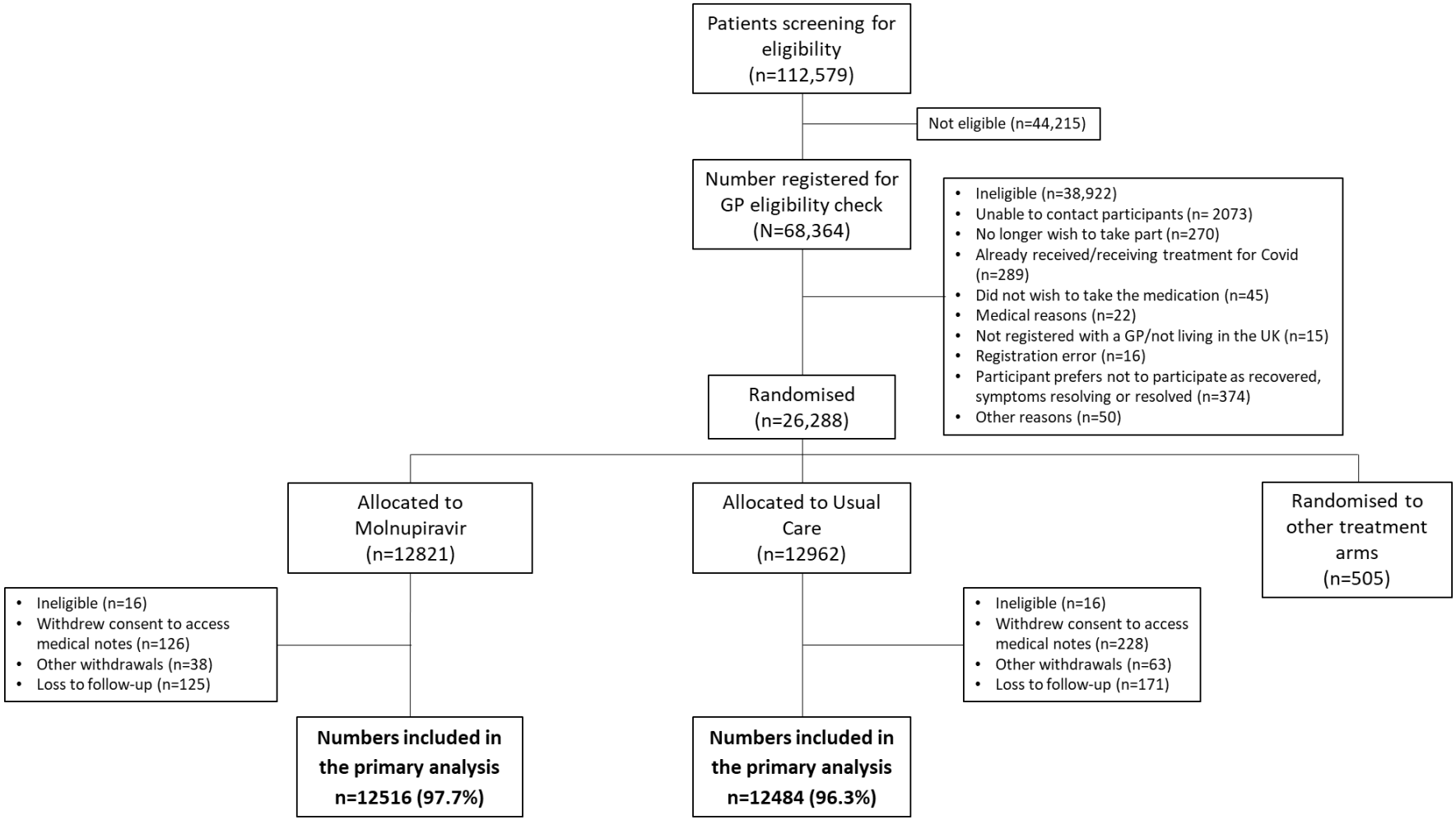
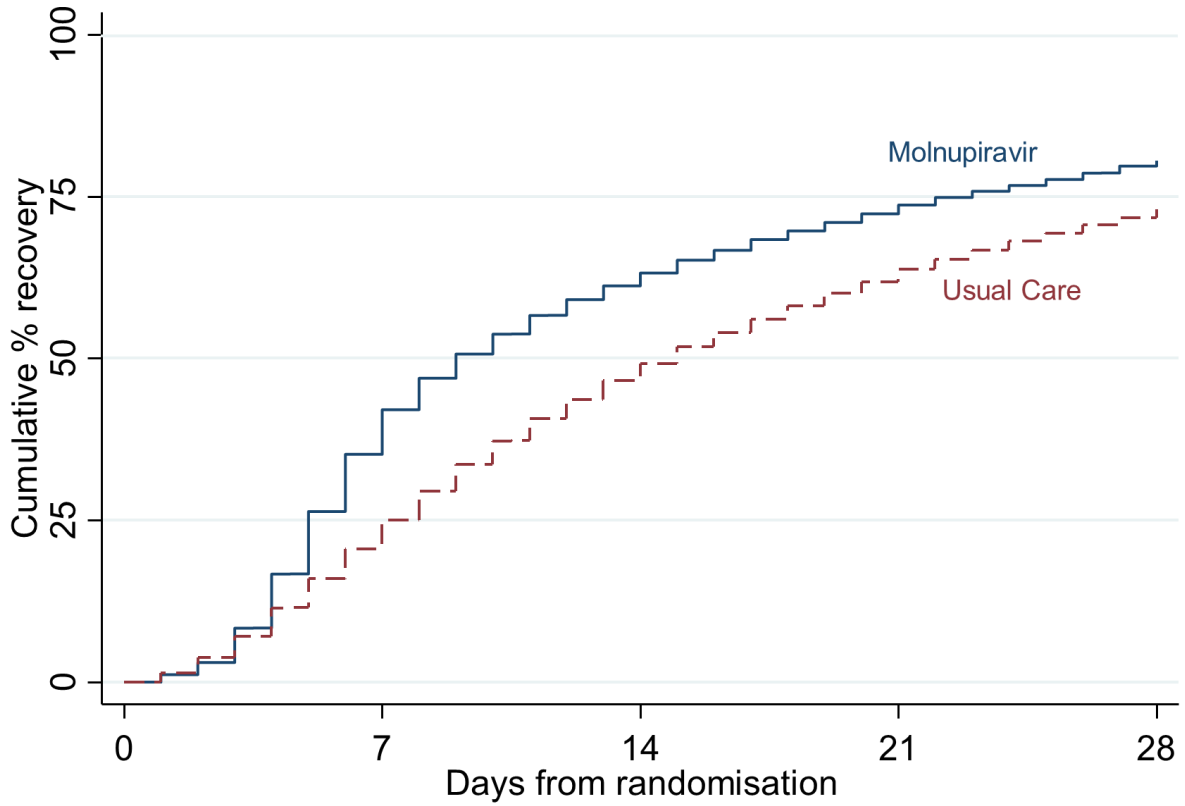


Figure 2 Time to first reported recovery



Cumulative number not yet recovered (recovered)					
Molnupiravir	12432 (0)	7948 (5179)	4670 (7734)	3228 (8966)	2173 (9741)
Usual Care	12151 (0)	9415 (2993)	6124 (5788)	4177 (7393)	2776 (8376)

Figure 3 Forest plot of subgroup analysis of hospitalization/death

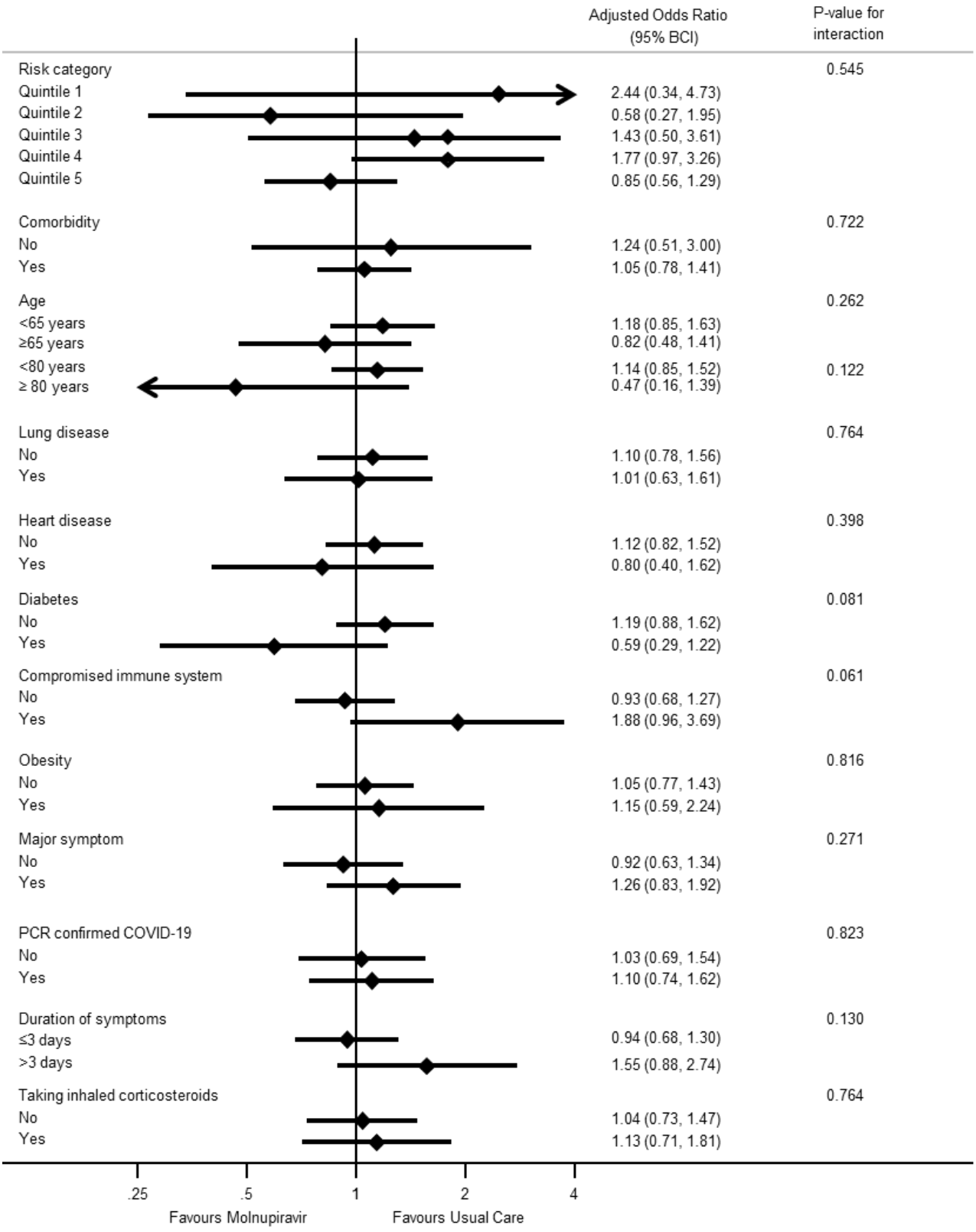


Figure 4 Forest plot of subgroup analysis of time to recovery

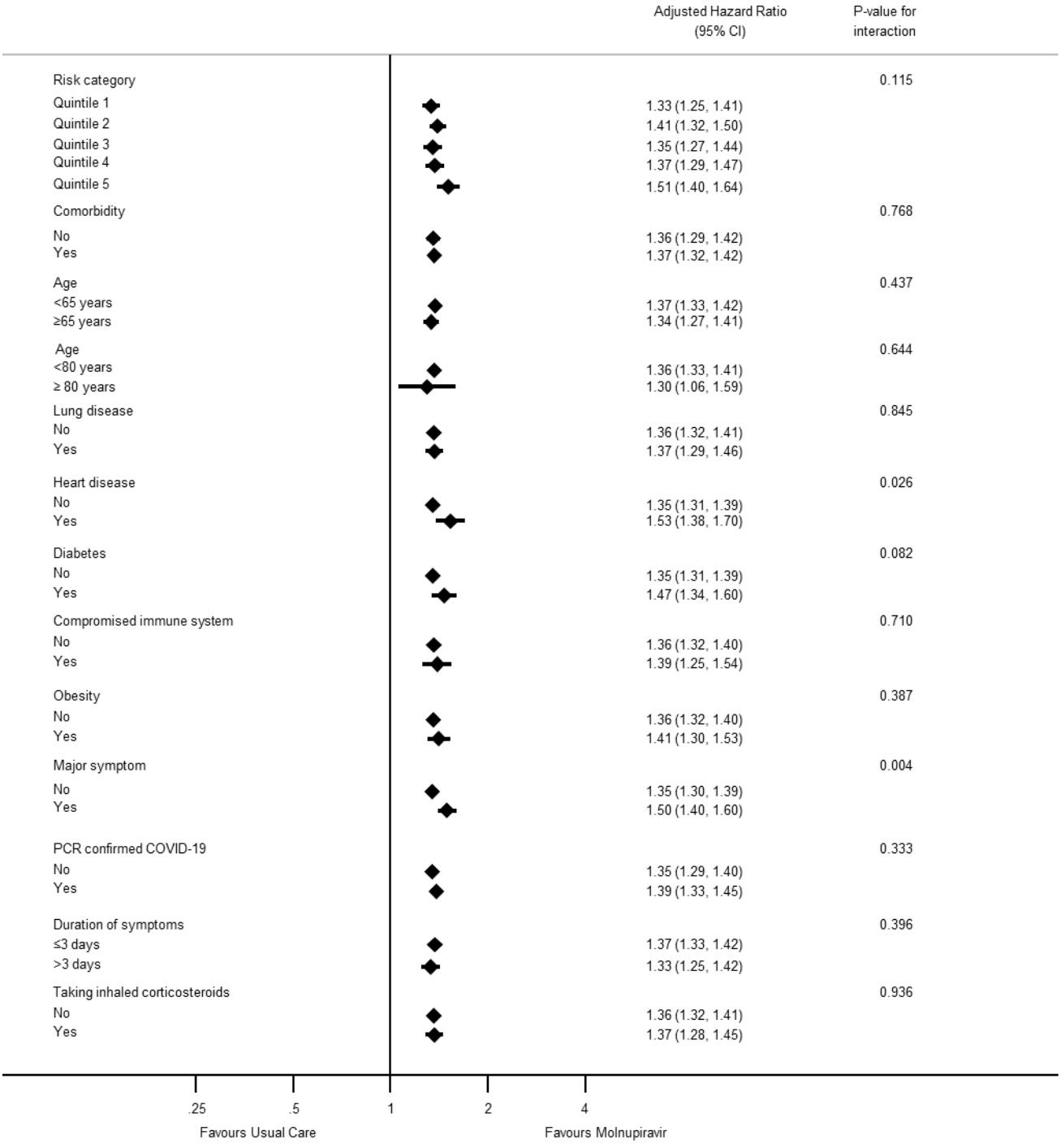


Table 1 Baseline characteristics of participants by treatment group

	Molnupiravir (N=12821)	Usual Care (N=12962)	OVERALL (N=25783)
Age, mean(SD)	56·7 (12·5)	56·5 (12·7)	56·6 (12·6)
Sex, n(%)			
Female	7451 (58%)	7650 (59%)	15101 (59%)
Male	5367 (42%)	5308 (41%)	10675 (41%)
Other	3 (<1%)	4 (<1%)	7 (<1%)
Days from randomisation to reporting receipt of medication for those with day 1 to 7 diaries*, median(IQR)	1.0 (1.0 to 2.0)		1.0 (1.0 to 2.0)
Days from start of symptoms to taking medication for those with day 1 to 7 diaries*, median(IQR)	3·0 (3·0 to 4·0)		3·0 (3·0 to 4·0)
Missing, n(%)	824 (3%)		
Ethnicity category, n(%)			
White	12088 (94%)	12182 (94%)	24270 (94%)
Asian	366 (3%)	434 (3%)	800 (3%)
Mixed Race	203 (2%)	189 (2%)	392 (2%)
Black	78 (<1%)	77 (<1%)	155 (<1%)
Other	86 (<1%)	80 (<1%)	166 (<1%)
NHS priority category, n(%)			
Aged ≥80	259 (2·%)	272 (2%)	531 (2%)
Aged ≥75 and <80	539 (4%)	577 (5%)	1116 (4%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1117 (9%)	1114 (9%)	2231 (9%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1496 (12%)	1464 (11%)	2960 (12%)
Aged ≥18 and <65 in an at-risk group	6541 (51%)	6591 (51%)	13132 (51%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at-risk group	746 (6%)	768 (6%)	1514 (6%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at-risk group	997 (8%)	1063 (8%)	2060 (8%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at-risk group	1126 (9%)	1113 (9%)	2239 (9%)
Predicted risk quintile, n(%)			
1 (lowest risk)	2491 (19%)	2558 (20%)	5049 (20%)
2	2679 (21%)	2636 (20%)	5315 (21%)
3	2524 (20%)	2660 (21%)	5184 (20%)
4	2784 (22%)	2767 (21%)	5551 (22%)
5 (highest risk)	2343 (18%)	2341 (18%)	4684 (18%)
Confirmed PCR positive, n(%)	5965 (46%)	5902 (46%)	11867 (46%)
IMD quintile, n(%)			
(Most deprived) 1	1234 (10%)	1182 (9%)	2416 (9%)
2	1913 (15%)	1956 (15%)	3869 (15%)
3	2569 (20%)	2592 (20%)	5161 (20%)
4	3216 (25%)	3213 (25%)	6429 (25%)
(Least deprived) 5	3839 (30%)	3960 (31%)	7799 (30%)
Missing, n(%)	50 (<1%)	59 (<1%)	109 (<1%)
Received vaccination, n(%)	12678 (99%)	12830 (99%)	25508 (99%)
Number of vaccine doses, n(%)			
1	87 (<1%)	88 (<1%)	175 (0<1%)
2	519 (4%)	458 (4%)	977 (4%)
3	11836 (92%)	12044 (93%)	23880 (93%)
4	236 (2%)	240 (2%)	476 (2%)
Missing, n(%)	143 (1%)	132 (1%)	275 (1%)

	Molnupiravir (N=12821)	Usual Care (N=12962)	OVERALL (N=25783)
Smoker, n(%)	795 (6%)	805 (6%)	1600 (6%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	6111 (48%)	6125 (47%)	12236 (48%)
Minor problem	4514 (35%)	4684 (36%)	9198 (36%)
Moderate problem	1936 (15%)	1896 (15%)	3832 (15%)
Major problem	260 (2%)	257 (2%)	517 (2%)
Fatigue, n(%)			
No problem	1251 (10%)	1216 (9%)	2467 (10%)
Minor problem	4721 (37%)	4853 (37%)	9574 (37%)
Moderate problem	5083 (40%)	5127 (40%)	10210 (40%)
Major problem	1766 (14%)	1766 (14%)	3532 (14%)
Muscle ache, n(%)			
No problem	3479 (27%)	3425 (26%)	6904 (27%)
Minor problem	4504 (35%)	4791 (37%)	9295 (36%)
Moderate problem	3763 (29%)	3684 (28%)	7447 (29%)
Major problem	1075 (8%)	1062 (8%)	2137 (8%)
Vomiting, n(%)			
No problem	10440 (81%)	10503 (81%)	20943 (81%)
Minor problem	1847 (14%)	1913 (15%)	3760 (15%)
Moderate problem	478 (4%)	477 (4%)	955 (4%)
Major problem	56 (<1%)	69 (<1%)	125 (<1%)
Diarrhoea, n(%)			
No problem	10600 (83%)	10732 (83%)	21332 (83%)
Minor problem	1649 (13%)	1681 (13%)	3330 (13%)
Moderate problem	471 (4%)	457 (4%)	928 (4%)
Major problem	101 (<1%)	92 (<1%)	193 (<1%)
Loss of smell or taste, n(%)			
No problem	9066 (71%)	9402 (73%)	18468 (72%)
Minor problem	2484 (19%)	2368 (18%)	4852 (19%)
Moderate problem	825 (6%)	800 (6%)	1625 (6%)
Major problem	446 (4%)	392 (3%)	838 (3%)
Headache, n(%)			
No problem	2702 (21%)	2820 (22%)	5522 (21%)
Minor problem	5194 (41%)	5215 (40%)	10409 (40%)
Moderate problem	3783 (30%)	3838 (30%)	7621 (30%)
Major problem	1142 (9%)	1089 (8%)	2231 (9%)
Dizziness, n(%)			
No problem	8446 (66%)	8382 (65%)	16828 (65%)
Minor problem	3087 (24%)	3295 (25%)	6382 (25%)
Moderate problem	1096 (9%)	1087 (8%)	2183 (9%)
Major problem	192 (2%)	198 (2%)	390 (2%)
Abdominal pain, n(%)			
No problem	10391 (81%)	10440 (81%)	20831 (81%)
Minor problem	1834 (14%)	1920 (15%)	3754 (15%)
Moderate problem	524 (4%)	542 (4%)	1066 (4%)
Major problem	72 (<1%)	60 (<1%)	132 (<1%)
Generally unwell, n(%)			
No problem	525 (4%)	535 (4%)	1060 (4%)
Minor problem	5028 (39%)	5145 (40%)	10173 (40%)
Moderate problem	5789 (45%)	5838 (45%)	11627 (45%)
Major problem	1479 (12%)	1444 (11%)	2923 (11%)
Fever, n(%)			
No problem	5670 (44%)	5765 (45%)	11435 (44%)

	Molnupiravir (N=12821)	Usual Care (N=12962)	OVERALL (N=25783)
Minor problem	4813 (38%)	4955 (38%)	9768 (38%)
Moderate problem	2107 (16%)	2042 (16%)	4149 (16%)
Major problem	231 (2%)	200 (2%)	431 (2%)
Cough, n(%)			
No problem	1410 (11%)	1343 (10%)	2753 (11%)
Minor problem	6153 (48%)	6384 (49%)	12537 (49%)
Moderate problem	4502 (35%)	4509 (35%)	9011 (35%)
Major problem	756 (6%)	726 (6%)	1482 (6%)
Wellness score, mean(SD)	5·1 (1·7)	5·2 (1·7)	5·1 (1·7)
People in household, n(%)			
0	1660 (13%)	1660 (13%)	3320 (13%)
1	6113 (48%)	6019 (46%)	12132 (47%)
2	2129 (17%)	2176 (17%)	4305 (17%)
3	1765 (14%)	1979 (15%)	3744 (15%)
4	808 (6%)	772 (6%)	1580 (6%)
Taking inhaled corticosteroids, n(%)	2990 (23%)	3152 (24%)	6142 (24%)
Taking inhaled corticosteroids for COVID, n(%)	183 (1%)	158 (1%)	341 (1%)
Monoclonal antibodies for COVID, n(%)	26 (<1%)	19 (<1%)	45 (<1%)
Comorbidities			
Lung disease, n(%)	3014 (24%)	3171 (25%)	6185 (24%)
Heart disease, n(%)	1000 (8%)	957 (7%)	1957 (8%)
Kidney disease, n(%)	227 (2%)	253 (2%)	480 (2%)
Liver disease, n(%)	159 (1%)	144 (1%)	303 (1%)
Neurological disease, n(%)	430 (3%)	438 (3%)	868 (3%)
Learning disability, n(%)	36 (<1%)	27 (<1%)	63 (<1%)
Down's syndrome', n(%)	24 (<1%)	30 (<1%)	54 (<1%)
Diabetes, n(%)	1483 (12%)	1512 (12%)	2995 (12%)
Weakened immune system, n(%)	1125 (9%)	1070 (8%)	2195 (9%)
Transplant recipient, n(%)	57 (<1%)	71 (<1%)	128 (<1%)
Obesity, n(%)	1968 (15%)	1944 (15%)	3912 (15%)
Mental illness, n(%)	198 (2%)	220 (2%)	418 (2%)
Hypertension, n(%)	2880 (23%)	2902 (22%)	5782 (22%)
Other vulnerability, n(%)	2295 (18%)	2341 (18%)	4636 (18%)

*Median and interquartile range presented for non-normally distributed variables.

Table 2: Primary and Secondary Outcomes

	Molnupiravir	Usual Care	Estimated treatment effect (95% BCI/CI)	Estimated benefit (95% BCI)	Pr(Superiority)/ P-value
Primary outcomes					
Number of hospitalisation	102	93			
Number of death	2	5			
Hospitalisation/death at 28 days, n (%)	103/12516 (0·8%)	96/12484 (0·8%)	1·06 (0·80 to 1·40)*		0·34*
Secondary outcomes					
First reported recovery, n/N (%)	9741/12432 (78%)	8376/12151 (69%)			
Time to first reported recovery (days), median (IQR)	9 (5 to 23)	15 (7 to not reached)	1·36 (1·32 to 1·40)†	4·17 (3·78 to 4·58)†	>0·999†
Early sustained recovery, n/N (%)	3631/11411 (32%)	2446/10826 (23%)	1·62 (1·53 to 1·72)‡		>0·999‡
Sustained recovery, n/N (%)	8558/12432 (69%)	7304/12151 (60%)			
Time to sustained recovery (days), median (IQR)	21 (10 to not reached)	24 (14 to not reached)	1·24 (1·21 to 1·28)†	3·80 (3·25, 4·31)†	>0·999†
Alleviation of all symptoms, n/N (%)	9000/9689 (93%)	8352/9407 (89%)			
Time to alleviations of all symptoms (days), median (IQR)	4 (2 to 7)	4 (2 to 9)	1·18 (1·15 to 1·22)†	0·66 (0·54, 0·78)†	>0·999†
Sustained alleviation of all symptoms, n/N (%)	8134/9689 (84%)	7383/9407 (79%)			
Time to sustained alleviation of all symptoms (days), median (IQR)	9 (3 to 23)	12 (4 to 25)	1·16 (1·13 to 1·20)†	2·01 (1·58, 2·45)†	>0·999†
Initial reduction of severity of symptoms, n/N (%)	10073/11954 (84%)	8862/11555 (77%)			
Time to initial reduction of severity of symptoms (days), median (IQR)	8 (5 to 18)	12 (7 to 24)	1·30 (1·26 to 1·34)†	2.35 (2.02 to 2.69) †	>0·999†
Rating of how well participant feels (0 worst, 10 best), mean (SD) [n]					
Day 7	7·3 (1·7) [11857]	6·8 (1·8) [11233]	0·5 (0·5 to 0·6)§		<0·001§
Day 14	7·9 (1·7) [11524]	7·6 (1·7) [10740]	0·3 (0·2 to 0·3)§		<0·001§
Day 21	8·2 (1·6) [10761]	8·0 (1·7) [9698]	0·2 (0·1 to 0·2)§		<0·001§
Day 28	8·4 (1·5) [10658]	8·3 (1·6) [9777]	0·2 (0·1 to 0·2)§		<0·001§
New infections in household	3890/10823 (36%)	3874/10557 (37%)	0·96 (0·91 to 1·02)*		0·90*
Any contact with NHS 111, n/N (%)	584/12431 (5%)	778/12145 (6%)	0·72 (0·64 to 0·80)*		>0·999*
Any contact with GP, n/N (%)	2432/12431 (20%)	2879/12146 (24%)	0·77 (0·73 to 0·82)*		>0·999*
Any contact with ambulance service (not hospitalised), n/N (%)	344/12426 (3%)	331/12131 (3%)	1·02 (0·87 to 1·180) *		0·43*
Any contact with community nurse, n/N (%)	42/550 (8)	53/543 (10)	0·78 (0·53 to 1·15)*		0·76*
Any contact with physiotherapist, n/N (%)	22/786 (3)	22/797 (3)	1·01 (0·57 to 1·82)*		0·0004*
Any contact with counsellor, n/N (%)	50/774 (7)	73/785 (9)	0·69 (0·49 to 0·98)*		0·89*
Any contact with social worker	27/12431 (<1%)	32/12142 (<1%)	0·84 (0·49 to 1·36)*		0·79*
Any contact with home carer	89/12430 (<1%)	95/12140 (<1%)	0·91 (0·67 to 1·20)*		0·77*
Any contact with occupational therapist	261/12430 (2%)	240/12142 (2%)	1·07 (0·89 to 1·27)*		0·25*
Any contact with hospital A&E	708/12431 (6%)	674/12143 (6%)	1·03 (0·92 to 1·14)*		0·32*
Any contact with respiratory outpatient clinic	234/12431 (2%)	252/12141 (2%)	0·90 (0·75 to 1·07)*		0·88*
Any contact with hospital at home for COVID-19	352/12431 (3%)	431/12142 (4%)	0·79 (0·68 to 0·90)*		>0·999*
Any contact with other services	584/12431 (5%)	647/12141 (5%)	0·87 (0·77 to 0·97)*		0·99*
Virology outcomes					
Intensive Samples					
Viral load below detection level, n/N (%)					

	Molnupiravir	Usual Care	Estimated treatment effect (95% BCI/CI)	Estimated benefit (95% BCI)	Pr(Superiority)/ P-value
Day 2	1/33 (3%)	0/38 (0%)	-		
Day 3	1/34 (3%)	0/38 (0%)	-		
Day 4	2/34 (6%)	0/39 (0%)	-		
Day 5	5/28 (15%)	0/38 (0%)	-		
Day 6	6/33 (18%)	1/39 (3%)	11·50 (1·07, 123·87) ¶		0·044¶
Day 7	7/34 (21%)	1/39 (3%)	20·72 (1·12, 102·23) ¶		0·039¶
log10Viral load, mean(SD)					
Day 2	6·66 (1·59)	7·11 (1·04)	-0·48 (-0·98 to 0·01)**		0·056**
Day 3	6·07 (1·48)	6·47 (1·07)	-0·42 (-0·92 to 0·07)**		0·092**
Day 4	5·32 (1·61)	5·87 (1·21)	-0·56 (-1·04 to -0·07)**		0·026**
Day 5	4·45 (1·52)	5·82 (1·08)	-1·41 (-1·91 to -0·92)**		<0·001**
Day 6	4·12 (1·50)	5·32 (1·28)	-1·23 (-1·72 to -0·73)**		<0·001**
Day 7	3·82 (1·40)	4·93 (1·38)	-1·11 (-1·60 to -0·63)**		<0·001**
All Samples					
Viral load below detection level, n/N (%)					
Day 5	20/238 (8%)	8/280 (3%)	5·78 (1·70 to 19·62) ††		0·005††
Day 7 ll	7/35 (20%)	2/40 (5%)	14·01 (1·06 to 184·75) ††		0·045††
Day 14	96/203 (47%)	134/241 (56%)	0·60 (0·31 to 1·14) ††		0·12††
log10Viral load, mean(SD)					
Day 5	4·88 (1·51)	5·89 (1·41)	-1·06 (-1·27 to -0·85)**		<0·001**
Day 7	3·86 (1·40)	4·85 (1·45)	-1·11 (-1·65 to -0·57)**		<0·001**
Day 14	2·72 (1·33)	2·41 (1·05)	0·27 (0·06 to 0·52)**		0·015**

* Bayesian logistic regression model adjusted for age, vaccination status, and comorbidity at baseline, with 95% Bayesian credible interval. Odds Ration < 1 favours molnupiravir. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥ 0·975 versus usual care.

†Estimated benefit in median time to recovery derived from a Bayesian piecewise exponential model adjusted for age and comorbidity at baseline, with 95% Bayesian credible interval. A positive value in estimated benefit in median time to recovery (or HR > 1) corresponds to a reduction in time to recovery in days in molnupiravir compared to Usual Care. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥ 0.975 versus usual care.

‡ Bayesian logistic regression model adjusted for age, vaccination status, and comorbidity at baseline, with 95% Bayesian credible interval. Odds Ration > 1 favours molnupiravir. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥ 0·975 versus usual care.

§ Linear mixed effect model adjusted for age, comorbidity and vaccination status· Participant fitted as a random effect. Estimated mean difference > 0 favours molnupiravir. Frequentist model estimates display P-value rather than a probability, P < 0.05 indicates statistical significance versus usual care.

ll Virology primary outcome

¶ Firth logistic regression adjusting for sex, age, and baseline $\log_{10}$(viral load)· Adjusted OR > 1 favours molnupiravir. Frequentist model estimates display P-value rather than a probability. P < 0.05 indicates statistical significance versus usual care.

**Mixed effect model adjusting for sex, age, and baseline $\log_{10}$(viral load); adjusted difference < 0 favours molnupiravir. Frequentist model estimates display P-value rather than a probability. P < 0.05 indicates statistical significance versus usual care.

†† Mixed effect logistic regression model adjusting for sex, age, and baseline log10(viral load); adjusted OR > 1 favours molnupiravir