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Therapeutics for people with COVID-19 [ID4038]

Assessment Report

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

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

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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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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.

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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.

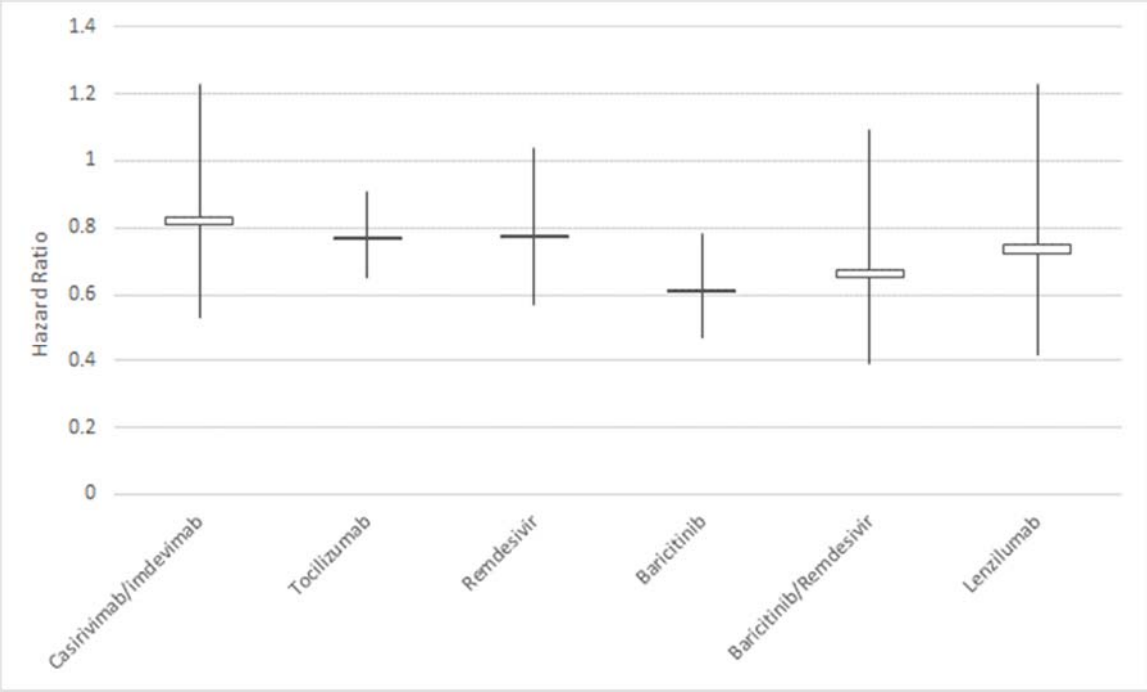

Figure 1: **The hazard ratio of avoiding death for interventions used to treat patients in hospital**

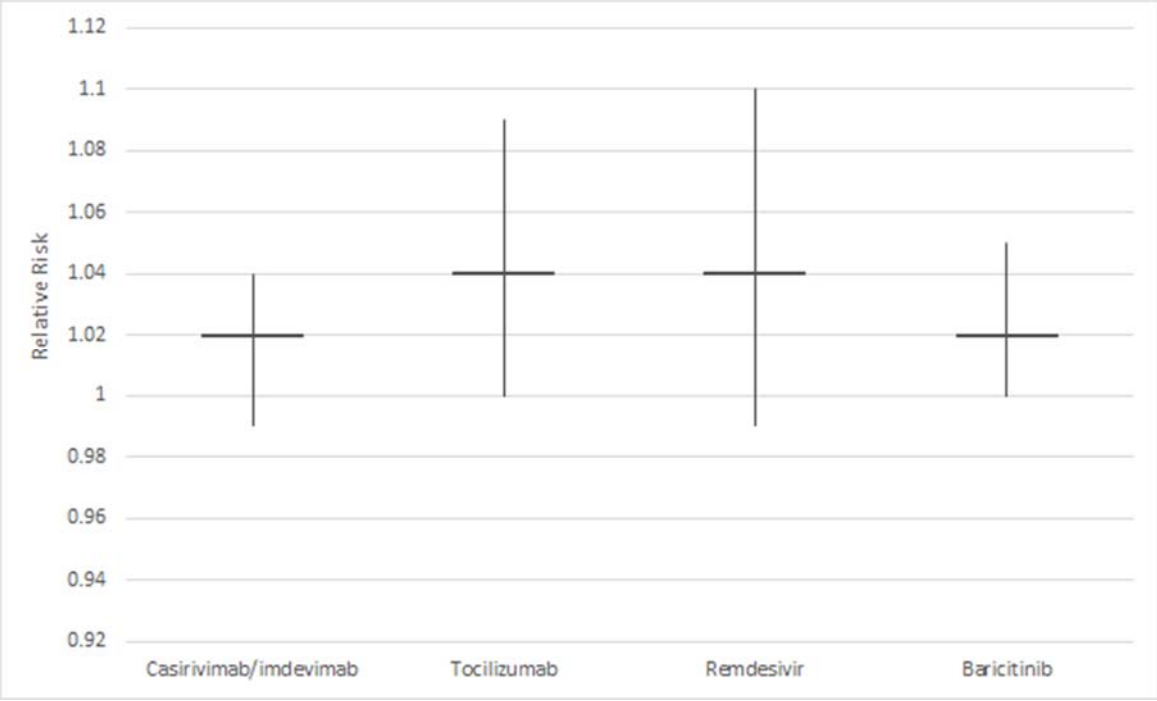

Figure 2: **The relative risk of clinical improvement at 28 days for interventions used to treat patients in hospital**

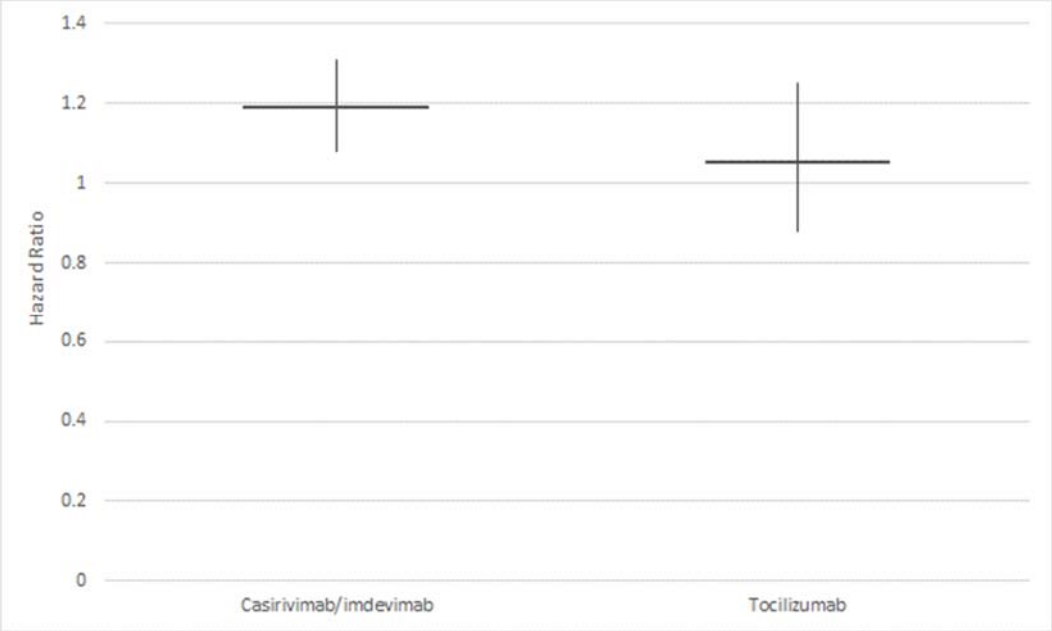

Figure 3: The hazard ratio of discharge for interventions used to treat patients in hospital

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.

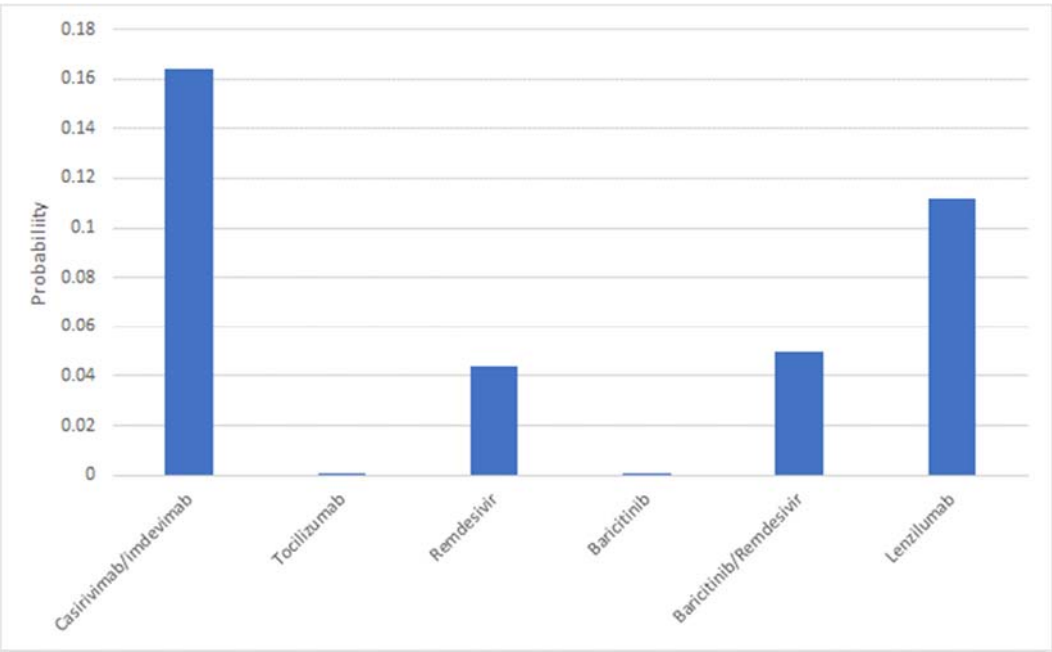

Figure 4: The probability that the intervention used in hospital is associated with increased mortality based on the lognormal distribution derived from the living systematic reviews

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.

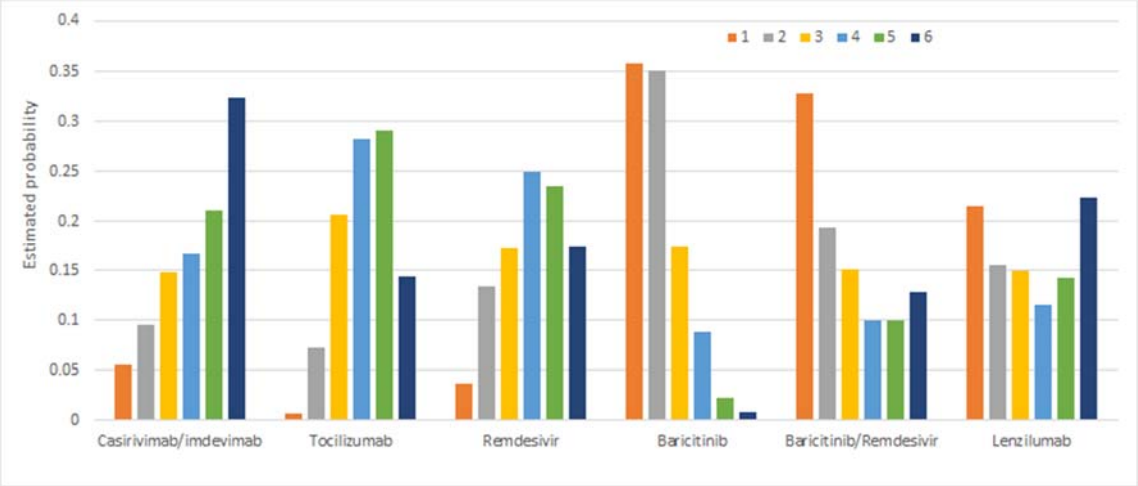

Figure 5: The estimated probability that each intervention is ranked first through to sixth for hazard ratio for mortality

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.

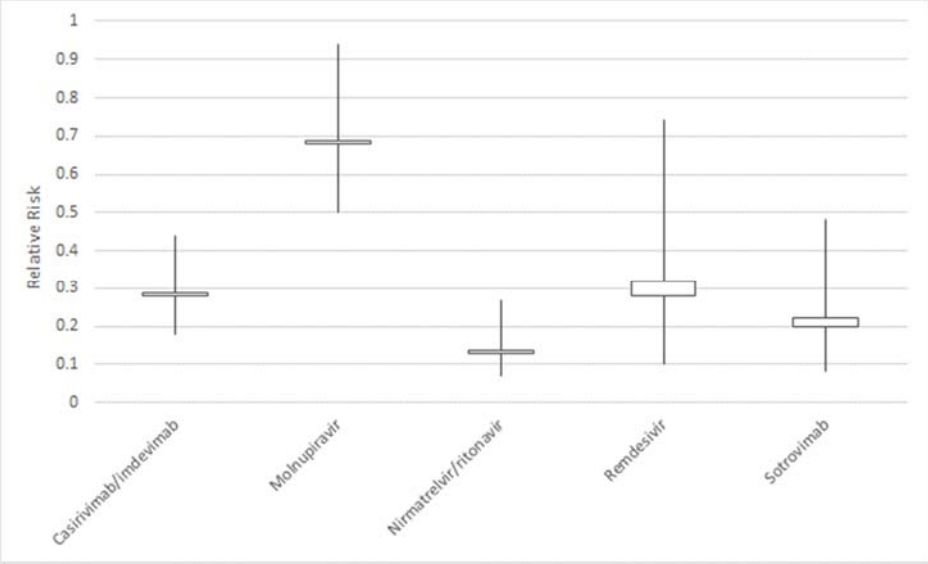

Figure 6: The relative risk of avoiding hospitalisation or death at 28 days for interventions used to treat patients in the community

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.

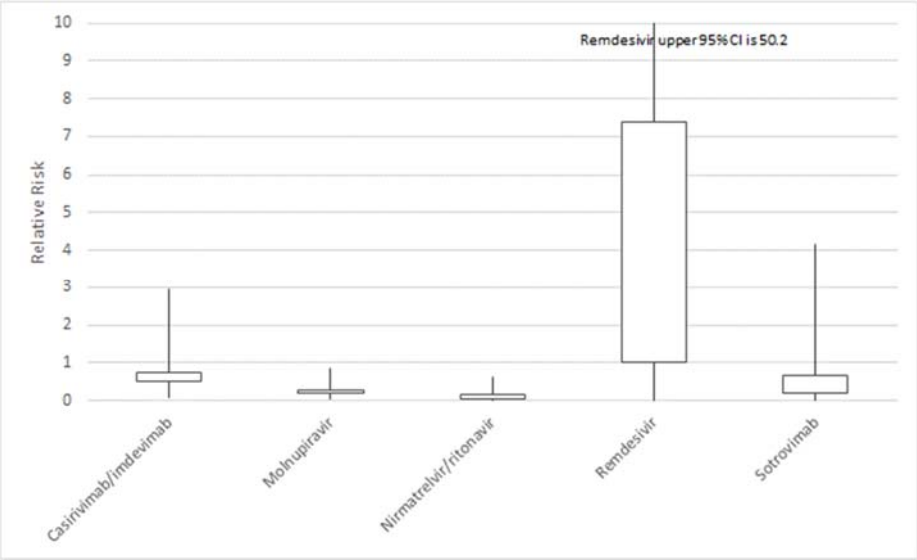

Figure 7: The relative risk of avoiding death at 28 days for interventions used to treat patients in the community

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.

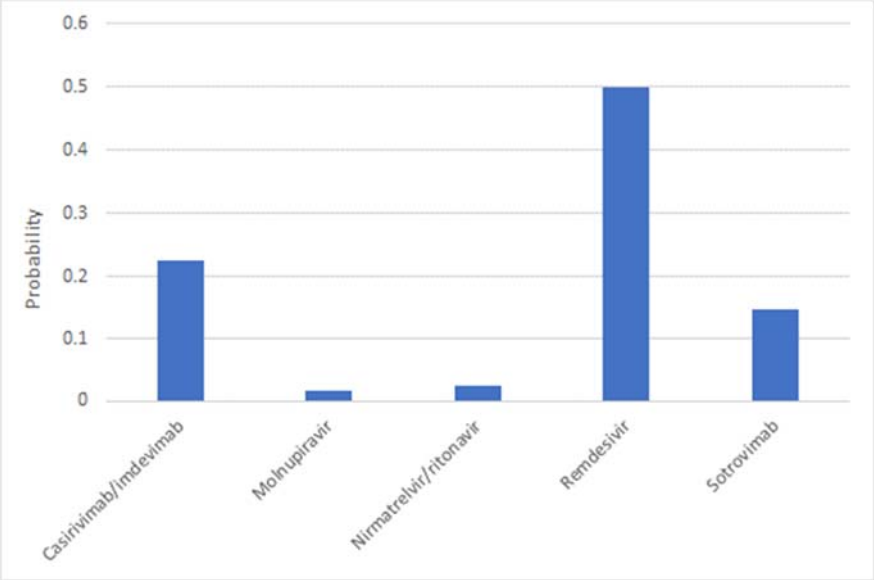

Figure 8: The probability that the intervention is associated with increased mortality based on the lognormal distribution derived from the living systematic reviews

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.

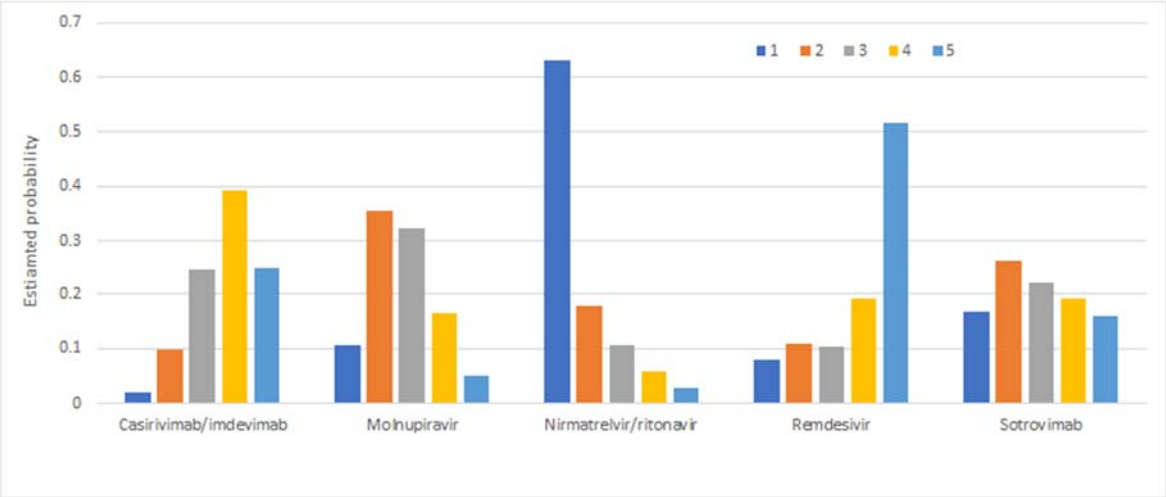

Figure 9: The estimated probability that each intervention is ranked first through to fifth for preventing mortality at 28 days

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.

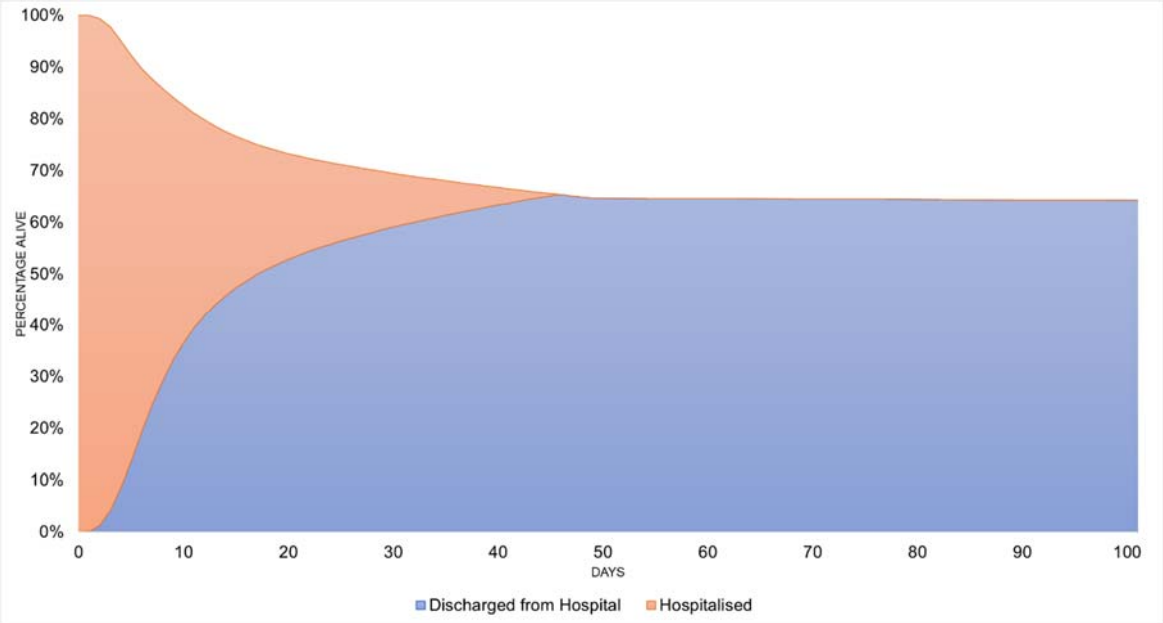

Figure 10: Simplified schematic of model structure (values are for illustration only)

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.

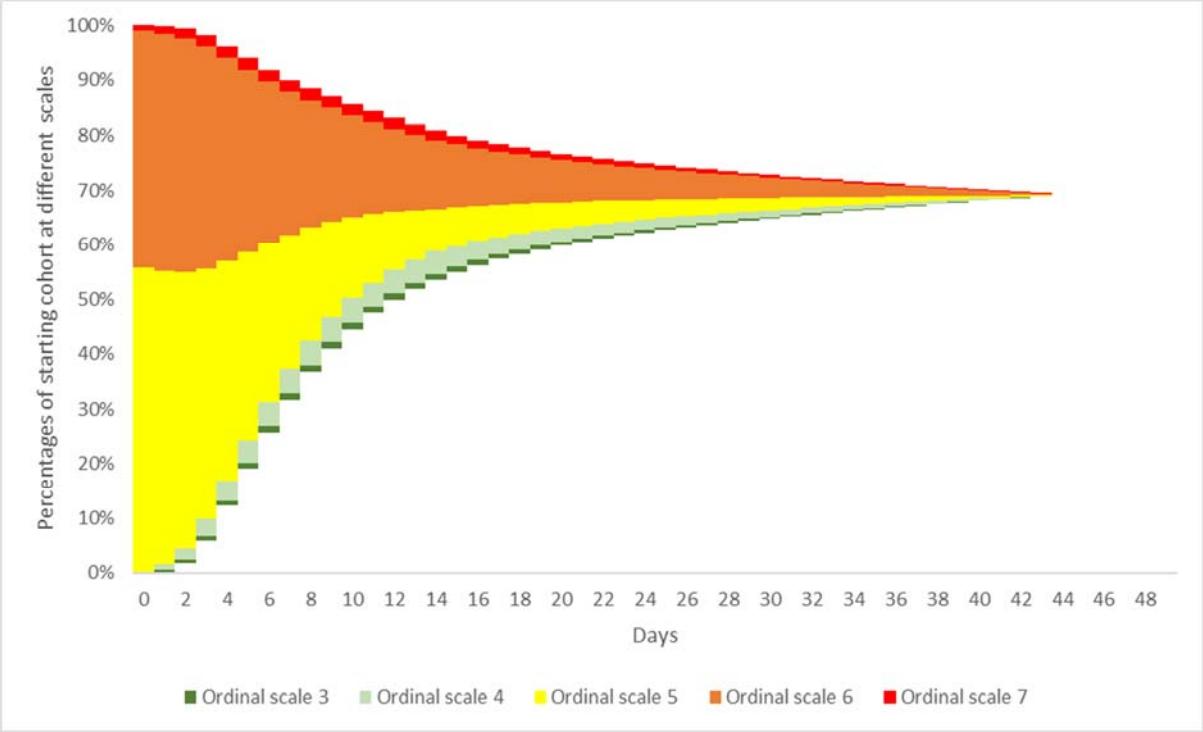

Figure 11: Illustration of ordinal scale occupancy during hospital stay of a cohort admitted to hospital requiring supplemental oxygen and receiving SoC treatment

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.

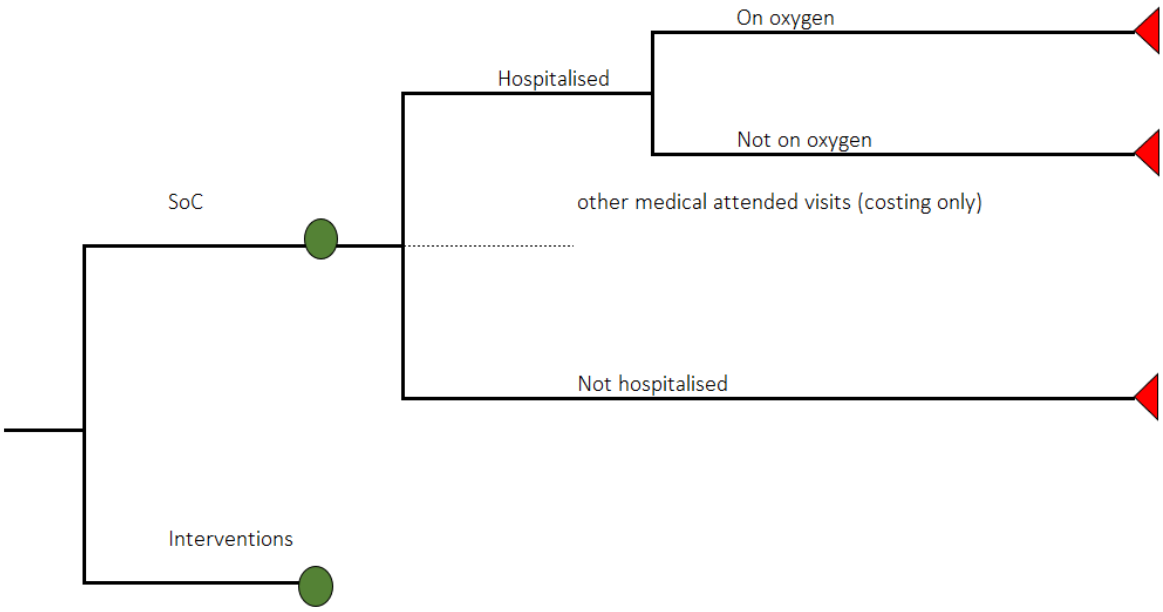

Figure 12: Structure of the decision tree used for the non-hospitalised cohort

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.

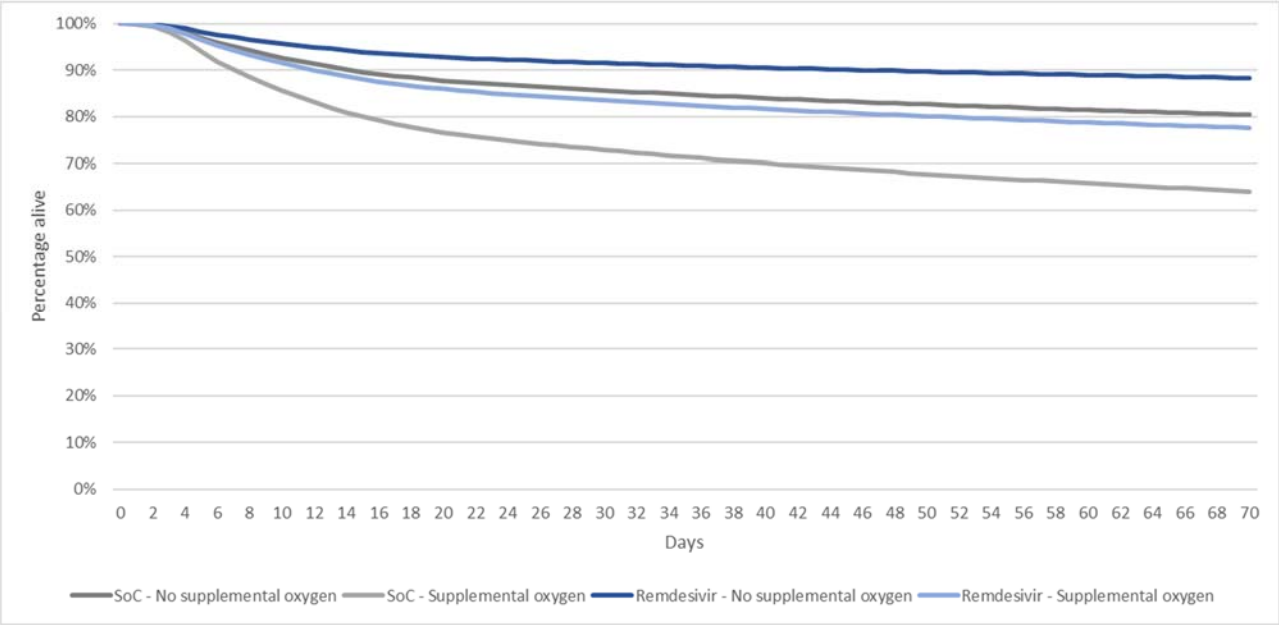

Figure 13: Illustration of OS curves used for the hospitalised cohort for SoC and remdesivir by oxygen requirement at entry

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.

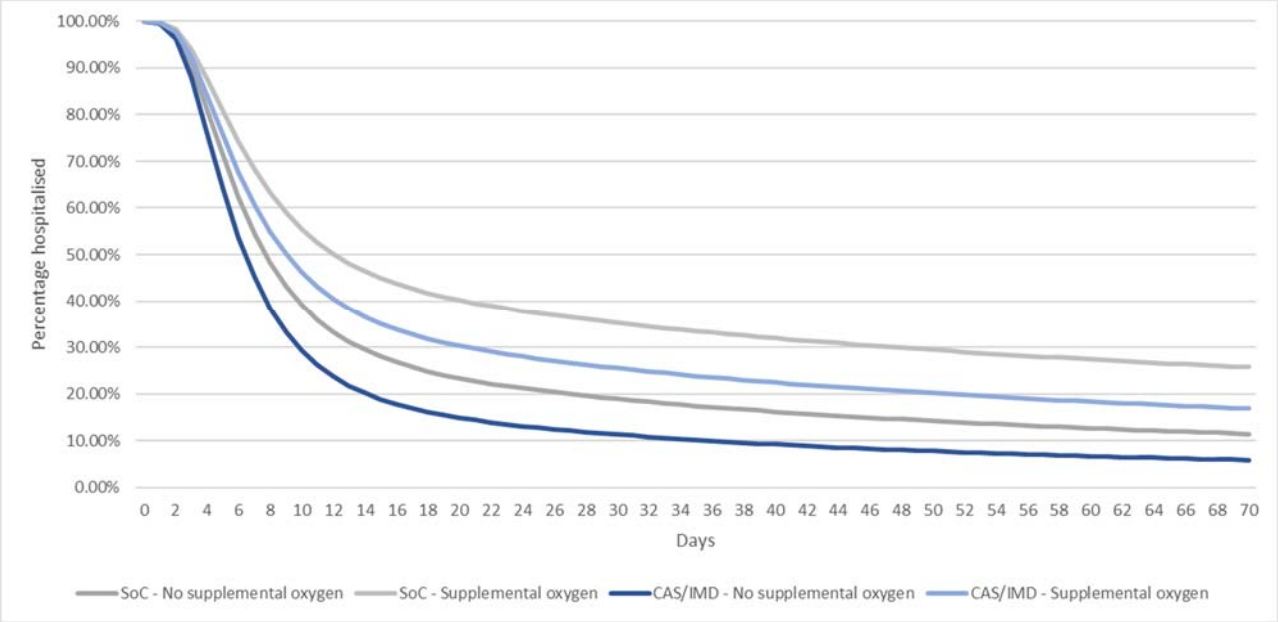

Figure 14: Illustration of time to discharge curves used for the hospitalised cohort for SoC and casirivimab/imdevimab by oxygen requirement at entry

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.

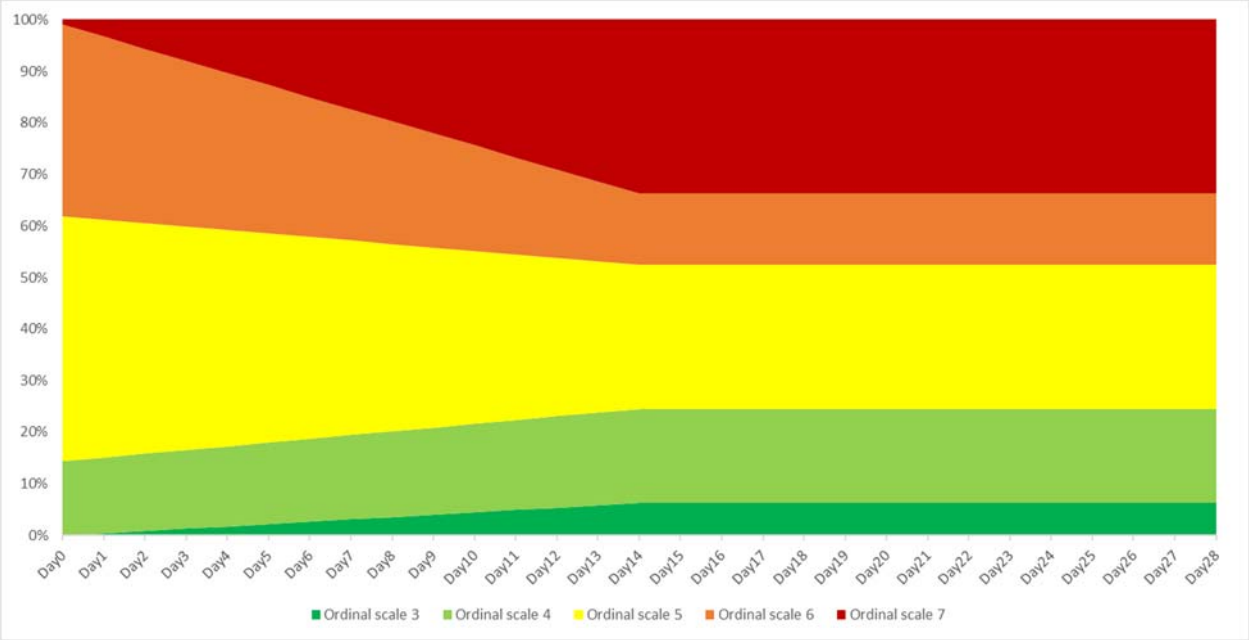

Figure 15: Linear assumptions for distribution across the five ordinal scales during hospital stay

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.

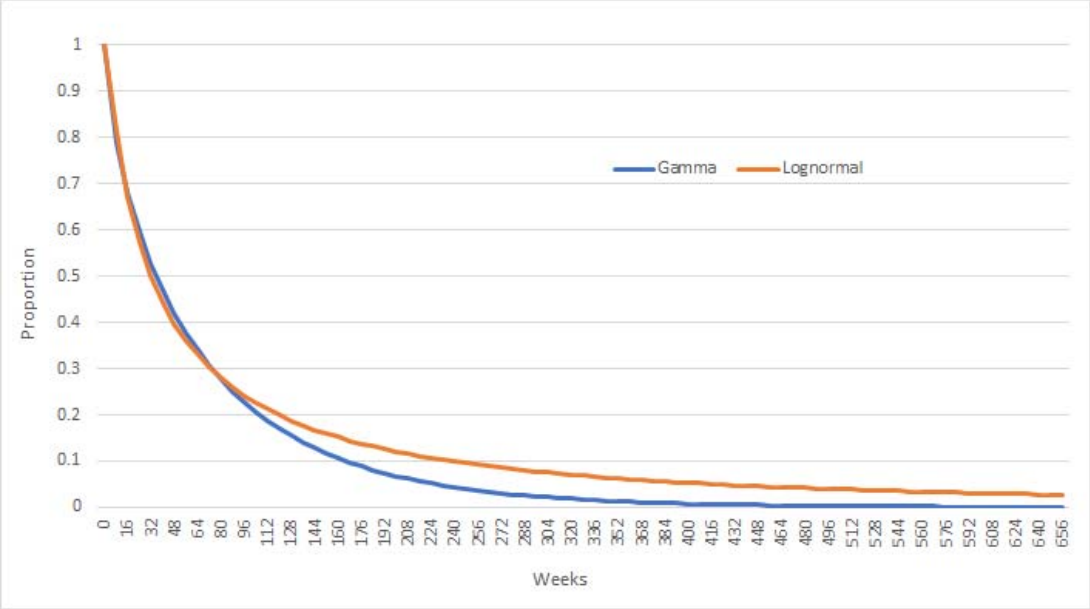

Figure 16: Assumed duration of long Covid

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.

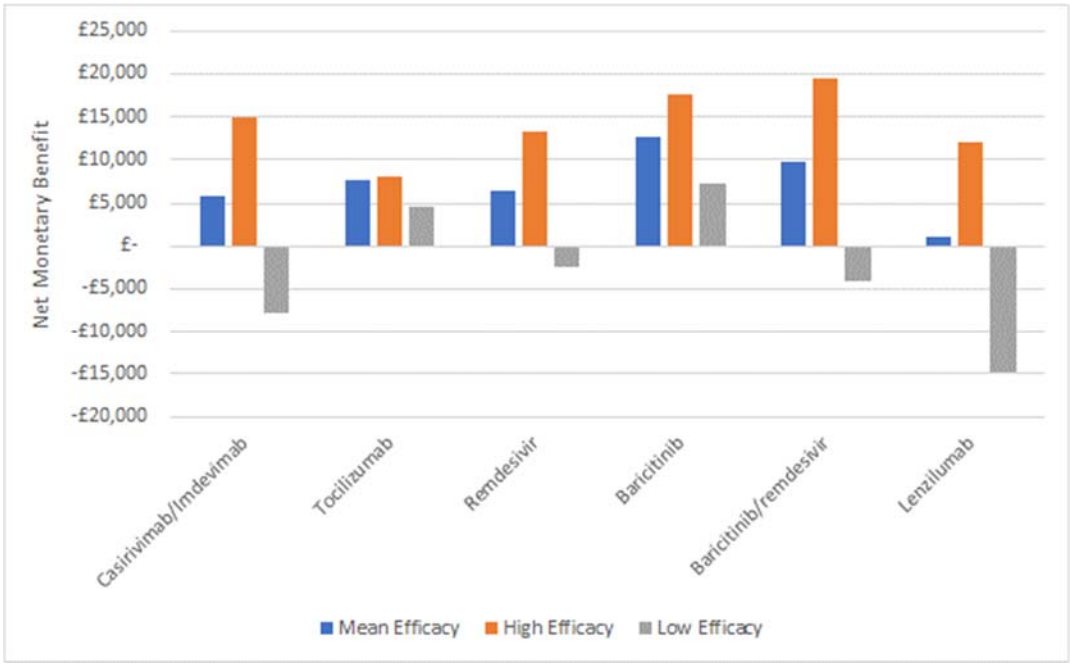

Figure 17: Base case net monetary benefits for patients admitted to hospital who require supplemental oxygen

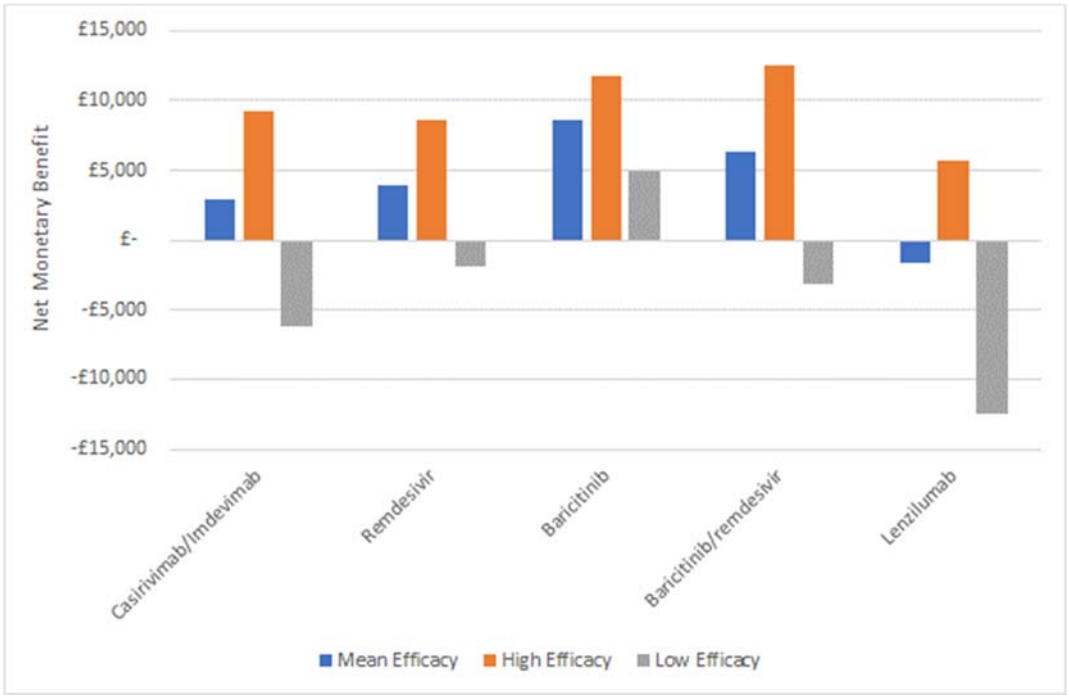

Figure 18: Base case net monetary benefits for patients admitted to hospital who do not require supplemental oxygen

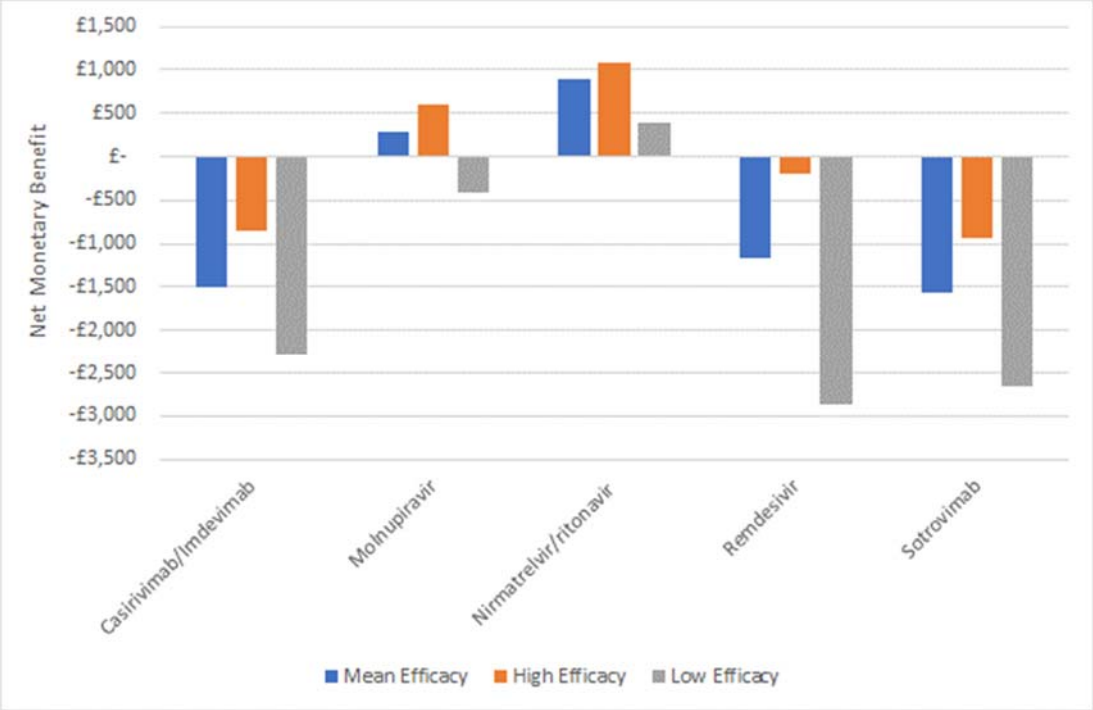

Figure 19: Base case net monetary benefits for patients with COVID-19 in the community and high-risk of hospitalisation

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.

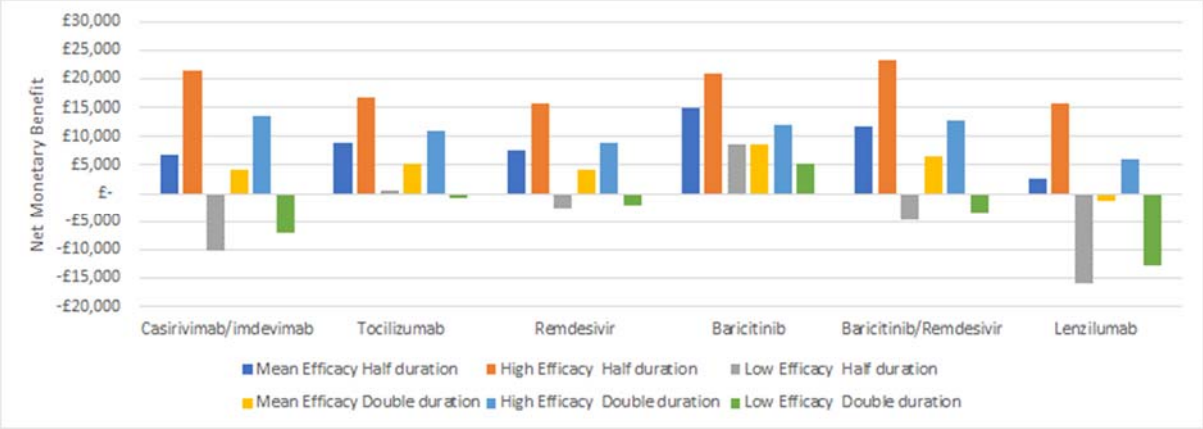

Figure 20: **The NMB results for patients admitted to hospital who require supplemental oxygen when the duration of long COVID is halved and doubled**

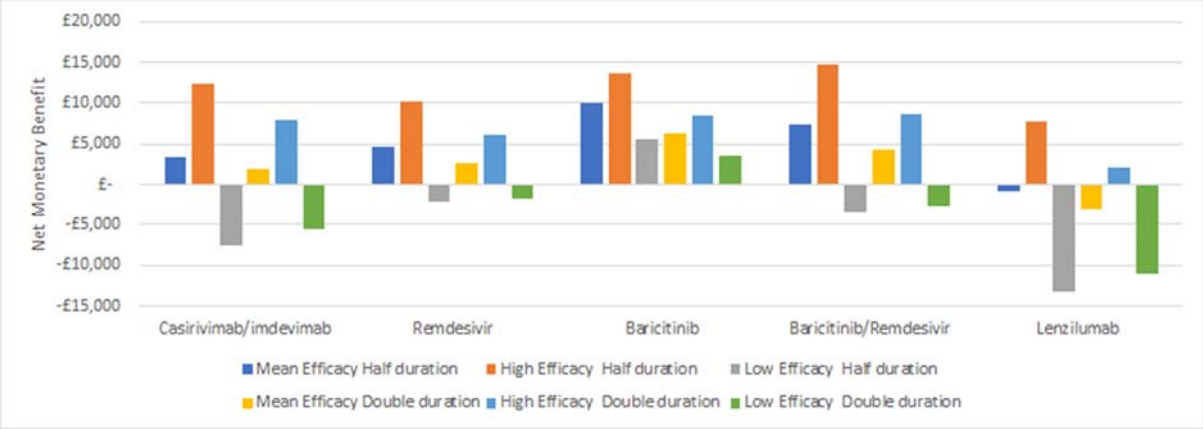

Figure 21: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the duration of long COVID is halved and doubled**

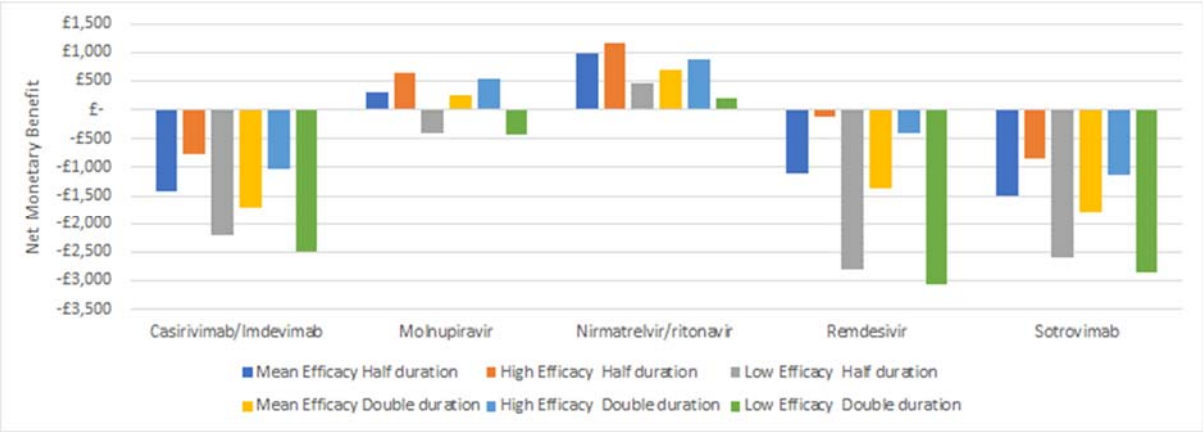

Figure 22: **The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the duration of long COVID is halved and doubled**

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.

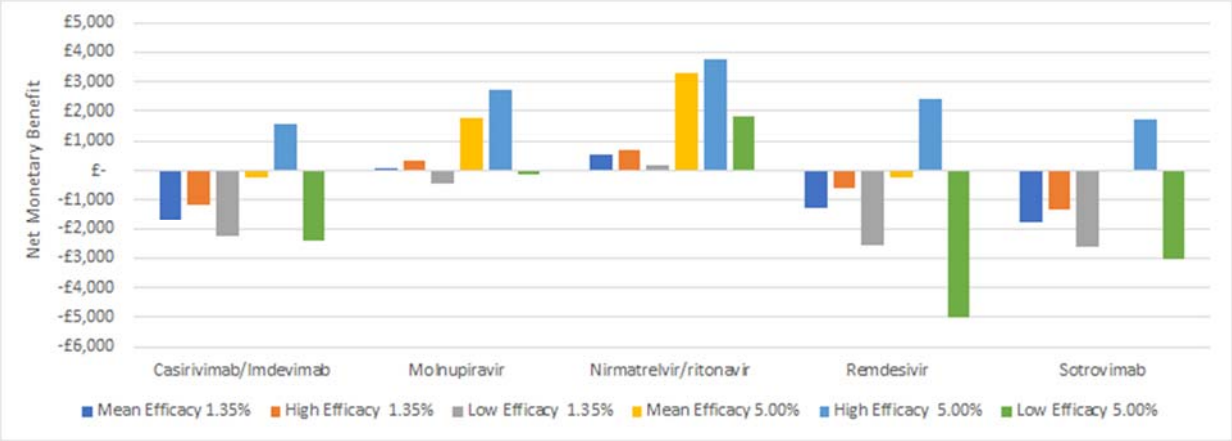

Figure 23: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the hospital admission percentage was changed

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.

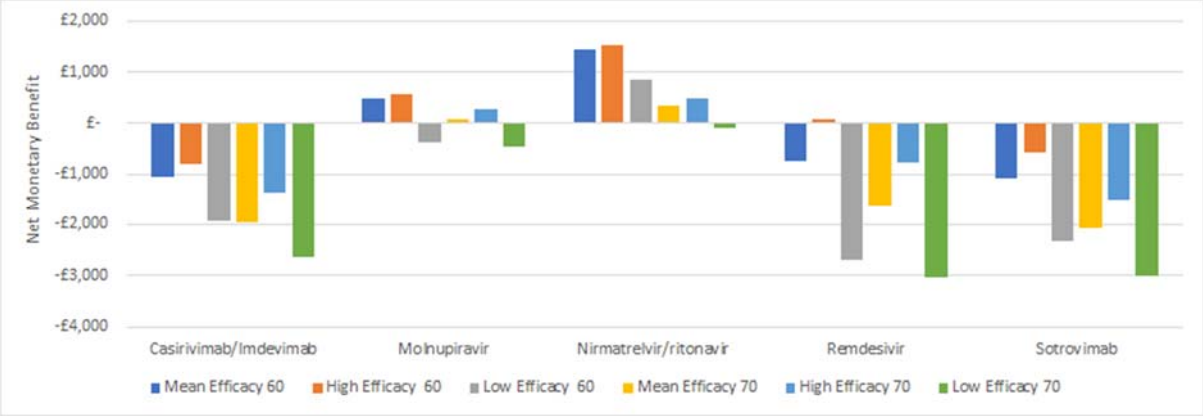

Figure 24: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the age was changed from 65 years to 60 years and 70 years

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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Andrew Metry (https://orcid.org/0000-0001-7412-6093) is a Research Associate at ScHARR, University of Sheffield. He was involved in all aspects of the project.

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All authors commented on the final monograph

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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