NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Therapeutics for people with COVID-19 [ID4038]

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Therapeutics for people with COVID-19 [ID4038]

Response to consultee, commentator and public comments on the Draft Guidance

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the draft guidance (DG; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final draft guidance (FDG).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the DG (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FDG and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the DG when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees (Company)

Comment number	Organisation name	Stakeholder comment	NICE Response
1	AstraZeneca (Comment 1)	**a) AstraZeneca consider that Evusheld should be positioned in a subgroup of its licensed indication where the highest unmet need exists** In response to consultation, AstraZeneca are seeking a recommendation for a specific target population within Evusheld's marketing authorisation. The target population would be for: The treatment of COVID-19 within five days from symptom onset in adults who: 1. Do not require supplemental oxygen, and 2. Are at increased risk of progressing to severe COVID-19, as defined by the McInnes report(1), and 3. Are unsuitable for receiving nirmatrelvir plus ritonavir The rationale for seeking reimbursement within this target population is provided below. ***b) There remains a considerable unmet need in patients at high-risk of severe COVID-19 outcomes for whom nirmatrelvir plus ritonavir is unsuitable*** It is important that the Committee thoroughly consider the inequity that currently exists. COVID-19 disproportionately affects high-risk populations, with substantial morbidity, mortality and societal burden.(2,3) Despite a shift in the COVID-19 landscape, patients who are immunocompromised in particular remain at substantial risk of severe COVID-19 resulting in hospitalisation and death. Reports	1a. Comment noted. Based on committee conclusions, tixagevimab plus cilgavimab is not recommended because it is unlikely to be effective at treating COVID-19 and it is not possible to reliably estimate their cost effectiveness. (Please see section 1 in FDG) 1b. Comment noted. Sotrovimab has been recommended for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 in FDG) 1c. Comment noted. At ACM2 the committee noted the clinical evidence for tixagevimab plus cilgavimab offered within 5 days from symptom onset. Taking account of the trial evidence generalisability concerns the committee concluded the clinical effectiveness of tixagevimab plus cilgavimab is highly uncertain in terms of reducing hospitalisation or mortality rates. (Please see section 3.12 to 3.17 in FDG)

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		from different countries show that immunocompromised individuals make up ≥40% of patients who are hospitalised with COVID-19.(2,4,5) Immunocompromised individuals are more likely to be hospitalised or die because of COVID-19, even when fully vaccinated;(6,7) up to 28% of intensive care admissions(8) and 18% of COVID-19–related deaths(5,9) in the UK are in this population. For context, immunocompromised individuals comprise <1% of the UK population. This substantial unmet need is not addressed by the current draft recommendations in the ACD. This is because, despite NICE recommending nirmatrelvir plus ritonavir for routine commissioning(10), a considerable unmet need remains, which could be met by Evusheld. A large proportion of the high-risk patients defined in the McInnes report(1) are unsuitable for treatment with nirmatrelvir plus ritonavir treatment, as it is contraindicated against numerous treatments, including anticancer drugs, antibiotics, and other drugs relied upon by populations defined in the McInnes report(11,12). In addition, contraindication to nirmatrelvir plus ritonavir is well documented in the literature.(13–16) This was acknowledged by patients and clinicians during consultation and in the ACD: *"There are many contraindications for nirmatrelvir plus ritonavir, severe renal and hepatic impairment and interactions with many common treatments" (page 19, ACD).* *Absence of monoclonal antibodies could give rise to an unmet need because some antivirals (for example nirmatrelvir / ritonavir, molnupiravir and remdesivir) are contraindicated. Some people who are at high-risk may not be offered antivirals because of these contraindications (page 70, committee slides).* Specifically, special warnings and precautions to use nirmatrelvir plus ritonavir refer to people with liver diseases and human immunodeficiency virus(11,12), two of the vulnerable subgroups defined in the McInnes report(1). Therefore, Evusheld would provide a valuable treatment option for patients who are unsuitable for nirmatrelvir plus ritonavir in a high-risk population.	

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		The potential for rebound infection with nirmatrelvir plus ritonavir suggests Evusheld would provide clinicians and patients with an important treatment option The Centers for Disease Control and Prevention issued a Health Alert Network Health Advisory to inform the public that patients treated with nirmatrelvir plus ritonavir have the potential for recurrence of COVID-19 (or COVID-19 rebound), which can occur 2 to 8 days after initial recovery.(17) Whilst information is still being collected, a recent retrospective cohort study comprising 13,644 adults in the US who contracted COVID-19 found that COVID-19 rebound was most common in people with underlying medical conditions who had been treated with nirmatrelvir plus ritonavir and molnupiravir.(18) Evusheld would provide an important option to people experiencing COVID-19 rebound, and for whom further treatment with nirmatrelvir plus ritonavir may not be suitable. ***c) Evusheld is more clinically effective and cost-effective when used within 5 days from symptom onset*** Though the license for Evusheld states that treatment should be given within 7 days of the onset of symptoms of COVID-19, the clinical effectiveness of Evusheld in protecting people from severe COVID-19 or death is greater when treatment is given within a shorter duration of time from symptom onset, as evidenced in **Error! Reference source not found.**. In relation to the 5-day results, it is worth noting that the clinical effectiveness of Evusheld is well understood. TACKLE was powered to detect significant differences in response to exposure to Evusheld vs placebo at 5 days. The 5-day analysis indicated that 62% of all patients that received Evusheld within the 7-day indicated treatment period, did in fact receive Evusheld within 5 days. The importance of rapidly providing treatment to patients is also well known, as reflected in the interim clinical commissioning policy for antivirals or neutralising monoclonal antibodies for non-hospitalised patients with COVID-19(10), where treatment within 5 days is an eligibility criteria for all included antivirals and monoclonal antibodies	

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		Therefore, selecting 5 days as a treatment cut-off for Evusheld aligns with how clinicians would seek to use Evusheld in clinical practice, would align with the cut-off used for all other oral anti-virals and monoclonal antibodies currently used in clinical practice, and given its improved clinical effectiveness, would represent a more cost-effective use of treatment for the NHS. **See** Error! Reference source not found. **in AstraZeneca DG consultation comments: Severe COVID-19 or death from any cause up to day 29 after receiving Evusheld: modified full analysis set Montgomery et al. 2022**(19) To conclude, Evusheld should be positioned as a treatment option given within 5 days of treatment onset for patients who are unsuitable for nirmatrelvir plus ritonavir. This would provide an important treatment for a vulnerable and severely underserved patient population, who according to the NICE ACD will have no treatment options available to protect them.	
2	AstraZeneca (Comment 2)	**a) It is not appropriate to assume and apply a class effect to Evusheld based on other neutralising monoclonal antibodies. In addition, treatment options outside of antivirals are essential now and for the future.** The ACD notes the clinical effectiveness of Evusheld in three specific places: *"It is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (all neutralising monoclonal antibodies) are effective against the Omicron variant." (page 5)* *"The committee noted the WHO's and FDA's strong recommendations against using casirivimab plus imdevimab and sotrovimab for the Omicron variant. It also noted in vitro evidence suggesting that tixagevimab plus cilgavimab lacks clinical effectiveness against the dominant circulating Omicron BA.5 subvariant (Focosi et al. 2022)." (page 18)* *"The WHO's recommendations against the use of casirivimab plus imdevimab and sotrovimab were reasonable. Based on similar evidence suggesting reduced neutralisation effect against new variants, the committee considered it reasonable*	2a. Comment noted. The committee considered 'Generalisability of trial evidence to current endemic context' and the individual treatment effects of the technologies being evaluated including for tixagevimab plus cilgavimab. 2a and b Comment noted. The committee also considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert

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		to extend the likelihood of reduced efficacy to tixagevimab plus cilgavimab." (page 19) All three statements appear to evaluate the clinical effectiveness of Evusheld, alongside two other neutralizing antibodies (casirivimab plus imdevimab and sotrovimab). Specifically, the third statement suggests that recommendations made by the WHO for casirivimab plus imdevimab and sotrovimab can be reasonably extended to Evusheld to suggest reduced efficacy against the Omicron variant, based on a similar evidence base. However, the presumption that such an extension can be made is without merit and in complete contrast to decisions made by regulators and competent authorities across the globe, including the MHRA. It is also in contrast with the mechanistic properties of Evusheld, while its well documented neutralizing activity contradicts the conclusions made by Focosi et al 2022. In fact, these statements demonstrate the need for alternative treatments outside antivirals**.** **Regulatory bodies support the continued use of Evusheld against Omicron** Whilst AstraZeneca acknowledge that the WHO and FDA recommends against the use of casirivimab plus imdevimab and sotrovimab, these recommendations were not extended to Evusheld. Specifically: • The FDA recommends the continued use of Evusheld at 600mg (20), and in October 2022 during which time Omicron BA.4 and BA.5 are predominant, affirmed that whilst there is evidence to suggest that Evusheld does not neutralise some specific variants "*Evusheld still offers protection against many of the currently circulating variants and may offer protection against future variants.*"(21). • The MHRA and EMA recommend the use of Evusheld treatment at 600mg, and state that "*Due to the observed decrease in in-vitro neutralisation activity against the Omicron subvariants BA.1, BA.1.1, BA.4 and BA.5 the duration of protection of Evusheld for these subvariants is currently not known*."(22,23)	advisory group' commissioned by NICE. (Please see section 3.12 to 3.17 in the FDG) Please note the MTA [ID4038] is evaluating tixagevimab plus cilgavimab within its current marketing authorisation in Great Britain for treatment of COVID-19. A separate appraisal [ID6136] is evaluating tixagevimab plus cilgavimab within its current marketing authorisation for prophylactic use against COVID-19.

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		• The WHO does not provide a recommendation with respect to Evusheld, positive or negative.(24) Given that regulatory bodies, who have considered the entire evidence base for Evusheld in their decision, continue to recommend the use of Evusheld in an environment where Omicron variants are predominantly circulating, we are unclear why NICE could decide it is therefore reasonable to "extend" the likelihood of reduced efficacy with Evusheld based on a single study by Focussi et al 2022, which has significant methodological limitations (see Issue 4). ***The unique combination and synergistic effect of Evusheld has not been considered*** The committee refers to one study (Focosi et al. 2022(25)) which suggests that Evusheld has less than desirable clinical efficacy against currently predominating subvariants Omicron BA.4/5. However, this study has significant methodological limitations (see Issue 4) and does not seem to consider the combination effect that is attainable in using two neutralising monoclonal antibodies in combination. AstraZeneca originally developed Evusheld as a combination of two antibodies capable of acting synergistically *in-vitro* to 3-fold higher potency than individual monoclonal potencies; with a combined dose of 79 ng/mL [16 ng/mL of cilgavimab and 63 ng/mL of tixagevimab] having the same activity as 250 ng/mL of each individual antibody alone.(26) Each antibody is highly potent on its own, but in a situation where the activity of one is significantly reduced, the potential exists for the other antibody to provide the required cover to neutralize the virus. In the case of BA.2, BA.4, and BA.5, where one of the antibodies appears to have lost neutralizing activity, the other antibody remains able to potently neutralize the virus. This is because the activity of each antibody is not dependent on the other. This also enables prevention against potential viral evolution in the case where one antibody is less active against a certain variant. Therefore, the potential exists for the Evusheld antibody combination to be better than either of the two alone. (27) A recent publication has shown that where tixagevimab has reported reduced efficacy against BA.4/5 and cilgavimab has shown reduced efficacy against BA1.1, the combination of tixagecimab and	

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		cilgavimab has continued to demonstrate neutralization activity, and has consistently shown neutralizing activity against variants of concern. (27) Should both combination antibodies demonstrate neutralizing ability, then the potential for significant synergy exist. Support for the concept of the synergy between tixagevimab and cilgavimab can be drawn from the BA.1 and BA.2 variants. Against these variants the IC_{50} for each antibody is substantially higher than the combination of both, even though the overall activity was reduced compared to the original SARS-CoV-2 strain.(28)(29) Despite the reduction in *in-vitro* neutralizing activity, Evusheld has been shown to be effective in preventing symptomatic and severe COVID-19 throughout the BA.1 and BA.2 waves (See Comment 2). These traits along with the long-acting benefit are unique characteristics of Evusheld compared with other monoclonal antibodies. Furthermore, the synergistic effects observed in real-world evidence contradict the conclusions made by Focosi et al. 2022, and AstraZeneca would reaffirm that Evusheld's mechanism of action, regulatory recommendations, and clinical evidence base should be evaluated on its own merits. ***b) Evusheld as a monoclonal antibody would provide those who need it the most with an important additional layer of protection during an evolving landscape*** The wording used in the ACD implies that there is a single Omicron variant, which is not the case. Monoclonal antibodies with reduced effectiveness against one subvariant have "recovered" their effectiveness against other, later subvariants, demonstrating that loss of clinical effectiveness is not linear. For example, for tixagevimab plus cilgavimab, a recent review of live virus in vitro neutralisation studies demonstrated that although this combination had reduced effectiveness against the original Omicron B.1.1.529 variant (range of half maximal inhibitory concentration [IC50] values: 147–6400 ng/mL), BA.1 subvariant (167–773 ng/mL) and BA.1.1 subvariant (1297–8090 ng/mL) compared with wild-type viruses (2.1–35 ng/mL), effectiveness was regained against the BA.2 (8.2–113 ng/mL), BA.3 (19–95 ng/mL), and BA.4 and BA.5 (38–224 ng/mL) subvariants.(30) Further to this, the example of casirivimab plus imdevimab is also of interest whereby this medicine was not effective against Omicron BA.1 variant but was subsequently able	

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		to neutralize Omicron BA.2, BA.2.12.2, BA.4, and BA.5 variants.(31) Again supporting the assertion that there is no single omicron variant and effectiveness between the variants is not linear. In the UK, there are currently several variants in circulation,(32) and in a scenario where one antibody treatment loses effectiveness against one variant, it is therefore likely that other antibody treatments will remain effective.(33) The more monoclonal antibodies that are approved and available for patient use, the better placed the UK is to respond to changes in what is a very dynamic clinical situation. Furthermore, as recently noted in a response to the UK government from several oncologists in Lee et al.(33), antibody treatments are not a "*magic wand*", but could provide considerable protection for the most vulnerable in our community. Evusheld would serve as an important additional layer of protection for the severely exposed high-risk patients who cannot confer protection from nirmatrelvir plus ritonavir. Considering the plethora of circulating variants, the effectiveness of antiviral and antibody treatment is likely to evolve and vary over time, which is an issue for all treatments recommended by NICE as part of this MTA. Emphasis on decision making to consider the predominant variant at that moment in time may confer numerous re-evaluations when other variants become predominant in the future. Evusheld will provide an important extra layer of protection in a dynamic and unpredictable disease landscape, and clinicians are unlikely to use any treatment that they deem ineffective based on what may or may not be circulating in the future.(33) The response in Lee et al.,(33) published in November 2022, also states: *"Ultimately, the benefit of prophylactic antibody treatments must be based on published and peer reviewed evidence from human studies and not crystal ball gazing on what might come next."* This approach has been well adopted by regulators internationally, which continue to recommend the use of Evusheld today, given the significant clinical evidence that	

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		exists in human studies for Evusheld during Omicron (see Issue 3) and the limitations in relying solely on non-human in-vitro data for decision making. To conclude, it has been demonstrated that the clinical effectiveness of Evusheld cannot be generalised across the neutralising monoclonal antibody class, and the availability of additional treatment options outside of antivirals are essential now and for the future.	
3	AstraZeneca (Comment 3)	**Clinical evidence in human studies show that Evusheld is clinically effective against the Omicron variant (including BA.4/5)** The ACD concludes that the clinical effectiveness of Evusheld against the Omicron variant is highly uncertain: *"There is some clinical evidence suggesting that baricitinib, molnupiravir, nirmatrelvir plus ritonavir, remdesivir and tocilizumab are effective at treating COVID-19. But, it is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (all neutralising monoclonal antibodies) are effective against the Omicron variant." (page 5)* The Company appreciates that for most monoclonal antibodies, clinical efficacy demonstrated in phase 3 treatment trials predates Omicron. For casirivimab plus imdevimab, efficacy was demonstrated in a phase 3 clinical trial (NCT04425629), with a 71.3% relative risk reduction (RRR) of COVID-19–related hospitalisation or all-cause death.(34) The COMET-ICE study of sotrovimab demonstrated 85% RRR of COVID-19 progression leading to hospitalisation or death.(35) The TACKLE clinical study of tixagevimab plus cilgavimab showed a 66.9% RRR in the endpoint of severe COVID-19 or all-cause death in patients where time from symptom onset to randomization was ≤5 days.(19) However, there is a substantial body of clinical evidence in real-world settings which demonstrates that Evusheld is consistently, highly clinically effective against the Omicron variant. See Appendix A for full details of these studies, which appears to have been overlooked by NICE and the EAG in their evaluations of clinical effectiveness. Furthermore, of all human controlled studies that have been conducted for Evusheld across alpha, beta, delta, and Omicron variants and subvariants, the results have	3. Comment noted. Please see responses to your previous comment #1c and #2a-b The recommendations for molnupiravir have been revised. Please see section 1 of FDG. The committee also cautioned against solely relying on non-randomised evidence when making conclusions on treatment effect. Please see section 3.11 of FDG.

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		been consistent and conclusive: Evusheld has been shown to significantly reduce COVID-19 infections, hospitalisations and death. No human controlled studies have reported otherwise. On the other hand, molnupiravir, despite being deemed by NICE to have "some clinical efficacy for treating COVID-19", has been shown to have no effect on reducing the risk of hospitalisations or deaths among higher risk, vaccinated adults with COVID-19, during a time period with predominantly Omicron strains circulating.(36) In addition, a study which compared molnupiravir and sotrovimab during a period when Omicron was circulating found sotrovimab to be more efficacious than molnupravir.(36) We urge NICE to consider all available clinical evidence for Evusheld during Omicron waves, as summarised below, in their decision making. ***Summary of evidence demonstrating Evusheld effectiveness against severe and fatal COVID-19 outcomes during Omicron predominant waves*** A recently published retrospective study in France evaluated early treatment with tixagevimab plus cilgavimab 300 mg/300 mg following COVID-19 infection in adult kidney transplant recipients at high risk of COVID-19 during Omicron and demonstrated a reduction in hospitalisations due to COVID-19 (3.8% vs 34%, P=0.006) and oxygen need (3.8% vs 23%, P=0.04) compared to no treatment. Similar but non-significant trends were observed for intensive care unit (ICU) admissions (3.8% vs 14.3%, P=0.17) and mortality (0 vs 3, P=0.13).(37) Furthermore, there are five further real-world evidence studies which consistently demonstrate the continued efficacy of Evusheld as prophylaxis during Omicron. A recent systematic literature review(38) provided an updated summary of the real-world clinical evidence of Evusheld conducted during Omicron predominant waves. The review concluded that Evusheld is effective in reducing hospitalisation, ITU admission and mortality, during the Omicron wave. The review focused on Evusheld as prophylaxis, but since the mechanism of action is identical, results can be generalised to the treatment setting. Furthermore, the outcomes of hospitalisation, ITU admission and mortality are highly relevant to the treatment setting.	

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		Out of the 17 identified studies, six reported controlled effectiveness comparisons, of which the five outlined below took place during Omicron waves. ***Young-Xu et al. 2022***(39) • Retrospective observational study comparing Evusheld 600 mg and 300 mg (n=1,733) with a control group (n=251,756). • Population considered US veterans (aged ≥18 years), immunocompromised or otherwise at high risk for COVID-19. • Dominating variants were BA.1, BA.2, and BA.2.12.1. • COVID-19 vaccination was received in 95% of patients. • Propensity-score matched study undertaken, which matched Evusheld (n=1,733) to the control (n=6,354 post matching). ***Al Jurdi et al. 2022***(40) • Retrospective cohort study comparing Evusheld 300 mg, 600 mg, and 900 mg (n=222) in vaccinated solid organ transplant recipients to age-matched, vaccinated solid organ transplant recipients (n=222). • Population considered US kidney, liver, and lung transplant recipients. • Dominating strains were BA.1.1.529, BA.2 and BA.2.12.1. • The patient population was focused on vaccinated patients. ***Kertes et al. 2022***(41) • Large retrospective study in members of the of the Maccabi HealthCare Services in Israel which compared Evusheld 300mg (n=825) to unmatched controls (n=4,299).	

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		• Population considered severely immunocompromised patients aged 12 and over. • Dominating strains were BA.1 and BA.2. • The majority were vaccinated. In the Evusheld group, 98.8% had received at least 1 vaccine dose and 91.3% had received 3–4 doses. In the control group, 88.0% had received at least one vaccine dose, and 76.3% 3–4 doses. ***Kaminski et al. 2022***(42) • Retrospective study comparing Evusheld 300 mg (n=333) to controls (n=97). • The population reflected kidney transplant recipients from Bordeaux University Hospital in France with no or low response to COVID-19 vaccines. • Dominating strains were BA.1 and BA.2. ***Chen et al. 2022***(43) • Comparison before and after receiving Evusheld in n=1,295 patients. • Patients received treatment at the University of California San Diego's Health System in the US, a quaternary referral centre, serving many patients who require complex subspecialty care. • Dominating strains were BA.1, BA.1.1, BA.2.12 and BA.5. • The majority were vaccinated. Of the 121 patients who developed COVID-19 infection prior to receipt of Evusheld, 84.3% had received at least one dose, 57.0% had received 3–4 doses. The corresponding figures for those who had COVID-19 infection following receipt of Evusheld was 97% and 72.2% respectively.	

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		The clinical effectiveness results from the studies listed above, are presented in See Figure **1**. Evusheld significantly reduced the risk of: • COVID-19 hospitalisation by 69.23% • Intensive therapy unit admission by 87.89%, • All-cause mortality by 81.29%, and • COVID-19-specific mortality by 86.36%, compared to no treatment.(38) **See Figure 1 in AstraZeneca DG consultation comments: Clinical effectiveness of Evusheld against breakthrough COVID-19 infection, hospitalisation, intensive care unit admission, mortality, and COVID-19 specific mortality Source:** Suribhatla et al. 2022 (38)  In conclusion, all available clinical evidence for Evusheld conducted in humans during the Omicron waves (including BA.4/5) demonstrates that Evusheld is consistently, highly clinically effective as a treatment or prophylactic against the Omicron variant and its subvariants. There is no evidence in human clinical studies to suggest otherwise. This additional evidence, in combination with the primary evidence base for Evusheld as a treatment for COVID-19 (i.e the TACKLE study),	

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		demonstrates that Evusheld is an effective treatment for COVID-19 against the Omicron variant (including BA.4/5).	
4	AstraZeneca (Comment 4)	**There is clear evidence that *in-vitro* neutralisation data alone cannot be used to determine whether a treatment will be effective or ineffective in clinical practice** The ACD appears to conclude that *in*-vitro evidence is robust enough to conclude that Evusheld may lack clinical effectiveness against the Omicron variant: "In-vitro evidence suggest[s] that tixagevimab plus cilgavimab lacks clinical effectiveness against the dominant circulating Omicron BA.5 subvariant (Focosi et al. 2022)." However, there is a clear body of evidence for Evusheld, which indicates that *in-vitro* neutralisation data cannot predict whether a treatment will be effective in clinical practice. ***There is no defined threshold for determining treatment ineffectiveness based on in-vitro neutralising activity.*** Given the speed at which COVID-19 variants can appear and become dominant, robust *in-vitro* studies are an important contributor to any therapeutic decision-making process because they can be completed relatively quickly compared with clinical trials and real-world studies. As such, conclusions regarding the effectiveness of monoclonal antibodies have been made based on half maximal inhibitory (IC_{50}) or effective (EC_{50}) concentration results from *in-vitro* neutralisation assays. However, the Company warns against over-reliance on this type of data for several reasons as described in this response. Although higher IC_{50}/EC_{50} values make it more possible that real-world effectiveness of a monoclonal antibody will be reduced, there is yet no agreed threshold for determining when a treatment is deemed ineffective based on *in-vitro* neutralising activity alone.	4. Comment noted. Please see responses to your previous comment #1c and #2a-b

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		Real-world evidence demonstrates statistically significant Evusheld effectiveness in variants where in-vitro analyses have shown limited neutralisation activity While there is no agreed or known published correlate for determining when a treatment is deemed ineffective based on neutralising activity, it is known that the higher the IC_{50} values the more likely that efficacy may be reduced. Despite this, even in variants with the greatest IC_{50} values i.e., BA.1 and BA.1.1, real-world evidence has continued to demonstrate a statistically significant and clinically meaningful reduction in the risk of developing symptomatic COVID-19 and hospitalisation and/or death. Evusheld has demonstrated clinical effectiveness against BA. 1 and BA.1.1, since real-world evidence covering BA.1 and BA1.1 (see Issue 3) demonstrates that Evusheld is statistically significant, with large magnitudes of effect, in reducing infections, hospitalisations, ICU admissions, and death. *In-vitro* live virus neutralisation data for these subvariants, suggest high IC_{50} values of [redacted] ng/ml for [redacted] respectively.(44,45,27) Therefore, Evusheld is expected to be clinically effective against any variant (BA.1, BA.2, BA.4/5) with an IC_{50} below [redacted] ng/ml (44,45,27). This however does not suggest clinical ineffectiveness for any IC_{50} beyond [redacted] ng/ml but one can conservatively infer real-world efficacy against emerging variants of concern: those that are neutralised to the same extent as, or even better than, [redacted] (numerically, a lower IC_{50}) would be expected to remain effective.(31) ***Fucossi et al. 2022, used as the basis for NICE's decision making for Evusheld's clinical effectiveness against Omicron has significant methodological limitations; in-vitro neutralisation results and interpretation differ considerably across studies*** Summarising data on reduction in monoclonal antibody neutralising activity against different Omicron subvariants clearly shows highly disparate results from different analyses of the same monoclonal antibody (See Figure **2**).(46)	

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		• The assays used are not well standardised technically,(33,47) sometimes using cell lines which have been shown to be inappropriate for assaying certain classes of monoclonal antibodies.(31) • An important, but not often acknowledged, limitation of many *in-vitro* studies is the range of antibody concentrations tested, which are often lower than the average maximum serum concentrations.(48) • In addition, there is a lack of standardisation regarding interpretation of results; for example, two different studies of tixagevimab plus cilgavimab against BA.5 described similar reductions in effectiveness (30.7-fold reduction in inhibition against BA.5(49) versus 21-fold reduction against BA.4/5(25)), yet the conclusions were different: the first study concluded that tixagevimab plus cilgavimab retained some neutralising activity, while the second stated that efficacy was lost. **See Figure 2 in AstraZeneca DG consultation comments: Fold reduction in neutralising activity of tixagevimab plus cilgavimab against SARS-CoV-2 VoCs vs ancestral/reference strains** **Abbreviations:** SARS-CoV-2 – Severe acute respiratory syndrome; VoCs – Variants of concern **Source:** National Center for Advancing Translational Services OpenData (50) When interpreting in-vitro neutralisation data of antibodies against COVID-19, it is vital to also critically appraise the technical methodologies used to draw any conclusions before inferring the likely impact on efficacy. This comment is particularly evident in the case for the conclusions drawn in Focosi et al., 2022, which have significant methodological limitations, and so AstraZeneca assert that these analyses do not provide evidence that tixagevimab plus cilgavimab lacks clinical effectiveness against Omicron BA.5. Focosi et al. 2022 make the following claim in their article that is not supported by the evidence they cite: *"…while the tixagevimab component has been ineffective against any Omicron sublineage so far (BA.1, BA.2, and BA.4/BA.5), the cilgavimab*	

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		component is ineffective against BA.1 and BA.4/BA.5 but has preserved efficacy against BA.2." Only Aggarwal et al.(51) supports their claim that cilgavimab is ineffective against BA.1, specifically B.1.1.529. Articles by Cao et al.,(52) Planas et al.,(53) Liu et al.,(54) VanBlargan et al.,(55) and Touret et al.(56) all report reduced—but not complete loss of—neutralising activity against BA.1 by cilgavimab. Similarly, Yamasoba et al.(57) reports reduced but not complete loss of neutralising activity against BA.4 and BA.5. Kimura et al.(58) is incorrectly cited by Focosi and Tucori as it reports the results of Yamasoba et al.,(57) not the results of separate analyses. The loss of neutralizing activity against BA.4 and BA.5 is also contrary to results reported elsewhere by Cao et al.,(59) which show cilgavimab effectively neutralizes BA.4 and BA.5 in vitro. These conflicting results are likely due to most laboratories cited by Focosi et al. used techniques with ACE2-overexpressing cells, despite such methods previously showing a clear lack of neutralisation of SARS-CoV-2 by certain classes of monoclonal antibodies, yet clinical efficacy has been retained.(31) At a fundamental level, comparison of in-vitro data across laboratories is hampered by the use of different cell lines that may be infected by SARS-CoV-2 variants to different extents. A more robust in-vitro assay method utilised by the Francis Crick Institute's COVID surveillance unit (Wu et al. 2022 (31) has recently concluded that, counter to the conclusions of other reports, sotrovimab, imdevimab, and cilgavimab were able to neutralise BA.2, BA.2.12.1, BA.4 and BA.5, dominant variants of concern circulating in the UK at the time of the analysis. In addition to presenting EC_{50} values, the authors of this study also demonstrated that these neutralising values were well below the maximum antibody serum concentrations reported in the Summary of Product Characteristics.(31) The conclusions made by Wu et al are also supported by real-world evidence as discussed in Issue 3. In contrast to the techniques employed in the studies included by Focosi et al., the study by Wu et al. 2022 utilised an assay calibrated with the WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reporting of neutralisation titres in International Units – an assay useful for standardised comparisons of different monoclonal antibodies against various variants.(31,60) Using this assay, the authors calculated IC_{50} values by fitting a four-parameter dose–response curve to	

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		288 independent data points, generated from three independent repeats of 12 independent titrations, each consisting of two technical replicates of a four-point dilution series against live virus variants. Some of the articles cited by Focosi et al, however, evaluated neutralisation using live viruses, others used lentivirus-based pseudoviruses or stomatitis-based lentiviruses. None performed assays to the strict standards of the assay method utilised by the Francis Crick Institute's COVID surveillance unit. In addition to the more rigorous and internationally recognised methodology utilised by Wu et al 2022, the authors also reported confidence intervals, rather than just point estimates. The reporting of confidence intervals is essential to evaluate the significance of any possible changes in neutralisation; particularly when considering IC_{90} values, which lie close to the plateau of the dose–response curve and are inherently noisy, both in cell-based assays and in fitting of a dose–response curve (the methodology utilised by the studies appraised by Focosi, et al. 2022). Furthermore, the study conducted by Wu et al. demonstrated that sotrovimab retained neutralisation activity against some variants in which other non-standardised methodologies reported a lack of neutralisation activity, such as was the case for BA.2. Focosi et al, have therefore not demonstrated that tixagevimab plus cilgavimab lacks clinical effectiveness. They make no attempt to discuss how apparent reduction of in vitro neutralising capacity in non-standardised assays relates to loss of efficacy in real-world clinical settings and present no data to show loss of clinical efficacy. Therefore, the studies reported and appraised by Focosi et al. should be reviewed critically and an appropriate quality control conducted to ensure the rigor and the scientific methodologies employed are appropriate to inform clinical and policy decision making. Moving forward, the use of *in-vitro* neutralising data should consider a more rigorous methodology, aligned with the MHRA's decision making. In conclusion, given the uncertainties, the conflicting nature of *in-vitro* neutralisation results and real-world evidence, it is clear that decision making based on neutralisation data alone is not a robust or sustainable methodology. Furthermore, NICE should consider the robustness of the methodology used and conduct a quality assessment to determine whether it complies with the standards set out by the WHO – in the case of Focosi et al, this does not meet the required standards.	

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5	AstraZeneca (Comment 5)	**In the proposed positioning, the cost-effectiveness of Evusheld should be evaluated against standard of care using the modified full analysis set and considering data within 5 days of symptoms onset.** Since AstraZeneca has revised the positioning of Evusheld to be for patients unsuitable to receive nirmatrelvir plus ritonavir, the only treatment option recommended by NICE in this population is standard of care (i.e. no interventional treatment). As such, Evusheld should be compared to standard of care based on data from the modified full analysis set in the TACKLE study, which considered Evusheld versus placebo. It is unclear why NICE have concluded that it is acceptable to use two different datasets for evaluating the clinical effectiveness of Evusheld in the TACKLE study (randomised set for all cause death and the modified full analysis set for hospitalization or death) as part of the economic analysis. Note that the randomised set also included patients that did not receive treatment. AstraZeneca would hope that NICE recommend a consistent approach is used for the data considered as part of the economic analysis. This should align with that of the primary efficacy analysis for which regulatory approvals have been granted, and as such the modified full analysis set should be used for the purposes of economic modelling. Furthermore, the modified full analysis set excluded 43 patients in the Evusheld and 33 in placebo group who were hospitalised at baseline for isolation purposes (in Japan and Russia), or were randomly assigned study drug after 7 days of symptom onset. Therefore, the modified full analysis set is representative of the population, and therefore the outcomes, of people who would be expected to receive treatment in the UK. Additionally, as already noted in AstraZeneca's response to the MTA Assessment Group report, and by the Assessment Group itself, the COVID-NMA utilised by NICE is flawed in several ways: • The trials included in the analyses were undertaken at different time-points, which given the dynamic nature of COVID-19 renders the disease landscape too dissimilar to allow meaningful comparison.	5. Comment noted. At ACM2 the committee noted the clinical evidence for tixagevimab plus cilgavimab offered within 5 days from symptom onset. Please also see responses to your comment #1.

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		• Similarly, the trials generally compared the intervention to the then-current standard of care, which have varied considerably throughout the pandemic. • The trial designs and reporting of efficacy outcomes also varied substantially – further exacerbating the limitations in any comparison between studies. • There are extensive imbalances between the trial populations, specifically with respect to age, disease severity, vaccination status, history of infection and available treatments in the standard of care arm. AstraZeneca reiterates that assuming none of these differences would be significant effect modifiers is naïve and we stand by our previous concern that these comparisons of treatment effects are substantially confounded and highly uncertain, and therefore inappropriate for decision making. Finally, as noted in Issue 1, our proposed positioning restricts Evusheld to treatment within 5 days from symptom onset. The current preferred economic modelling produced by the EAG utilises treatment data within 7 days of symptom onset for the hospitalisation or death outcome, and all-cause mortality outcome. Therefore, aligned with other interventions included in the MTA, all analyses which include Evusheld should be consistently undertaken using 5-day cut-off data in the economic model; in-line with the optimised positioning in which AstraZeneca is seeking reimbursement. In conclusion, the appropriate comparator for Evusheld in the economic evaluation is standard of care using the modified full analysis set considering data within 5 days of symptoms onset.	
6	AstraZeneca (Comment 6)	**The risk of hospitalisation for the highest-risk population is inconsistent with the most up to date evidence.** The ACD states that: "*The committee acknowledged significant uncertainty in estimating the hospitalisation rate for the population who have high risk of progressing to severe COVID-19. Based on the strength of the evidence it concluded that it was likely to*	6. Comments noted. The committee considered a wide range of hospitalisation rates including the 15.9% by Shields et al. 2022. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort and 4% for people

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		fall between the underestimate of PANORAMIC at 0.77% and the estimate of 2.79% from the interim database analysis." (page 24) AstraZeneca can demonstrate that this range severely underestimates the real-world risk of the patients who would benefit from Evusheld. As already noted in AstraZeneca's response to the MTA Assessment Group report, acknowledged by NICE and the EAG, and confirmed by experts at the ACM, the value of 0.77% sourced from PANORAMIC is an underestimate. "*The clinical experts agreed given the committee's preferred definition of high risk (see section 3.6) that 0.77% could be an underestimation because the highest risk group may have been underrepresented in PANORAMIC*". *(page 24)* The PANORAMIC study is not reflective of the relevant population since it enrolled patients above the age of 50 regardless of comorbidities or lack thereof. Additionally, access to antivirals and neutralising monoclonal antibodies were available at the time of enrolment, meaning McInnes high-risk patients who received treatment were unlikely to have been enrolled. In AstraZeneca's response to the MTA Assessment Group report, we presented a recent study by Shields et al. (61), at that point under peer-review but has now since been published. Shields et al. 2022 assessed the impact of vaccination on hospitalisation and mortality from COVID-19 in patients with primary and secondary immunodeficiency in the UK, which aligns closely with the target population for the submission – as noted in the MTA committee slides on slide 8(62). The study included a cohort of 140 patients infected between January 2021 and March 2022. Study participants represents patients infected after the deployment of vaccination and the routine use of antiviral and monoclonal antibody treatments in inpatient and outpatient settings. Furthermore, the majority of infections occurred later in the pandemic, after patients had received at least two vaccine doses, after the more transmissible B.1.1.529 (Omicron) SARS-CoV-2 variant became dominant, and after legal restrictions on social interactions had been lifted.	contraindicated to nirmatrelvir plus ritonavir. Please see section 3.22 in FDG. Please also see sections 3.4 to 3.7 for the definition of high-risk in the FDG.

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		For patients who were not treated with antivirals or neutralising monoclonal antibodies by the COVID-19 Medicine Delivery Units during the Omicron period, the rate of hospitalisation was reported as 15.9%. We are confused why NICE would not consider this study relevant, or even comment on its applicability in the MTA committee slides or the ACD, but did consider the PANORAMIC study relevant for decision making despite the significant limitations and confounding noted. We would like to reiterate by again underlining the importance of using an appropriate measure for hospitalisation. Given that the underlying risk of hospitalisation is a key driver of the cost-effectiveness, it is crucial that the latest available evidence is used. Shields et al. demonstrates that the currently used value range of 0.77% to 2.79% is a considerable underestimation. This hypothesis is supported when considering evidence presented on page 282 of the Committee papers (Committee papers *Table 1: Literature Review Search Results*), reflecting even higher risks in certain subgroups of the McInnes population, during Omicron dominated periods. The following proportions of patients hospitalised from McInnes populations were identified: • **Chinnadurai et al. 2022**(63) (Haemodialysis): 0.0% • **Parry et al. 2022**(64) (chronic lymphocytic leucaemia): 7.7% - **Gleeson et al. 2022**(65) (immunosuppressed kidney transplant recipients): 20.8% - **Bradwell et al. 2022**(66) (haematological malignancy): 26.4% In addition, a targeted literature review undertaken by AstraZeneca identified three additional sources, reporting crude rates of hospitalisation for COVID-19 positive, predominantly vaccinated high-risk patients during Omicron waves:	

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		• **Ashby et al. 2022**(67) (haemodialysis): Ranging from 16.1% (one vaccine dose) to 9.8% (three vaccine doses) • **Trindade et al. 2022**(68) (lung transplants): 17.9% • **Anjan et al. 2022**(69) (solid organ transplants): 31.9% These reviews clearly show that there are large variations within the McInnes high-risk clinical subgroups, with certain rates as high as >30%(69). This warrants that the economic modelling should at consider a lower bound of 5.48%, as presented on slide 8 in the MTA committee presentation(62), and an upper bound of 15.9%, as evidenced by Shields et al.(61)	
7	AstraZeneca (Comment 7)	**AstraZeneca again reiterates a response to the EAG assessment report, as the mortality assumptions and approach remain counter-intuitive and results in clinically implausible estimates.** The way the model developed by the EAG currently implements all-cause mortality means that patients who receive outpatient treatment and subsequently end up hospitalised, have a much higher risk of inpatient death compared to hospital patients who did not receive treatment. In some low-efficacy scenarios, this leads to 121 times higher inpatient mortality for some treatments compared to standard of care. As a consequence, in the current model, Evusheld is associated with increased all-cause and inpatient mortality compared to standard of care, based on a relative risk of all-cause death at 28 days greater than one (RR=1.18) and a multiplier for Evusheld inpatient mortality of 2.92. This is an implausible assumption which contradicts all available clinical trial data. Phase III, randomised, double-blind, clinical trial TACKLE, which evaluated the efficacy and safety of Evusheld for early outpatient treatment of COVID-19 demonstrated a statistically significant reduction in the relative risk of all-cause mortality compared with placebo; at treatment initiation within five days of symptom onset, the relative risk was 0.33 (95% CI 0.03–3.15).(19)	7. Comment noted. Comment noted. Based on DG consultation comments, the AG updated its assumption and capped the mortality rate to equal 1 for the low-efficacy scenario. Please see section 3.10 of FDG.

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		Therefore, AstraZeneca stands by the view that it is inappropriate for the EAG and NICE to accept this inherently flawed modelling approach, which significantly biases the ICER estimates in favour of standard of care, despite contrary evidence. The assumption that Evusheld is associated with increased all-cause and inpatient mortality is perverse in the context of the robust randomised clinical trial data available. The EAG themselves acknowledge that the assumption is unreasonable (page 36 and 61 of the EAG report): • *"…it may be seen as unlikely that an intervention that causes a statistically significant reduction in the composite endpoint of hospitalisation or death would cause an increase in the number of deaths…" and* • *"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."* AstraZeneca appreciates the time-limitation, but it is not reasonable that this should be allowed to impact the robustness of the assessment. We are furthermore surprised that this comment made during AstraZeneca's response to the EAG report was not even discussed during the committee meeting, or raised in the ACD. As a solution to the modelling issue, we suggested that the inpatient mortality multiplier be set to 1.0 for all treatments, which in the case of Evusheld still biases in favour of standard of care in light of the available evidence – but not to the extent currently modelled. This should be implemented moving forwards, and while not an optimal solution (such as using the actual robust and peer reviewed clinical trial data), would at least remove the unreasonable assumption that a statistically significant reduction in all-cause death and all-cause hospitalisation or death would translate to an increased risk of death.	

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8	AstraZeneca (Comment 8)	In See Table **1** below we have reproduced the base case ICER as per the MTA report and the analysis presented by the EAG for reference. **See Table 1 in AstraZeneca DG consultation comments: EAG base case** AstraZeneca has proposed that Evusheld be restricted to a population where nirmatrelvir plus ritonavir is unsuitable, and treatment is administered within 5 days of symptom onset. We maintain that in this positioning, Evusheld should be compared to standard of care using the modified full-analysis set from the TACKLE study, considering data within 5 days of symptom onset (Issue 5). In addition, given that the relevant comparator is standard of care, and data are available which supports the efficacy of Evusheld for different variants of concern, this implies that low and high efficacy scenarios are not relevant and the mean efficacy scenario is most appropriate for decision making. In See Table **2** we present economic analyses for this population, and we also show the impact using a more plausible range of hospitalisation rates from 5.48% to 15.9% (Issue 6), and the impact of not assuming Evusheld leads to increased inpatient mortality (Issue 7). Results using the low and high efficacy scenarios are presented for completeness. **See Table 2 in AstraZeneca DG consultation comments: Economic analyses relevant to the target positioning for Evusheld** The analyses above report that the ICER varies between £537 and £18,122 depending on the hospitalisation rate used in the economic model. Given that AstraZeneca have presented robust data which supports a hospitalisation rate of 15.9%, the most plausible base case ICER for Evusheld as a treatment for COVID-19 is £537 versus standard of care. In addition, even in scenarios where overly conservative or inappropriate assumptions are used (i.e. hospitalisation rate of 2.79% and inpatient mortality of 2.30), the ICER is still below a cost-effectiveness threshold of £30,000 per QALY. As a result, Evusheld represents a cost-effective treatment and should be recommended by NICE within AstraZeneca's proposed positioning as a treatment for COVID-19.	8. Comment noted. Please see responses to your previous comment #1. Based on committee conclusions, tixagevimab plus cilgavimab is not recommended because it is unlikely to be effective at treating COVID-19 and it is not possible to reliably estimate their cost effectiveness.

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		Additional information: [redacted]. **See Table 3 in AstraZeneca DG consultation comments: Economic analyses using the PAS price**	
9	Gilead Sciences Limited (Comment 1)	Gilead acknowledges the unique and inherent challenges of carrying out an assessment of the clinical and cost-effectiveness of medicines for COVID-19 in a pandemic and post-pandemic setting. However, we have significant concerns about the conduct of this technology appraisal, primarily regarding robustness, fairness, and a lack of methodological transparency. We believe that NICE has not acted fairly and that, depending on the outcome to this consultation process, there is a risk that NICE may make unreasonable recommendations regarding the use of remdesivir (Veklury®) and other therapeutics for the treatment of COVID-19. If so, this would be detrimental to patients, both in the UK and internationally, given that NICE guidance is extremely influential globally. Gilead believes that NICE has not acted fairly and that NICE's recommendation in respect of remdesivir is unreasonable based on the evidence submitted to NICE, for the following reasons (these are further elaborated in our detailed response): a) By failing to follow its own published process and methods, NICE has acted unfairly: for example, companies did not have the opportunity to make a full evidence submission (including a de novo cost effectiveness analysis). In addition, the Evidence Assessment Group (EAG) did not conduct its own independent literature review (for lack of time) and did not validate the input from an outsourced provider. b) The living network meta-analysis (NMA) methodology used to inform decision-making has significant limitations and excluded important clinical	Comment noted **NICE published process:** 1a. Comment noted. The process statement and the reasons for resequencing the steps of the MTA have been published on the NICE website here: https://www.nice.org.uk/guidance/gid-ta10936/documents/supporting-documentation **Network meta-analysis** 1b. Comment noted. The AG used the systematic reviews in line with best practice guidance for assessing

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		evidence without clear justification. For example, the living NMA methodology / process does not take all available evidence into account, and does not align with published and preferred NICE manual relating to systematic identification of evidence (section 3) (1). COVID-19 is now comprised of 11 variants, all of which are being monitored by WHO, and we need a comprehensive evidence base that monitors this thoroughly. Without this, the appraisal of the benefit, is inequitable and unbalanced. c) The Committee's adoption of the low efficacy scenario for remdesivir and its reliance on the resulting cost-effectiveness estimates to develop recommendations is unreasonable and flawed. The Committee choses to adopt an extreme position on the evidence for remdesivir in its deliberation on the cost-effectiveness estimates by choosing to consider only the low- and mean- efficacy scenarios. According to the NICE methods guide, these data should be used instead to inform a probabilistic analysis in order to generate mean expected incremental cost-effectiveness ratios (ICERs) that reflect the uncertainty with regards to remdesivir. The approach taken departs so significantly from established NICE methods that Gilead respectfully requests this be referred to the Decision Support Unit (DSU) for independent review. d) Key economic evidence has been excluded from the appraisal and the EAG model is not a reliable basis for decision-making, with significant errors identified following the first committee meeting. Companies were not permitted to submit their own *de novo* cost-effectiveness analyses, and instead the EAG model was used to inform all decision making. There are significant areas of concern relating to the EAG model, including the multiple errors that were not corrected before the Committee deliberated on the evidence at the Appraisal Committee Meeting. e) Important evidence relating to time to discharge (TTD) from hospital and mortality for remdesivir has been overlooked and should be incorporated into the economic model to inform decision making. In particular, the EAG	COVID-19 treatments. All key clinical trials were considered by committee in the second meeting. Please see section 3.10 of FDG. **Efficacy scenario:** 1c. Comment noted. The committee considered mean and low efficacy for remdesivir for mild COVID-19 setting. For severe COVID-19 setting, the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit for remdesivir compared with standard care. The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Please see section 3.20 and 3.30 of FDG. The committee noted that the heterogeneity in the trial populations and the generalisability issues across the trials made the uncertainty challenging to parameterise. Therefore, the appropriate type of uncertainty would not have been captured in the probabilistic sensitivity analysis. Please see section 3.10 of FDG. **Model issues:** 1d. Comment noted. Prior to second committee meeting, the AG addressed any errors and key concerns with the model flagged during AG report

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		does not consider data from the ACTT-1 trial on TTD, which clearly shows that remdesivir patients have a reduced TTD compared to placebo (8). f) The Committee has not taken all the clinical evidence into account, including the SOLIDARITY trial. The Draft Guidance does not reflect the full body of data available, nor is it in line with the broad range of evidence-based guidelines from around the world. Because of this, the clinical benefits of antivirals across the disease spectrum of COVID-19 have been underestimated. Remdesivir is an important anti-viral option for helping hospitalised patients to recover significantly faster and reduce the likelihood of disease progression and mortality. g) If the Draft Guidance is published in its current form, it will create considerable equality challenges for multiple groups, including those with protected characteristics, because of limited access to anti-viral treatment in the hospital setting. For example, this includes hospitalized patients (especially those requiring supplemental oxygen), paediatric patients under 12 years of age, and patients with co-morbidities and contraindications relating to renal and hepatic impairment. h) Gilead considers that the Draft Guidance has resulted from a process that has not been robust or methodologically sound. Gilead requests that the Committee modifies its decision to reflect the issues raised in the consultation. We request that NICE: • Fully considers the additional clinical evidence submitted by Gilead, which is important to produce an evidence-based recommendation for remdesivir. • Re-considers the inclusion of SOLIDARITY, which as stated in the Draft Guidance itself "*would have likely impacted the final conclusions for remdesivir*". • Develops the guidelines for remdesivir based on the best available evidence and an appropriate measure of uncertainty, by applying a consistent approach across all treatments to the consideration of the low-,	consultation and draft guidance consultation. **Time to discharge:** 1e. Comment noted. The AG provided a scenario for committee for the second committee meeting in which time to discharge for remdesivir was informed by ACTT 1. (Please see section 3.10 and 3.23 of FDG) 1f. Comment noted. See response to comment #1b and c **Equality issues:** 1g. Comment noted. The committee considered potential equality issues including treatment for children and disability – people contraindicated to nirmatrelvir plus ritonavir. An alternative treatment – sotrovimab, has been recommended for people (aged 12 years and over) meeting the McInnes defined high-risk of severe COVID-19 criteria and who are contraindicated to nirmatrelvir plus ritonavir (Please see section 3.32 and 3.33) The committee said that in theory it would be willing to accept an ICER slightly more than what is usually acceptable if it addressed such health inequalities. However, it noted that departing from NICE's usual range

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		medium- and high- efficacy scenarios, rather than applying an arbitrary low-efficacy scenario inconsistently to remdesivir. • Re-evaluate data that has informed international guidance on the use of COVID-19 antivirals across the spectrum of disease, and in combination with immunomodulators, to rectify the gaps in treatments available for hospitalised patients in the Draft Guidance. • Refers the approach taken by the EAG to the DSU for consideration as this departs so significantly from NICE established methods, and could be considered as setting a precedent for future MTAs. Gilead therefore requests an external independent review of the methodology used for the COVID-19 MTA. • Gives detailed reasons for inclusions and exclusion of sources of evidence, as well as the rationale for selecting certain outcomes from each study selected. The information should be presented in a PRISMA diagram, and the appraisal should adhere to the NICE Reference Case.	needs to be done with caution, because it risks displacing funding from more cost-effective treatments elsewhere in the NHS, with an overall net loss of health gain. Even considering greater flexibility, the ICERs of alternative treatments for younger children were substantially higher than what is considered a cost-effective use of resources. 1h. Comments noted. See responses to comment #1 a to g
10	Gilead Sciences Limited (Comment 2)	**Failure to follow NICE's published process and methods** Gilead believes that NICE has failed to act fairly by not following its own published process and methods for technology appraisals. NICE has adapted and re-sequenced the steps of the MTA to such an extent that deviates materially from the normal MTA process. This is unfair to Gilead and other stakeholders and also undermines the robustness of the Committee's decision-making and credibility of the Draft Guidance. In particular: 1. The EAG was commissioned, and the Evidence Assessment Report (EAR) was published, before NICE started the technology appraisal process. (1) Nonetheless, the EAG, using the justification of lack of time, did not conduct its own independent, systematic literature review, instead relying on an outsourced provider whose input the EAG did not validate or subject to quality control. This is contrary to the principles for evidence collation reflected in the Manual, and in particular, section 5.5.	2.Comment noted. See response to comment #1a **2.1.** Comment noted. See response to comment #1b

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		2. Companies, including Gilead, were not given the opportunity to make a *full* evidence submission (including a de novo cost effectiveness analysis) before the development of the EAR but instead were only asked to comment on the EAR, without being able to submit additional evidence. This contradicts – for example - sections 1.3.1 and 5.5-5.6 of the Process and Methods Manual (the Manual**)** (1). Gilead's request to submit a de novo cost-effectiveness model was rejected by NICE which we believe to be unfair. As a result, Gilead lost the opportunity to fully participate in the appraisal and inform the Committee. The fact that the EAG did not consider all the relevant data sources has led to subsequent shortcomings in the application of assumptions and methodology. 3. Relevant evidence has been excluded by the EAG and was not considered by the Committee. For example, the SOLIDARITY trial (2) was excluded from the EAR without a clear justification due to a lack of systematic approach. This decision was unreasonable and unfair, as further described in section 3.3 of this response. (1) 4. Companies did not have an opportunity to discuss commercial in confidence patient access schemes (PAS) net price discounts or commercial access agreements before the start of the evaluation. Given that the usual process was not followed, there was also a lack of clarity over whether and when commercial discussions would take place. This contradicts 5.5.6 section of the Manual (1). With less opportunities to settle on an appropriate commercial arrangement, it means that Gilead's participation in the technology appraisal was unfairly constrained. 5. In section 5.5.6 of the Manual NICE states that it "*aims to make sure that companies bringing technologies forward for possible use in the NHS can make the best plausible case for its product, to the ultimate benefit of the NHS and patients*" (1). However, in addition to not having the opportunity to make an evidence submission, companies were not able to make a meaningful contribution in the Committee meeting: for example, each company was only given the opportunity to answer one question in the whole Committee meeting, despite the complexity of the topic, attendant uncertainties, number of products involved, and clear contention over some of the assumptions. (1)	2.2. Comment noted. See response to comment #1a,b,e 2.3. Comment noted. See response to your comment #1b, c and e 2.4. Comment noted. The company could have proposed a commercial arrangement in response to the consultation on the EAR or in response to consultation on the draft guidance. 2.5. Comment noted. Consultees were given the opportunity to provide comments during AG report consultation and DG consultation. During committee meetings companies were given the opportunity to flag factual accuracies by the Chair, in line with the Manual. 2.6-2.9. Comment noted. Please see response to your comments: • #1b (Network meta-analysis) • #1c (Efficacy scenarios) • #1d (Model issues)

Comment number	Organisation name	Stakeholder comment	NICE Response
		6. The Draft Guidance is based on flawed economic modelling which deviates from NICE's methods and processes. For example, not all of the economic evidence has been taken into account. 7. The economic model produced by the EAG and discussed by the Committee was later admitted containing errors. The model was updated only after the Committee meeting and a further corrected version was issued after the Draft Guidance was published. This demonstrates a lack of quality control that would normally be expected before an economic model is submitted to the Committee. It also raises the risk that the Committee made its recommendations on the basis of an incorrect model. 8. NICE did not provide sufficient justification for its conclusions and approach on a number of issues, such as: the rationale for excluding certain sources of evidence, or the Committee's adoption of the low efficacy scenario for remdesivir. 9. The recommendations made in the Draft Guidance cannot be justified by the evidence presented; the rationale of selection of certain sources of evidence are unclear and lack full transparency. Section 3.2.1 section of the Manual states that the evidence must be "*Assembled systematically and synthesised in a transparent way that allows the analysis to be reproduced*". This has not happened with this appraisal to date. Gilead has previously highlighted to NICE its concerns about the fairness of this appraisal process. Given the extensive differences between this process and NICE's published process and methods, we question if NICE may have exceeded its powers.	• #1e (Time to discharge) Comment noted. No action required.

11	Gilead Sciences Limited (Comment 3)	**The living NMA methodology excludes key clinical evidence without clear justification, resulting in significant limitations of the evidence presented to the committee and ultimately to unreasonable conclusions being made in the Draft Guidance** The methodology used to identify and synthesise evidence that underpins the Draft Guidance has the following limitations: a) The approach is not in line with established methods for the systematic and transparent identification and synthesis of evidence as the inclusion and exclusion of clinical evidence is not justified (as outlined in section 3.2.1 of the Manual (1)). b) As a result of unclear inclusion criteria for evidence, high quality information is disregarded in favour of low-quality evidence with high risk of bias. c) The excluded evidence includes robust data sources such as SOLIDARITY AND ACTT-1, that are relevant and important for NICE's recommendations. **3. 1 The approach is not in line with established methods for the systematic identification and synthesis of evidence as the inclusion and exclusion of clinical evidence is not justified** a) The most relevant or applicable data has not been selected for many of the interventions, including remdesivir, with key trials such as SOLIDARITY (2) and CATCO (Canadian sub study of SOLIDARITY) (3) excluded from the EAG analyses without a clear justification due to a lack of systematic approach. b) A full systematic literature review was not deemed feasible in the EAG report given the timescale of the project, and so instead a pragmatic, alternative approach was undertaken where evidence was sourced from two living systematic reviews (COVID-NMA and metaEvidence (4,5)). However, this approach has compromised the quality and robustness of the assessment resulting in a biased evaluation. c) For the development of the NMA, a mathematical model was constructed that used the data from these living systematic reviews to simulate the experiences of patients in hospital, requirement for supplemental oxygen, until discharge or death.	3a/c-3.1a/d. Comment noted. Please see response to your comments: • #1b (Network meta-analysis) • #1e (Time to discharge)

		d) The dynamic nature and regular update of the living systematic review and subsequent NMA is extremely valuable in a rapidly evolving landscape such as in the context of COVID-19. e) However, the EAG state in their report that "*checking of the extracted data by the EAG against the original RCT publications for accuracy could not be undertaken within the timescales of the project*" (EAG report, v3, page 28), which undermines the reliability of the evidence. **3.2 As a result of unclear inclusion criteria for evidence, high quality information is disregarded in favour of low-quality evidence with high risk of bias** • It is unclear from the information provided why certain sources of evidence were not included in the evidence base for this appraisal. This lack of transparency regarding data selection is unsystematic and contrary to the normal NICE methods, as outlined in section 3.3 of the Manual (1). • Trials with methodology that was not robust, such as Wang et al. (2020) (6), and Mahajan et al. (2021) (7) were included. In the risk of bias analysis conducted by the COVID-NMA initiative, Wang et al. (2020) (6) is categorised as having "some concerns", and Mahajan et al. (2021) (7) is considered to have a high risk of bias. In contrast, SOLIDARITY is considered to have a low risk of bias in the same analysis (4). • There was also no clear rationale for the inclusion of some trial outcomes over others. An example is the inclusion of the pivotal study ACTT-1 (8) to look at time to death outcomes, even though the primary endpoint was time to recovery. The inclusion of mortality data from SOLIDARITY (2) would have made more sense to be included given its status as a primary endpoint in a much larger population. • Similarly, the EAG discount the outcome of time to discharge for remdesivir, which is an outcome that could easily be retrieved from ACTT-1 (8). • Furthermore, the choice to include a study that was halted early due to the lockdown in China and was therefore underpowered (Wang et al., 2020 (6)) is concerning given that this study was selected to assess the outcomes time to death and clinical improvement. Therefore, the outcome has no statistical significance, and should not have been included in the NMA.	3.1e. Comment noted. Please see response to your comment: • #1b (Network meta-analysis) During AG report consultation and Draft guidance consultation no errors were flagged by consultees regarding EAG extracted data 3.2. Comment noted. Please see response to your comment: • #1b (Network meta-analysis) The company provided NMA was considered by committee. (Please see section 3.10 of FDG)

		3.3 The excluded evidence includes robust data sources such as SOLIDARITY AND ACTT-1 that are relevant and important for NICE's recommendations. • There is no justification for the exclusion of clinical evidence provided in the EAG report. Both ACTT-1 (8) and SOLIDARITY (2), amongst others constitute more robust data sets from which to retrieve the aforementioned outcomes for assessment. • Other sources that could strengthen the evidence base for decision-making, but were not considered by the living NMA methodology include Garibaldi et al., 2021 (9) and Mozaffari et al., 2022 (10) • With regard to SOLIDARITY in particular, this is the full data set for which DISCOVERY is a sub study and was included (see table 23 of the EAG report), so it is not clear why the EAG has not used the full data set, which would enable a more comprehensive appraisal of the available evidence. • In addition, NICE has recently updated the living guidelines for the management of COVID-19 (11) using the SOLIDARITY data set which confirms the relevance of this source of evidence. • It is acknowledged in the Draft Guidance that the inclusion of SOLIDARITY in the NMA would have likely changed the recommendation for remdesivir. The SOLIDARITY trial found there was no significant difference in in-hospital mortality at Day 28 between remdesivir and control [remdesivir 14.5%, control 15.6% (RR 0.91; 95% CI 0.82-1.02, P=0.12)] (2). However, there was significant mortality benefit associated with remdesivir in patients who were on oxygen (low or high-flow) but not ventilated [remdesivir 14.6%, control 16.3% (RR 0.87; 95% CI 0.76-0.99, P=0.04]; which is consistent with the findings in ACTT-1 of mortality benefit in the group on low-flow oxygen (2,8). • To reflect the importance of the SOLIDARITY trial data Gilead has updated the NMA used to derive the time to death summary outcome for remdesivir. Previously the NMA for the time to death outcome included three studies which – altogether – had less than 2,000 patients combined (6,8,12). SOLIDARITY adds roughly another 8,000 patients, therefore bolstering the significance of the analysis. In this additional analysis Gilead considered the overall population, the oxygen no ventilation population as well as the no oxygen population:	3.3. Comment noted. Please see response to your comment: • #1b (Network meta-analysis) The company provided NMA was considered by committee. (Please see section 3.10 of FDG)

		○ Overall population – RR 0.86 (0.76–0.98) ○ Oxygen no ventilation population – RR 0.87 (0.76–0.99) ○ No oxygen population – RR 0.76 (0.46–1.28) • In a first step Gilead has recreated the original forest plot from the COVID-NMA, which shows a summery outcome of HR of 0.77 (0.57-1.04) for time to death using a fixed effects log hazard model. [Please see figure 1-4 in Gilead DG consultation comments] • As can be seen from the updated NMA results the summary outcome now reports an upper confidence interval below 1 for both the total population as well as the oxygen no ventilation population, suggesting a clear clinical benefit of treatment with remdesivir. Even in the no oxygen population subgroup the upper CI now goes down to 1, while still showing less deaths on remdesivir versus the control (i.e. 25 vs. 33 deaths) (2). Arguably, the upper CI from the no oxygen population would drop further given the lower patient numbers in the subgroup compared to the oxygen no ventilation population. • Given the updated NMA results for the oxygen/non ventilated patients align with the findings of ACTT-1 (which is a randomised controlled trial), these results are robust and reliable enough to support an assessment of clinical effectiveness in this specific population, supporting its inclusion as a source of data. Furthermore, the full dataset from SOLIDARITY is more applicable than DisCoVeRy data included in the assessment report, for the reasons outlined in sections 3.1- 3.3 of this response. • Although these real-world evidence sources were not included in the living systematic review and NMA due to not being randomised, they are useful in contextualising the results from SOLIDARITY and ACTT-1. • For example, the mortality benefits of remdesivir are also reflected in a recently published RWE trial (13) which compared 24,856 remdesivir-exposed patients against 24,856 propensity score–matched control patients, finding a statistically significant 17% reduction in inpatient mortality among patients hospitalized with COVID-19 (hazard ratio: 0.83 [95% CI, 0.79-0.87]).	

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		• Similar results are also reported by Mozaffari et al. (10), which report that remdesivir was associated with a reduction in mortality at 14 days (hazard ratio [95% confidence interval]: 0.76 [0.70–0.83]) and 28 days (0.89 [0.82–0.96]) In view of the significant limitations of the evidence presented to the Committee (some of which were highlighted by the EAG itself), it was unreasonable for NICE to draw the conclusions made in the Draft Guidance (including ranking of therapies against each other) from the evidence presented. Gilead requests that NICE fully considers the additional clinical evidence submitted by Gilead, which is important to produce an evidence-based recommendation for remdesivir. In particular, Gilead requests that NICE re-considers the inclusion of SOLIDARITY, which as stated in the Draft Guidance itself "would have likely impacted the final conclusions for remdesivir".	Comment noted. Please see response to your comment: • #1b (Network meta-analysis) The company provided NMA was considered by committee. (Please see section 3.10 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
12	Gilead Sciences Limited (Comment 4)	**The Committee's adoption of the low efficacy scenario for remdesivir and its reliance on the resulting cost-effectiveness estimates to develop recommendations is unreasonable and flawed** a) In section 3.12 of the Draft Guidance (14), the Committee notes that it considers remdesivir's mechanism of action may not fit the stated treatment aims, because antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation. No clinical evidence to support the Committee's view is put forward. b) Nonetheless, the Committee then proceeds to adopt an extreme position on the evidence for remdesivir in its deliberation on the cost-effectiveness estimates, choosing to consider only the low- and mean- efficacy scenarios. The limitations of this approach are outlined below. c) Section 3.9 of the Draft Guidance (14) chooses to consider the EAG scenarios using the upper and lower confidence limits of each efficacy estimate from the NMA rather than using probabilistic sensitivity analysis (PSA) to assess uncertainty. Scenarios were therefore developed to represent 'lower efficacy' and 'higher efficacy' estimates. We note that the EAG cautioned the Committee that these efficacy scenarios had limitations because they represented additional uncertainty to that in the evidence base and are not grounded in clinical evidence. d) Ignoring this advice, the Committee determined that these low, mean, and high efficacy scenarios can be used to explore uncertainty in relation to the generalisability of evidence to the newer COVID-19 variants. e) In section 3.21 of the Draft Guidance (Hospital setting without supplemental oxygen), the ICERs for remdesivir compared to standard of care (SoC) are reported as £10,114 (mean-efficacy estimate) and dominated (low-efficacy estimate). The Committee states that because of uncertainty about the clinical effectiveness of remdesivir in this setting, it preferred the low-efficacy scenario. f) Uncertainty in the available evidence is reflected by the range of efficacy estimates with a mean estimate and upper and lower estimates. Typically,	4.Comment noted. Please see response to your comment #1c (Efficacy scenarios) 4a. Comment noted. The statement has been removed from the FDG following stakeholder comments. 4b. Comment noted. For the second committee meeting, the company provided NMA was considered by committee. (Please see section 3.10 of FDG). Please also see response to your comment #1c (Efficacy scenarios) 4c. Comment noted. Please also see response to your comment #1c (Efficacy scenarios) 4d. Comment noted. Please also see response to your comment #1c (Efficacy scenarios) 4e. Comment noted. The committee was aware that the AG presented ICERs for remdesivir in severe COVID-19 setting without supplemental oxygen. However, the committee did not consider that this setting was within the marketing authorisation for remdesivir in Great Britain (Please see section 2 of FDG). It had separately considered remdesivir for people with

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		and according to section 4.7.12 of the Manual (1), these data would be used to inform a probabilistic analysis, generating mean expected ICERs that reflect the uncertainty in the evidence. However, in this appraisal, and without providing a justification, the Committee has determined to arbitrarily select the 'low-efficacy' scenario to reflect its uncertainty with regard to remdesivir. This is an extreme position and lacks any credibility, as the decision to do so is not underpinned by clinical evidence and, as stated, is not aligned with the published methodology. In the low-efficacy scenario, SoC is associated with greater QALYs and lower costs compared to remdesivir – remdesivir is therefore dominated by SoC. In other words, the model estimates that supportive care without treatment intervention will generate superior clinical outcomes compared to remdesivir. Relying on this as the basis for decision making is absurd and unreasonable.	mild COVID-19 who do not need supplemental oxygen and who have an increased risk of progression to severe COVID-19 (Please see section 3.28 of FDG). 4f. Comment noted. See committee responses about the efficacy scenarios in section 3.10 and 3.12
13	Gilead Sciences Limited (Comment 5)	**Important economic evidence has been excluded from the appraisal and the EAG model does not reliably enable an incremental analysis of COVID-19 therapeutics** There are limitations in the economic model developed by the EAG that result in concerns over its appropriateness for decision making. This section focuses on the limitations of the economic model developed by the EAG. 5.1 <u>Low confidence in the EAG model resulting from multiple corrections to the model following consideration of its results</u> • Gilead lacks confidence in the economic modelling, as corrections were made to the model and outputs following the identification of errors after the Committee meeting, and after Draft Guidance was published. Important errors of this sort are typically identified in a proper quality control of the model considerably in advance of Committee. 5.2 <u>Limitations of the EAG model</u> a) As well as previously discussed limitations relating to the choice of scenarios, other issues identified include length of stay assumptions (assumed equal for remdesivir and standard of care, leading to a higher	5. Comment noted. Please see response to your previous comment #1d (Model issues) 5.1. Comment noted. Please see response to your previous comment #1d (Model issues) 5.2 a-c. Comment noted. Based on DG consultation comments, the AG

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		length of stay (LOS) cost for remdesivir and lower quality-adjusted life years (QALYs) due the model structure). This is in direct contrast to the clinical picture, where remdesivir has demonstrated improvements in time to discharge, as outlined below. b) Where relative treatment effects for certain comparators are not available the model adopts the arbitrary assumption that there is equivalence between active therapies and standard of care (SoC). This appears to be based on the conclusion that where treatment effects are available, they are close to unity relative to SoC and have little impact within the analyses. Gilead believes that this assumption is not justified as additional evidence to inform outcomes – such as time to discharge for remdesivir for example – was available and would have been identified by the EAG if a systematic review of the published literature had been conducted, rather than relying on external, unvalidated data sources. c) As an example, within the EAG economic model, in the hospitalised context, the hazard ratios for mortality for remdesivir and tocilizumab are 0.7791 and 0.7718 respectively, with those for clinical improvement being 1.0404 and 1.0403 respectively. Not only might such differences in point estimates be considered spurious, but the assumption applied for remdesivir for discharge is that there is no effect versus SoC whereas the effect for tocilizumab is 1.05. This implies a benefit for tocilizumab versus remdesivir in the current model based entirely on the arbitrary assumption that remdesivir has no impact on discharge despite having a virtually identical effect to tocilizumab in terms of clinical improvement. d) Furthermore, data is available for remdesivir from the ACTT-1 trial which demonstrates that the time to discharge (TTD) benefit is 1.27 over placebo, (8) which implies that remdesivir has superior TTD compared with the recommended tocilizumab.	updated its assumption and capped the mortality rate to equal 1 for the low-efficacy scenario. Please see section 3.10 of FDG. 5.2 b/d. Comment noted. Please see response to your previous comment #1e Time to discharge (Please see section 3.10 and 3.23 of FDG) 5.2 e-h. Comment noted. Please see response to your previous comment #1e Time to discharge (Please see section 3.10 and 3.23 of FDG for

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		See Figure 5 in Gilead DG consultation comments: Kaplan-Meier Curves of Time to Discharge or to a National Early Warning Score (NEWS) of ≤2 by Treatment Group (ITT Population) e) In one instance the hazard ratio for remdesivir relative to placebo is applied as 1.00 with a confidence interval of 0 – 50 based purely on application of a continuity correction in both arms, due to zero events. Set against the other evidence both for remdesivir and other therapies this is implausible f) In the example of remdesivir versus tocilizumab it is apparent that minor rounding of point estimates and an assumption of the discharge HR then being in line with other parameters (rather than being dismissed as inconsequential and arbitrarily assumed equal to SoC), would remove any QALY difference between these active therapies. g) The comparison between remdesivir and tocilizumab is merely illustrative of the general point that arbitrary assumptions and minor numerical differences may overstate any apparent differences between therapy options. **h)** As a result of the limitations of the analyses, even though tocilizumab, baricitinib and remdesivir are similarly cost-effective the Committee does not recommend remdesivir. The similarity in cost-effectiveness between the three treatments can easily be seen when looking at **See Figure below, which shows that no meaningful differentiation can be made between tocilizumab, baricitinib and remdesivir regarding cost-effectiveness when all efficacy scenarios are considered.** **See Figure 6 in Gilead DG consultation comments: Cost-effectiveness comparison of baricitinib, tocilizumab, remdesivir and baricitinib/remdesivir across efficacy scenarios using the EAG model version 5 – hospital setting, with oxygen**	committee's final assumptions for time to discharge for all treatments assessed in severe COVID-19 setting)

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14	Gilead Sciences Limited (Comment 6)	**Important evidence relating to time to discharge (TTD) from hospital and mortality for remdesivir has been overlooked and should be incorporated into the economic model to inform decision making** 6.1 Time to discharge The EAG model does not consider data from the ACTT-1 trial (8) on time to discharge (TTD) which clearly shows that remdesivir patients have a reduced TTD compared to placebo (median difference = 4 days earlier discharge). Instead, the EAG model assumed that time to discharge (TTD) for remdesivir was equal to SoC in hospitalised patients. This is especially confusing as the EAG applied a hazard ratio (HR) to the SoC TTD curve in their model, thereby conferring an advantage in costs and quality adjusted life years (QALYs) for one treatment, while ignoring this for others. Gilead has therefore amended version 5 of the EAG model to account for the improved TTD for remdesivir over SoC. This has been done by modifying P10:P2511 in the "Trace_Hosp_Oxy_Rem" as well as the "Trace Hosp NoOxy Rem" sheet to apply the hazard ratio (i.e. "HR_Rdv_TTDischarge") so that: *=MIN(1-(OFFSET(INDIRECT("Ttdischarge_SoC"&A2),E10,0)^HR_Rdv_TTDischarge), N10)* Applying the favourable HR (=1.27) for remdesivir from the ACTT-1 trial (8) in the EAG model improves both costs and QALYs for remdesivir. As visualized (Figure 7) below applying a HR for TTD yields lower cost for remdesivir compared to tocilizumab in two out of three scenarios whereas efficacy in terms of QALYs seems even between the two treatments, with a marginal difference in favour of tocilizumab in the low efficacy setting and a similar marginal difference in favour of remdesivir in the high efficacy scenario.	6-6.1. Comment noted. Please see response to your previous comment #1e Time to discharge (Please see section 3.10 and 3.23 of FDG for committee's final assumptions for time

		See Figure 7 in Gilead DG consultation comments: Comparison of costs and QALYs for remdesivir and tocilizumab across efficacy scenarios in the hospital setting (with oxygen) using the amended EAG model The way in which the EAG decided to model TTD also raises some concerns with regards to the validity of the cost-effectiveness model, due to the interaction between TTD and survival in the hospitalised setting. Assuming patients are discharged from hospital equally across treatments means that patients receiving treatments with better survival outcomes stay in hospital for longer due to the way in which health state occupancy is set up in the EAG model. This results in an assumption that having patients die quicker is beneficial (as it saves costs due to reduces health state occupancy in costly hospital states), therefore penalizing treatments with better survival outcomes. **See Figure 8 in Gilead DG consultation comments : Interaction between hospital discharge and survival in the EAG model (illustrative)** 6.2 Mortality / time to death As explained in section 3.3 of this response, Gilead has recreated the meta-analysis results used to inform the time to death outcome for remdesivir. Furthermore, Gilead has incorporated these updated meta-analysis results into the latest version of the EAG model (v5.1) and shared this amended model with NICE as additional evidence. As can be seen from Figure 9 below remdesivir is already highly cost-effective in 5 out of 9 scenario & setting combinations using the EAG model v5.1, indicating a strong likelihood of representing good value for money. **See Figure 9 in Gilead DG consultation comments: ICER (remdesivir against SOC) across efficacy scenarios and settings** When applying the updated NMA analysis for time to death, the results for remdesivir become even more favourable, as now 6 out of 9 scenario & setting combinations demonstrate high cost-effectiveness against SOC, with one more	to discharge for all treatments assessed in severe COVID-19 setting)

		scenario & setting combination being reasonably cost-effective as shown in Figure 10 below. In the hospital setting (with oxygen) remdesivir is now cost-effective across all efficacy scenarios. **See Figure 10 in Gilead DG consultation comments: ICER (remdesivir against SOC) across efficacy scenarios and settings, using updated NMA results** Combining the results of the updated meta-analysis with the reasonable assumption that remdesivir patients are being discharged earlier from hospital compared to SOC patients, results for remdesivir against SOC become extremely cost-effective across efficacy scenarios in both hospital settings (no oxygen and oxygen) as demonstrated in Figure 11 below. **See Figure 11 in Gilead DG consultation comments: ICER (remdesivir against SOC) across efficacy scenarios and settings, using updated NMA results (SOLIDARITY overall population) and time to discharge hazard ration (1.27) for remdesivir** As can be seen in Figure 11 above, remdesivir is dominant compared to SOC in the hospital setting even when considering the low efficacy scenario. Similar results can be seen when considering subgroups from the SOLIDARITY trial (i.e. “Oxygen no ventilation” and “No Oxygen”) and re-running the meta-analysis using these estimates. A more detailed summary of the cost-effectiveness results compared to SOC has been provided to NICE in an Excel file. 6.3 <u>Reduced hospital length of stay & lower costs with remdesivir</u> Various studies have shown that the use of remdesivir significantly reduces the hospital LOS which translates to cost-savings for national healthcare systems. (15,16)	6.2 Comment noted. Based on DG consultation comments, the AG updated its assumption and capped the mortality rate to equal 1 for the low-efficacy scenario. Please see section 3.10 of FDG. Please also see response to your comment #6.1

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		As pointed out by Ruggeri et al. (17) in their conclusion "*remdesivir has the potential to reduce the negative effects of the Coronavirus disease, improving patient conditions and reducing death tolls, and can also save scarce healthcare resources during this pandemic, resulting in a shorter hospital stay and fewer ICU admissions*".	6.3 Comment noted. Please see response to your previous comment #1e Time to discharge (Please see section 3.10 and 3.23 of FDG for committee's final assumptions for time to discharge for all treatments assessed in severe COVID-19 setting)

Comment number	Organisation name	Stakeholder comment	NICE Response
15	Gilead Sciences Limited (Comment 7)	**The committee has not taken all the clinical evidence into account** This Draft Guidance does not reflect the full body of data available, nor is it in line with the broad range of evidence-based guidelines from around the world including the European Society of Clinical Microbiology and Infectious Diseases (18), the World Health Organisation (WHO) (11), the U.S. National Institute of Health (19), and the NICE COVID-19 Rapid Guideline. (20) As part of this response to the Draft Guidance we are submitting additional analyses to cover aspects of cost-effectiveness as well as clinical effectiveness (intervention/comparators/ outcomes). NICE's Draft Guidance states that remdesivir's efficacy is uncertain or no better than the Standard of Care is erroneous and inappropriate given remdesivir's marketing authorisation and the clinical evidence submitted by Gilead to date. According to its licensed indication (21), remdesivir is approved for the treatment of both patients with non-severe and severe disease, for adult patients requiring supplemental oxygen (low-or high-flow oxygen or other non-invasive ventilation) and for paediatric patients below 12 years. Remdesivir is the only anti-viral treatment approved for these indications. Remdesivir is an important anti-viral option for helping hospitalised patients to recover significantly faster and reduce the likelihood of disease progression and mortality. 7.1 **NICE has misinterpreted the phases in the natural history of COVID-19 and underestimated the clinical benefits of antivirals across the disease spectrum of COVID-19** a) Gilead considers that the summaries of clinical effectiveness in the Draft Guidance are not reasonable. NICE has given insufficient consideration to segmenting the patient population according to oxygen use within the hospital setting. This split does not reflect sequencing in clinical practice or recognise the key stages of disease progression. It also does not reflect the correct wording of the regulatory labels of the various interventions, despite signposting to these at the beginning of the document.	7. Comment noted. Please see responses to your comment #1b (Network meta-analysis) and #1c (Efficacy scenarios) 7.1a-b Comment noted. The severe COVID-19 setting treatment pathway was guided by NICE COVID-19 Rapid Guideline and the interim

		b) The use of the different therapies considered in this MTA at different stages of disease progression is important to understand. For example, the use of therapies with an immunomodulatory mode of action too early (such as in a patient not yet requiring supplementary oxygen support) could be detrimental to a patient's outcomes as outlined in the RECOVERY trial for dexamethasone (22). NICE sees these treatments as mutually exclusive in the Draft Guidance, and discounts this clinically important point when assessing clinical and cost effectiveness of the therapies, even though NICE's living guidelines for the management of COVID-19 splits patient groups in hospital by oxygen usage. c) In section 3.12 of the Draft Guidance, the Committee notes that it considers remdesivir's mechanism of action may not fit the stated treatment aims, because antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation. d) The natural history of progression with SARS-CoV-2 includes a viral replication phase and an inflammatory phase, as demonstrated by this graphic. Contrary to the inference made by the Draft Guidance, these phases overlap – that is, they do not stop at the point of hospitalization. Given that viral replication is a key driving factor for the systemic inflammatory response among patients with severe COVID-19, the antiviral mechanism of action of remdesivir is a critical component of the multifaceted care of patients with severe disease. (23–25) e) We acknowledge the majority of clinical benefit for antivirals will be felt in the early phases of COVID-19 infection, as evidenced by the PINETREE phase 3 study in which remdesivir vs placebo led to 87% relative risk reduction in hospitalisation or all cause death (26). However, there is a significant group of individuals for whom access to antivirals in hospital settings has proven efficacy in preventing mortality and disease progression, and an increasing body of evidence regarding prevention of 'long COVID' sequelae. Those patients who are hospitalised at high risk of	commissioning policies. Please see section 3.9 of FDG. 7.1 c-d Please see response to your comment #4a. The statement has been removed from the FDG.

		disease progression are not accommodated equitably, or given due consideration within the current draft NICE guidance. *f)* In addition, Gilead requests that the Committee reconsiders including the results from the SOLIDARITY trial, which – as stated in the Draft Guidance itself – "*would have likely impacted the final conclusions for remdesivir*". 7.2 **Combination therapies which include remdesivir are recommended for treating patients with severe COVID-19** **Infection with SARS-CoV-2 includes a viral phase and an inflammatory phase. Patients with severe and critical COVID-19 can have prolonged viral phase (24) with uncontrolled inflammatory response. Combination therapies are recommended by guidelines for treating patients with severe COVID-19 (11,18–20,27) – RCTs and RWE also demonstrate that remdesivir provides additional benefits when used in combination with immunomodulators – these treatments appear mutually exclusive in the NICE Draft Guidance, which negates evidence-based practice.** 7.2.1 <u>Remdesivir in combination with Dexamethasone demonstrates better outcomes than Dexamethasone alone</u> • Remdesivir provides significant survival benefits in patients on low-flow O_2 when used in combination with Dexamethasone (Dex) compared to Dex alone. This is based on a retrospective, multicenter study of remdesivir in hospitalized adults (28) • Prospective, sequential controlled cohort study of remdesivir + DEX vs DEX alone in patients requiring non-invasive O2 support - Remdesivir/dexamethasone treatment is associated with significant reduction in mortality, length of hospitalization, and faster SARS-CoV-2 clearance, compared to dexamethasone alone. (29) • Nationwide, population-based cohort study of 30-day mortality among 1,694 patients treated with remdesivir+DEX+SoC compared to 1,053 patients who received SoC alone - Treatment of moderate to severe COVID-19 with remdesivir and dexamethasone was associated with	7.1 e. Comment noted. Please see response to your comment #1g (Equality issues) 7.1 f. Comment noted. Please see responses to your comment #1b (Network meta-analysis) and #1c (Efficacy scenarios) 7.2 Comment noted. NICE can only evaluate remdesivir within its current marketing authorisation in Great Britain. (Please see section 2.4 of FDG)

		significantly reduced 30-day mortality and need of MV compared to SoC treatment. (30) • Additional observational data which shows that treatment with remdesivir, dexamethasone, or both, in patients hospitalized with COVID-19 was associated with a reduction in mortality and a reduced incidence of neurological complications in an additive manner (31) • In hospitalized patients with COVID-19 pneumonia receiving low-flow oxygen and dexamethasone, in-hospital death rates and rates of transfer to the intensive care unit or death were 8.9 and 17.8% (HR: 0.46, 95% CI: 0.21–1.02, p = 0.06) and 20.0 and 35.6% with and without remdesivir, respectively (HR: 0.45, 95% CI: 0.23–0.89, p = 0.015) (32) • In a retrospective, cohort study - remdesivir + DEX was associated with faster time to clinical improvement, faster development of IgG antibodies, & decreased in-hospital death when initiated prior to, or simultaneously with Dex vs late introduction or no remdesivir exposure (33) 7.2.2. <u>Benefits of remdesivir + Immunomodulator vs remdesivir only or SoC</u> • • ACTT-2 (34), an adaptive Phase 3 randomized, double-blind, PBO-controlled, multicenter global trial demonstrated remdesivir in combination with Baricitinib in hospitalized patients with COVID-19 not requiring ventilation (moderately ill) or those requiring non-invasive or invasive ventilation (severely ill), compared to remdesivir alone, significantly improved time to recovery from 8 days to 7 days. The greatest impact was seen in patients requiring high flow oxygen or non-invasive ventilation (shorter time to recovery from 18 days to 10 days) • Padilla et al. 2022 (35) – A cohort study of hospitalised patients who received Dex and Tocilizumab alone or Tocilizumab + remdesivir demonstrates that remdesivir decreases the risk of mortality and need for	

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		invasive mechanical ventilation (IMV) in patients with high viral loads and low-grade systemic inflammation • In a study of Baricitinib (36) with or without remdesivir in hospitalised patients with COVID-19, a retrospective sub-group analysis demonstrated Baricitinib + remdesivir was associated with a reduction in risk of death vs usual care RR 0.87 (95% CI 0.77-0.98, p-0.026) 7.3 **The Committee ignored variant stability of remdesivir and inappropriately disregarded evidence that remdesivir is effective in treating COVID-19 variants, including Omicron** In section 3.10 of the Draft Guidance, the Committee acknowledges that *"Most of the clinical evidence is from studies done before the Omicron variant of SARS-CoV-2 (the virus that causes COVID-19). So there are significant uncertainties in the clinical evidence."* The Committee then arbitrarily (and without justification) introduces an approach for considering different mechanisms of action separately, (for anti-inflammatories, antivirals, and others), without supporting evidence for this approach. The Committee notes that most evidence for the anti-inflammatories (baricitinib and tocilizumab) was generated during the earliest waves of the pandemic. It then concludes, without supporting evidence, that the relative benefit for anti-inflammatories can be generalised to later waves of the pandemic. For antiviral treatments (molnupiravir, nirmatrelvir plus ritonavir, remdesivir), the Committee notes that there is observational data to support antiviral efficacy against later variants. Surprisingly, this evidence is apparently disregarded owing to a lack of systematic assessment. However, contrary to its approach with anti-inflammatory treatments, which are afforded an assumption of generalisability without supporting evidence, the Committee concludes that the evidence on antivirals is uncertain for newer variants. This piecemeal approach to the interpretation of available evidence is entirely at odds with NICE's preferred methods for decision making and is unfair and unreasonable.	7.3-7.4 Comments noted. The committee considered recent in vitro evidence for antivirals in the second committee meeting. The committee concluded there was no in vitro evidence showing reduced clinical efficacy of the antivirals (molnupiravir, nirmatrelvir plus ritonavir, remdesivir)

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		In fact, Remdesivir has consistently been shown to have excellent stability to COVID-19 variants of concern (including Omicron), as highlighted in the publications below. Unlike some other therapies, which are affected by changes in the virus's spike protein, remdesivir targets the highly conserved viral RNA-dependent RNA polymerase (RdRp). No genetic changes in the RdRP region have been identified that are associated with remdesivir resistance. 7.3.1 <u>Remdesivir as a candidate to treat future variants of concern:</u> • The Draft Guidance emphasises that key evidence for remdesivir cannot be considered as there is uncertainty around the effectiveness of remdesivir to treat the Omicron variant • Given that it is impossible to predict which variant might rise to become the next big variant of concern it is unreasonable to exclude evidence on these grounds alone • Both in vitro and RWE data support the claim that remdesivir is effective in treating variants of concern – remdesivir therefore is an ideal candidate to treat unknown future variants of concern 7.3.2 <u>Supporting in vitro data:</u> • In vitro analyses support remdesivir's activity against variants of concern (VOC) including Alpha, Beta, Gamma, Delta and Omicron specific variants (37–39) • Evidence that suggests that BA2.12.2, BA.4 and BA.5 share a similar level of susceptibility to remdesivir as the ancestral strains of SARS-CoV2 remdesivir retains antiviral potency against clinical isolates of all known SARS-CoV-2 variants in vitro (21,38,40–42). Figure 12 demonstrates that remdesivir is effective against all VOCs, with all VOCs showing no reduction in susceptibility. See **Figure 12 in Gilead DG consultation comments: Remdesivir antiviral activity against clinical isolates of SARS-CoV-2 variants**	across the variants tested. Please see section 3.14 to 3.16 of FDG.

		7.3.3 <u>Real world evidence during Omicron phase:</u> • A retrospective cohort study by Piccicacco et el. 2022 (43) showed that high risk patients receiving remdesivir had significantly lower likelihoods of a hospitalization and/or emergency department visits during the Omicron surge than those treated with sotrovimab (11% versus 23.3%; OR = 0.41, 95% CI = 0.17–0.95) • A prospective cohort study showed that early outpatient treatment with remdesivir significantly reduces hospitalization or death by 84% in high-risk, majority immunosuppressed patients with Omicron variant COVID-19 compared to patients treated with SoC (44) • In a prospective cohort study (45) in outpatient adult solid organ transplant recipients (n=192) during the Omicron BA.2 wave (April-May 2022), early remdesivir significantly decreased the hospitalisation rate compared with patients treated with SoC: adjusted hazard ratio 0.12 (95%CI: 0.03 to 0.057). The adjusted number needed to treat to prevent one hospitalization was 15.2 (95%CI: 13.6 to 31.4). No patient that received early remdesivir needed ICU admission or died. 7.4 **Preliminary data shows treatment with remdesivir during the acute phase might lead to reduction in post-acute COVID-19 sequalae** • In a prospective study of 449 hospitalised COVID-19 patients with at least 6 months follow up, analysis of the prevalence of risk factors for long COVID-19 syndrome demonstrated remdesivir treatment led to a 35.9% reduction in LCS rate (OR=0.641; 95% CI 0.413-0.782, p<0.001) (46) 7.5 **Emerging studies are evaluating the potential impact of remdesivir on readmission rates in hospitalised patients** • A multicentre cohort study (n=2062) demonstrated patients were less likely to be readmitted within 30 days if they received remdesivir relative to not receiving remdesivir; associations were strongest for those with mild disease (RR: 0.31; 95% CI: 0.13,0.75). Overall, being treated with remdesivir was associated with a 35% decrease in risk of dying in the 30-days following discharge (HR: 0.65; 95%: 0.49,0.85) (47)	

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16	Gilead Sciences Limited (Comment 8)	**If published, the Draft Guidance will create treatment gaps and equality challenges** Because NICE has misunderstood the phases in the natural history of COVID-19, the Committee has failed to evaluate and make recommendations for treatment options across patient groups in hospital by oxygen use. The absurd gaps in treatment available for vulnerable patient groups demonstrates that NICE's conclusions are unreasonable. **8.1 The lack of any routine recommendation of antiviral provision in the hospital setting (especially for those requiring supplemental oxygen) goes against evidence based clinical practice and international guidelines, particularly for those at high risk of disease progression** • If approved, the Draft Guidance would result in a clear treatment gap in the hospitalized setting for access to antivirals in appropriate patients in Ordinal scale categories 4 and above. • Gilead is concerned that the draft guidance from NICE does not recommend a treatment option for hospitalised patients who do not require supplemental oxygen. Tocilizumab is specifically recommended for patients who need supplemental oxygen or mechanical ventilation which therefore creates a treatment gap in the hospital setting. 8.1.1 <u>Supporting evidence</u> • Patients with severe COVID-19 can have prolonged viral replication (up to 4 weeks after symptom onset) and therefore require an anti-viral intervention. Studies such as the one conducted by Ali et al., 2022 (3) demonstrate that remdesivir has a significant effect on outcomes of importance to patients and health systems. • As evidenced by the SOLIDARITY study (2), those treated with remdesivir who required oxygen (low or high flow) without mechanical ventilation, had a statistically significant reduction in mortality [remdesivir 14.6%, control 16.3% (RR 0.87; 95% CI 0.76-0.99, P=0.04]; this is consistent with the finding in ACTT-1 of mortality benefit in the group on low-flow oxygen (8).	Comment noted. Remdesivir does not currently have marketing authorisation in Great Britain for people who do not need supplemental oxygen unless they are at increased risk of severe COVID-19. NICE can only evaluate remdesivir within its current marketing authorisation in Great Britain. (Please see section 2.4 of FDG) NICE has recommended two treatment options for people who do not need supplemental oxygen and who are at an increased risk of severe COVID-19 based on McInnes high-risk definition. Please see section 1 of FDG. Also please see section 3.32 in FDG and response to your comment #1g (Equality issues) The committee considered SOLIDARITY evidence. Please see

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		The SOLIDARITY data led to the WHO guidelines being updated to conditionally recommend remdesivir for both non-severe and severe COVID-19 patients. (11) • Results of a systematic review and individual patient data meta-analysis showed reduced mortality with remdesivir in hospitalized COVID-19 patients requiring no or conventional oxygen support (48) 8.1.2 Real world data demonstrating the use of early remdesivir in hospitalized patients prevents progression/ reduces mortality: • Remdesivir initiated upon hospital admission was associated with improved survival among patients with COVID-19, Multi-centre observational cohort in USA. (10) • Paranjape et al., 2021 (49) – retrospective observational study (USA) of 475 patients hospitalized with COVID-19, concluded that early treatment led to improved clinical outcomes (shortened length of stay, reduced risk of MV and death). This effect was more pronounced in patients on lower oxygen requirement at baseline and was seen both with and without the use of corticosteroids. • Wong CKH et al., 2022 (33) – nationwide retrospective cohort analysis of remdesivir vs control demonstrated significantly shorter time to clinical improvement, shorter length of hospital stay, lower risk of in-hospital death, reduced time to achieving low viral load and IgG antibody positivity. • Garcia-Vidal C et al., 2021 (50) - Remdesivir was associated with 62% reduced odds of death versus SoC and its survival benefit increased with shorter duration of symptoms. **8.2 The Draft Guidance will create equality challenges for multiple groups, including those with protected characteristics, because of limited access to anti-viral treatment in the hospital setting** The NICE Draft Guidance implies that there may be no anti-viral COVID-19 therapies available for paediatric patients under 12 years of age. Given that age is a protected characteristic, not enabling access to the only antiviral licensed for this population will create an equality issue, because there will be no alternatives available to this group of patients.	response to your previous comment #1b (Network meta-analysis) 8.2 Comment noted. Sotrovimab has been recommended for people contraindicated to nirmatrelvir plus ritonavir. Please see responses to your earlier comment #8.1

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		In addition, Gilead is concerned about NICE recommending Paxlovid – a drug which has been found to have high contraindications (up to 15% of patients as reported by Lim et el. 2022 (51) and >37% for patients with comorbidities and 27% in older patients according to Hoertel et al. 2022 (52). According to Blueteq data there are higher rates of requests for remdesivir than other antivirals in patients >80 years of age (per 100,000 COVID-19 cases). This is the age with the highest death rates, which are likely to have high rates of co-morbidities, such as renal and hepatic impairment. Co-medications would likely prevent the use of Paxlovid due to contra-indications. Gilead is concerned that these patients with potential contraindications to Paxlovid will not have appropriate access to COVID-19 antivirals if Paxlovid is the only recommended antiviral. Gilead agrees with NICE's assessment that there are important equality considerations in this appraisal – many people are at an increased risk of hospitalisation and death, including people from Black, Asian and other minority ethnic family backgrounds. Importantly, data from ESPAUR (53) report that treatments used in hospitals, such as remdesivir, had a higher percentage of requests for patients in the most deprived IMDs (index multiple deprivation deciles). However, should the Draft Guidance be finalised, some patients will have no antiviral treatment option, creating equality and fairness challenges. It is NICE's obligation to treat people fairly and consider this alongside clinical and cost-effectiveness data when making a recommendation, consistent with section 3.1.4 of the Manual (1). **See Figure 13 in Gilead DG consultation comments:: Rate of requests in Blueteq (per 100,000 COVID-19 cases) by therapeutic, age group and sex, from the English surveillance programme for antimicrobial utilisation and resistance ESPAUR Report 2021 to 2022**	
17	GlaxoSmithKline (Comment 1)	The draft guidance only recommends nirmatrelvir/ritonavir for treating COVID-19 in adults with an increased risk for progression to severe COVID-19. The draft guidance does not recommend any other antiviral or antibody therapies, including	**NICE published process:** The process statement and the reasons for resequencing the steps of

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		sotrovimab. This guidance, if implemented, could result in significant health inequality and unmet need in vulnerable patient populations, by denying them access to sotrovimab – an efficacious and cost-effective therapy which has provided significant patient and public health benefits since being approved for use in this indication in late-2021. To date, over 38,000 doses of sotrovimab have been administered by COVID Medicines Delivery Units (CMDUs) in England in the past 11 months (NHS 2022a), demonstrating clinical confidence in sotrovimab's effectiveness, tolerability, and safety. Denying alternative COVID-19 therapeutics risks a lack of options for early treatment against future variants of the SARS-CoV-2 virus. GSK is concerned that the protective value of therapeutics with alternative and additional mechanisms of action to oral antivirals has not been considered. A pre-print publication by an academic group considers the possibility of a future 'Omicron-like event' resulting in the emergence of a brand-new variant (Peacock et al. 2022). They conclude that it is not clear how likely or commonly we should anticipate such events, but that it would seem prudent to have strategies in place in the event they do occur. GSK believes that having a range of medicines available for the early treatment of COVID-19 is one part of a strategy to plan for any future Omicron-like disruptive evolutionary event where population health could be at significant risk. In addition, GSK is concerned that this specific MTA is out of process for NICE and has resulted in draft guidance that does not reflect the values and process that NICE typically follows for evaluations of health technologies. Our response to this consultation on the Draft Guidance document breaks down our concerns and comments into the following key topics: 1.1 Evidence for sotrovimab's sustained clinical effectiveness not being appropriately considered 1.2 Inequality and unmet need for patients at the highest risk of severe COVID-19 disease 1.3 Consideration of the most recent evidence for hospitalisation rates in those patients at the highest risk of severe COVID-19 disease 1.4 Validity of the External Assessment Group's low effectiveness scenario	the MTA have been published on the NICE website here: https://www.nice.org.uk/guidance/gid-ta10936/documents/supporting-documentation 1.1 **Sotrovimab's clinical effectiveness**: Comment noted. The committee considered the COMET-ICE trial evidence, alongside the in vitro and OpenSAFELY observational evidence for sotrovimab. The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing BQ.1 and BQ.1.1 subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.19 in FDG) 1.2 **Equality issues**: Comment noted. The committee considered potential equality issues including 'disability – people contraindicated to nirmatrelvir plus ritonavir'. The committee noted the unmet need and equality issues have been partly addressed by recommending sotrovimab, for people (aged 12 years and over) meeting the McInnes defined high-risk of severe COVID-19 criteria and who are contraindicated to nirmatrelvir plus

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		1.5 Use of the CMDU micro-cost to estimate the administration costs for community treatments We also cross-reference to additional evidence and data presented in Appendix A, as requested by NICE. We believe these data and evidence are highly pertinent and request that they are carefully reviewed and considered by the NICE Committee and External Assessment Group to ensure that all high-quality and recent evidence are considered as part of this appraisal in a robust, transparent and systematic way. **GSK requests that the Committee considers recommending sotrovimab in patients who are ineligible for (or contraindicated to) treatment with nirmatrelvir/ritonavir. These patients are at the highest risk of severe COVID-19 outcomes, including hospitalisation, and therefore sotrovimab offers an effective, well-tolerated, and cost-effective therapeutic option for these patients with significant unmet need and with no other community COVID-19 treatment options.**	ritonavir (Please see section 3.32 and 3.33) 1.3 **Hospitalisation rates**: Comments noted. The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort and 4% for people contraindicated to nirmatrelvir plus ritonavir. Please see section 3.22 in FDG. 1.4 **Low efficacy scenario**. Please also see response to your previous comment #1.1. The committee considered that low efficacy scenarios represented an attempt to address some aspects of uncertainty in the absence of alternative methods to model the uncertainty. At DG consultation, consultees highlighted that a probabilistic sensitivity analysis would be a better way to capture the uncertainty. The committee noted that the heterogeneity in the trial populations and the generalisability issues across the trials made the uncertainty challenging to parameterise. Therefore, the appropriate type of uncertainty would not have been captured in the probabilistic sensitivity analysis. Please see section 3.10 in FDG. 1.5 **Administration costs**. The committee considered a lower

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			administration cost for neutralising monoclonal antibodies of £410, equivalent to the cost used for providing an oral antiviral.
18	GlaxoSmithKline (Comment 2)	**GSK does not believe that all relevant evidence has been considered in producing this draft guidance**. a) <u>Clinical effectiveness of sotrovimab</u> While acknowledging that most of the clinical evidence is from studies that pre-date the Omicron variant, GSK does not agree that it is highly uncertain whether sotrovimab is effective against the Omicron variant. While the committee believed that the WHO's and FDA's recommendation against the use of sotrovimab was reasonable, this conclusion does not take into account the totality of available evidence. A recent independent publication from the Francis Crick Institute, the National Institute of Health Research, and University College London (UK) has challenged the negative assessment of sotrovimab by the WHO and urged a reassessment based on limitations and variability of in vitro data and lack of correlation to clinical effectiveness in emerging real-world evidence (Wu et al. 2022). A subsequent publication has further underscored the need for care when extrapolating between neutralizing assays and the clinical efficacy of monoclonal antibodies (Cox et al. 2022). The correspondence in The Lancet by Owen and colleagues elaborate on the reasoning behind the WHO Therapeutics and COVID-19: Living Guideline's strong recommendation against sotrovimab which appears to be predominantly based on clinical pharmacology modelling approaches (Owen et al. 2022). GSK would like to reinforce the lack of a validated pharmacology model that can consistently and reliably correlate in vitro neutralization to predicted clinical efficacy. In the absence of a reliable correlation between in-vitro neutralization and efficacy, other data modalities – including pre-clinical in vivo and observational – are of particular relevance and importance. While recognising that observational studies can be subject to confounding bias, there are well established methodologies for removing and testing for confounding bias such as those	2a and c. Comment noted. Please see response to your comment #1.1. **In vitro evidence and framework:** The committee also considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. 2b. The committee considered additional evidence (Addetia et al. 2023) on sotrovimab. (Please see section 3.12 to 3.18 in the FDG)

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		employed by Zheng et al, using the OpenSAFELY data source in the UK (Zheng, Green, et al. 2022). To help inform the Appraisal Committee and the External Assessment Group of the latest real-world evidence supporting the continued clinical effectiveness of sotrovimab, GSK has conducted a systematic literature review of emerging observational data obtained during the Omicron BA.2 variant wave. This indicates that sotrovimab 500 mg IV retains clinical effectiveness in preventing severe outcomes, despite moderate reductions in in-vitro neutralization with Omicron BA.2. A recent pre-print publication of a study of the Discover Database in North-West London (Patel et al. 2022) reports clinical outcomes associated with sotrovimab by periods of Omicron BA.1, BA.2, and BA.5 (post-hoc exploratory analysis) predominance. These data, in conjunction with preclinical data supporting in vivo antiviral activity of sotrovimab against Omicron BA.2 and Omicron BA.5 viral variants in a hamster model of infection, reinforce the lack of validated models to predict correlates of efficacy based solely on in-vitro neutralization. This systematic literature review, and the preclinical data, are provided in Appendix A. The variability of in-vitro results based on cell lines and assay systems and a lack of models to incorporate the role of Fc effector function, which triggers the body's own innate immune cells to fight SARS-CoV-2 infection, may also contribute to inconsistency between clinical effect and in-vitro results. As of 30 November 2022, sotrovimab continues to neutralize all tested variants with moderate reductions in in-vitro neutralization for Omicron BA.2 sub-lineages; this contrasts with other clinical stage mAbs in which substitutions found in circulating variants are associated with significant reductions in susceptibility or a loss of activity. GSK continues to investigate the role of sotrovimab against viral variants with moderate reductions in susceptibility to better understand its ongoing role in early treatment of appropriate high-risk patients with COVID-19. It should also be noted that the recent increase in Omicron BA.2 sub-lineage variants suggests that the near future may be a mix of sub-lineage variants (sometimes referred to as the 'variant soup'), as opposed to one dominant variant. Therefore, assessing the effectiveness of an early-treatment in just one specific sub-lineage variant may be of limited value when considering the effectiveness of treatments across the population who are at risk of COVID-19 from many sub-	

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		lineage variants. This speaks again to the importance of well-conducted and recent observational studies which do not discriminate by sub-lineage type. GSK asserts that the current WHO and FDA guidance, which advises against sotrovimab, disadvantages patients who have a high unmet need and are at high risk of COVID-19 progression. This includes those living with liver disease, renal disease, solid organ transplants, solid cancers, haematological diseases, and immune-mediated inflammatory disorders.(Green et al. 2022). [redacted] Consideration of neutralisation in-vitro assays, in isolation, does not provide a necessary robust and established causal relationship with clinical effectiveness. While in-vitro data has a role to play in estimating the possible effectiveness of antibody therapies in neutralising current variants of SARS-CoV-2, GSK notes the complexity of the evolving variant landscape and the difficulty in establishing a feasible clinical trial design, and the lack of a validated pharmacology model that could consistently and reliably correlate in-vitro neutralization to predicted clinical efficacy. Consequently, GSK continues to generate and monitor preclinical and RWE data to inform the ongoing benefit-risk assessment of sotrovimab. GSK is concerned that not all available evidence on the effectiveness of sotrovimab has been taken into consideration using formal systematic methods. This is contrary to NICE's clinical evidence hierarchy and guidance for the methodology of evidence synthesis. Further, we note the latest "NICE Health Technology Evaluations; The Manual" and agree that Real World Evidence is an important source of data when a randomised controlled trial (RCT) is not available or appropriate. b) <u>Dual Functionality of sotrovimab</u> As expressed in its Summary of Product Characteristics (SmPC) (GSK 2021), sotrovimab, unlike other COVID-19 therapeutic monoclonal antibodies (mAbs), is a dual-action, engineered human IgG1 mAb that binds to a conserved epitope on the spike protein receptor-binding domain of SARS-CoV-2. It was derived from a parent antibody (S309) isolated from memory B cells of a survivor of severe acute respiratory syndrome coronavirus (SARS-CoV) from 2003. Sotrovimab contains an "LS" mutation in the Fc region to prolong serum half-life. Furthermore, this	

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		mutation in the Fc region allows it to activate CD8+ T lymphocytes for immune destruction of infected cells. In Appendix A (Section 2.2), a full description with references to preclinical studies is provided to describe how the effect change associated with the cell-mediated immune response of sotrovimab's mechanism of action is not captured in in-vitro assays. As referenced in WHO and FDA recommendations, this is a plausible reason why in-vitro assays, in isolation, do not align with the RWE on sotrovimab's effectiveness. c) <u>Real World Evidence</u> Consequently, we request that the EAG and Appraisal Committee carefully consider the importance and relevance of a study by the OpenSAFELY academic collaboration recently published in the BMJ on the continued effectiveness of sotrovimab versus molnupiravir in the Omicron-variant era (Zheng, Green, et al. 2022). The authors concluded that in routine care of adults in England with COVID-19 in the community and at high risk of severe outcomes from COVID-19, those who received sotrovimab were at a substantially lower risk of severe outcomes of COVID-19 compared with molnupiravir. The study was conducted at a time where BA.1 and BA.2 were the dominant variants and where moderate fold change in in-vitro neutralisation for BA.2 was observed, suggesting a lack of robust and predictable correlation between in-vitro neutralisation and clinical outcomes. A retrospective cohort study of individuals treated with sotrovimab with either BA.1 or BA.2 variant classification was recently published as a pre-print manuscript by a team from the UK Health Security Agency (Harman et al. 2022). A stratified Cox regression model was used by Harman and team to estimate the hazard ratios (HRs) of hospital admission with a length of stay of two or more days. The results suggest that the risk of hospital admission is similar between BA.1 and BA.2 cases treated with sotrovimab in the community. Additional evidence on sotrovimab clinical effectiveness provided by GSK, includes a pre-print publication of a study of the Discover Database in North-West	

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		London (Patel et al. 2022). This is a retrospective cohort study of non-hospitalized adult (≥18-year-old) patients who received early treatment for or were diagnosed with COVID-19 between December 1, 2021, and May 31, 2022. Outcomes (hospitalisation or death) were reported for 28 days after the COVID-19 diagnosis. Subgroup analyses were conducted in patients with advanced renal disease, those aged between 18–64 and ≥ 65 years, and by periods of Omicron BA.1, BA.2, and BA.5 (post-hoc exploratory analysis) predominance. Based on robust and consistent emerging observational data obtained during the Omicron BA.2 variant wave, sotrovimab retains clinical effectiveness, despite moderate reductions in in-vitro neutralization, against Omicron BA.2 and likely other similar Omicron BA.2 sub-lineage variants such as Omicron BA.5. These data, in conjunction with other preclinical data in Appendix A supporting in vivo antiviral activity of sotrovimab against Omicron BA.2 and Omicron BA.5 viral variants in a hamster model of infection, reinforce the lack of validated models to predict correlates of efficacy based solely on in-vitro neutralization. Furthermore, in vitro experiments have demonstrated sotrovimab's ability to induce antibody-dependent cellular cytotoxicity and antibody- dependent cellular phagocytosis which may contribute to overall antiviral activity in vivo (Cathcart et al. 2022; Case et al. 2022; Bruel et al. 2022). The variability of in-vitro results based on cell lines and assay systems and a lack of models to incorporate the role of Fc effector function may also contribute to inconsistency between clinical effect and in-vitro results. A total of 696 patients were prescribed sotrovimab, 337 were prescribed nirmatrelvir/ritonavir, 470 were prescribed molnupiravir, and 4,044 eligible high-risk untreated patients were included. Patients receiving sotrovimab were mostly older than 65 (36.9%), had at least three high-risk comorbidities (47.6%), and had severe renal disease (29.3%). The study shows, in total, 5/696 (0.7%) patients on sotrovimab, <5/337 (0.3–1.2%) patients on nirmatrelvir/ritonavir, 10/470 (2.1%) patients on molnupiravir, and 114/4,044 (2.8%) untreated patients were hospitalised with COVID-19 as the primary diagnosis. Similar results were observed across all subgroups and during Omicron subvariant periods. A new study (Zheng, Campbell, et al. 2022), published as a pre-print on December 4, 2022, and hence not captured in our SLR, identified patients on kidney replacement therapy (KRT; dialysis and kidney transplantation) as being at the highest risk of severe outcomes from COVID-19. Using OpenSAFELY-TPP linked to the UK Renal Registry (UKRR) as a data source to identify patients on	

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		KRT, the author compared the clinical effectiveness of sotrovimab against molnupiravir in preventing severe outcomes in KRT patients in non-hospitalised settings. The author identified 2367 individuals as renal patients, of whom 1852 received sotrovimab treatment and 515 received molnupiravir treatment between December 16, 2021, and August 1, 2022, spanning the BA.2 and BA.5 predominance period. The study authors also conducted a complementary analysis using data from patients in the Scottish Renal Registry (SRR) treated with sotrovimab or molnupiravir, following similar analytical approaches. In England, over the 28 days of follow-up following the start of treatment, there were 38 cases (1.6%) of COVID-19-related hospitalisations or deaths, with 21 (1.1%) in the sotrovimab group and 17 (3.3%) in the molnupiravir group. Sotrovimab compared to molnupiravir was linked to a significantly decreased incidence of 28-day COVID-19-related hospitalisation or mortality in multiple-adjusted analyses (hazard ratio, HR=0.35, 95% CI: 0.17 to 0.71; P=0.004), with results remaining robust in sensitivity analyses. In the SRR cohort, over the 28 days of follow-up following the start of treatment with sotrovimab (n = 723) or molnupiravir (n = 270), there were 19 cases (1.9%) of COVID-19 related hospitalizations or deaths. In multiple-adjusted analyses, sotrovimab showed a trend toward lower risk of 28-day COVID-19 related hospitalisation/death than treatment with molnupiravir (HR=0.40, 95% CI: 0.13 to 1.21; P=0.106). In both datasets, sotrovimab had no evidence of association with other hospitalisation or death compared with molnupiravir (HRs ranging from 0.73-1.20; P>0.05). GSK also conducted a retrospective cohort study (data on file, see summary on section 2.4.1 of Appendix A) using data from the Hospital Episode Statistics (HES) database in England. This study provides useful data on the clinical characteristics and hospitalisation rates over time of people who have received sotrovimab and were hospitalised due to COVID-19. [redacted]	

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19	GlaxoSmithKline (Comment 3)	Inequality and Unmet Need The Committee's decision, as indicated in the draft guidance, results in no therapeutic options being available to patients for whom nirmatrelvir/ritonavir cannot be prescribed. **This will disadvantage people who are the most vulnerable to experiencing the severe outcomes of COVID-19.** As per the latest SmPC for nirmatrelvir/ritonavir (Pfizer 2021), treatment is contraindicated in patients with severe renal impairment and contraindicated in patients with severe hepatic impairment. It is also contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions. Nirmatrelvir/ritonavir is also contraindicated with medicinal products that are potent CYP3A inducers where significantly reduced plasma nirmatrelvir/ritonavir concentrations may be associated with the potential for loss of virologic response and possible resistance. The clinical experts at the Committee meeting stated that patients are often prescribed mAbs when oral antiviral therapy is contraindicated or because drug interactions are likely. Generally, this arises in the most vulnerable patients and was similarly reflected in an OpenSAFELY observational study, which reported the clinical characteristics of recipients of COVID-19 therapeutics in non-hospitalised settings (Green et al. 2022). According to this study, sotrovimab is more frequently administered than nirmatrelvir/ritonavir in patients with immune-mediated inflammatory disorders, solid cancer, haematological diseases, stem cell transplant recipients, renal disease, liver disease, and immunosuppression due to HIV or AIDS. Table 1 within Green et al. 2022 shows that, holistically, sotrovimab is prescribed for 55% of this highest-risk group, while nirmatrelvir/ritonavir is only prescribed in 18% of cases and molnupiravir in 27%. Another published observational study (Gahir et al. 2022) conducted by a team at University College London Hospital (UCLH), UK, and presented at the British Infection Association (BIA) identified 872 COVID-19 treatment-eligible patients who attended the COVID Medicine Delivery Unit (CMDU) in North Central London (NCL) between 10 February and 2 May 2022. It was estimated that 36% of treatment-eligible patients could not take nirmatrelvir/ritonavir due to contraindications, and 5% of those who began treatment with nirmatrelvir/ritonavir had to discontinue the treatment.	3. Comment noted. Please see response to your comment #1.2 (Equality issues)

		Research shows that key patient groups for whom nirmatrelvir/ritonavir is contraindicated are at the highest risk of experiencing severe COVID-19, for instance, kidney replacement therapy (KRT; dialysis and kidney transplantation) patients were identified (Zheng, Campbell, et al. 2022) as having the worst prognosis for COVID-19 infections. As a result, this draft guidance may increase health inequalities compared with the current situation where several treatment options are available through the Interim Clinical Commissioning Policy (NHS 2022b). It is important to acknowledge that though the epidemiology of the COVID-19 pandemic has changed in the general population over time, the risks of severe outcomes for groups of people considered to be at the highest risk of severe infection remain very high. According to a retrospective study (Nab et al. 2022) conducted for NHS England, standardised death rates in transplant recipients remained constant across successive waves at 10 per 1,000 person-years. There was also only a small decrease in the mortality rate between the waves of cases in people with kidney disease, haematological malignancies or other conditions associated with immunosuppression. Another observational study (Zerbit et al. 2022) found that of the 57 COVID-19 vaccinated patients with haematological malignancies diagnosed with SARS-CoV-2 infection, 22.8% (n = 13) were hospitalised for a severe form of COVID-19 and 23% (n = 3) of the hospitalised patients died. Further analysis shows patients receiving T-cell or B-cell immunotherapy accounted for the totality of hospitalisation cases (*n* = 13). It has also been shown by (Tenforde et al. 2021)), that vaccine effectiveness is lower in the immunocompromised group (59.2%; 95% CI: 11.9 to 81.1%) than in those without immunosuppression (91.3%; 95% CI: 85.5 to 94.7%). People who are immunocompromised are four times more likely to die of COVID-19 and have prolonged symptoms that can last longer. The UKHSA publication on the risks and outcomes of COVID-19 (PHE 2020) indicated that the outcomes due to COVID-19 are largely influenced by ethnic and socioeconomic disparities. According to the data, people of ethnic minorities and those living in deprived areas have higher rates of diagnosis and death. People of Bangladeshi ethnicity had around twice the risk of death as people of white British ethnicity. When compared to White Britons, people of Chinese, Indian, Pakistani, Other Asian, Black Caribbean, and other black ethnicities had a 10 to 50% higher risk of death. The data also showed that mortality rates from COVID-19 in the most deprived areas were more than double those in the least deprived areas, for both males and females. This is greater than the inequality seen in mortality rates in pre-pandemic years, indicating greater inequality in outcomes of COVID-19.	

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		A more recent UKHSA pre-print publication validating the QCovid4 risk prediction algorithm (Hippisley-Cox et al. 2022) reports significantly elevated mortality hazard ratios (versus high-risk patients prioritised for COVID-19 therapeutics) for men for several conditions. These include the following conditions: kidney transplant (6.1-fold increase); Down's syndrome (4.9-fold); radiotherapy (3.1-fold); type 1 diabetes (3.4-fold); chemotherapy grade A (3.8-fold), grade B (5.8-fold); grade C (10.9-fold); solid organ transplant ever (2.4-fold); dementia (1.62-fold); Parkinson's disease (2.2-fold); liver cirrhosis (2.5-fold). Other conditions associated with increased COVID-19 mortality included learning disability, chronic kidney disease (stages 4 and 5), blood cancer, respiratory cancer, immunosuppressants use, oral steroids use, COPD, coronary heart disease, stroke, atrial fibrillation, heart failure, thromboembolism, rheumatoid/SLE, schizophrenia/bipolar disease sickle cell/HIV/SCID; type 2 diabetes. Results were similar in the model in women, and also when evaluating the risk of COVID-19 hospital admission. Treatment with nirmatrelvir/ritonavir may be contraindicated for a significant number of patients living with many of these conditions. A large proportion of the deprived community and black, Asian, and minority ethnic people are more likely to suffer from co-morbidity, putting them at the highest risk of severe COVID-19. An academic study using NHS data concluded that *"…individuals from a BAME background are more likely to be diagnosed with COVID-19 and more likely to be admitted to hospital and intensive care, compared to the general population of England."* (Alaa et al. 2020). It should be noted that the UKHSA study (Hippisley-Cox et al. 2022) suggests that health inequalities due to COVID-19 attributed to ethnicity may be decreasing, due to improved vaccination status and public health services. Not recommending sotrovimab has the potential to disadvantage those who are most vulnerable to COVID-19 infection, as well as most vulnerable to the outcomes of COVID-19 infection Therefore, we request that the Committee recommends sotrovimab to ensure that the most vulnerable patient groups continue to be protected from the severe outcomes associated with COVID-19. Future sub-group analysis in a nirmatrelvir/ritonavir ineligible population should account for the additional increased risk of severe outcomes that these highest-risk patients can experience. Also, GSK asks the Committee to give particular consideration to the fact that recommending more than one treatment for COVID-19 will help reduce health inequalities due to COVID-19, a key principle that is considered important for all NICE guidance (NICE).	

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20	GlaxoSmithKline (Comment 4)	Hospitalisation rate GSK is aligned with the Committee on the definition of a high-risk population being those as defined in the McInnes report (DHSC 2022), instead of the inclusion/exclusion criteria for study participants in the PANORAMIC study (Butler 2022). The patient population as defined in the McInnes report represents those who have most to benefit from monoclonal antibodies due to the severity of their clinical outcomes if not treated once symptomatic with COVID-19. We do not believe that the outcomes from the PANORAMIC trial should be the referenced base case hospitalisation rate when evaluating this high-risk group. The hospitalisation rate in PANORAMIC is artificially low, as noted by the Committee, because the study excluded participants at the higher end of the risk group. Consequently, conducting cost effectiveness analyses based on the PANORAMIC-defined high-risk definition undervalues treatments used in patients with the highest risk of hospitalisation and other severe outcomes from COVID-19 infection. Furthermore, such patients are often ineligible for nirmatrelvir/ritonavir (Green et al. 2022). It is notable that the hospitalisation rate in the highest-risk sub-groups, where sotrovimab is primarily used, is consistently higher than in both the general population and the PANORAMIC-defined "high-risk" populations. The relevant hospitalisation rates in these patient groups range from 7.69% in chronic lymphocytic leukaemia patients to 26.42% in haemato-oncology patients (see the targeted literature review, section 2.5 of Appendix A). According to an OpenSAFELY study (Nab et al. 2022), the prognosis for the highest risk groups (McInnes population) is much poorer regardless of variants, particularly for immunocompromised or transplant recipients, and has not changed since the pandemic began. We request that the Committee reconsiders these elevated risks and especially for people ineligible for nirmatrelvir/ritonavir. In particular their baseline hospitalisation rates merit closer reconsideration. The targeted literature review (section 2.5. of Appendix A) reports high baseline hospitalisation rates in Omicron-era studies with a sample size greater than 30 for untreated patients with COVID-19 and who are in long term care (4.51% hospitalisation rate, (Krutikov et al. 2022)); kidney transplant recipients (20.83%, (Gleeson et al. 2022)); chronic lymphocytic leukaemia patients (7.69%,(Parry et al. 2022)); and haematological malignancy patients (26.42%,(Bradwell et al. 2022)). A more recent published observational	4.Comment noted. Please see response to your comment 1.3 (Hospitalisation rates)

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		study that was not identified in the targeted review (Zerbit et al. 2022) found that of the 57 COVID-19 vaccinated patients with haematological malignancies diagnosed with SARS-CoV-2 infection, 22.8% (n = 13) were hospitalised for a severe form of COVID-19 and 23% (n = 3) of the hospitalised patients died. **Based on these published studies during the Omicron-era in relevant clinical sub-groups at the highest-risk of hospitalisation, a baseline hospitalisation rate of at least 4.51% is warranted.** Future sub-group analysis in a nirmatrelvir/ritonavir ineligible population should account for the significantly increased risk of severe outcomes that these highest-risk patients can experience, including the high baseline hospitalisation rates demonstrated in the targeted literature review and reported above (see Section 2.5 in Appendix A).	
21	GlaxoSmithKline (Comment 5)	<u>Validity of the EAG's low effectiveness scenario</u> The EAG conducts a low effectiveness scenario to inform the Committee regarding the sensitivity of the model results to key parameter inputs, but acknowledges the limitations associated with these scenarios in terms of how they are modelled. The low effectiveness scenario is informed from the upper end of the confidence intervals for the two clinical trial endpoints used in the model – hospitalisation and mortality. However, many of the studies were not powered to detect a statistically significant difference in mortality, and therefore low numbers of events can result in a very large confidence interval for this endpoint. It should be noted that RWE for sotrovimab has demonstrated a reduction in COVID-19 related mortality (Zheng, Green, et al. 2022; Cheng et al. 2022). For several treatments, including sotrovimab, the low effectiveness scenario results are an illogical scenario where sotrovimab reduces hospitalisation but increases mortality, when compared to standard of care. We believe this scenario is invalid and does not appropriately inform the Committee of the uncertainty associated with the clinical endpoints. If these scenarios are necessary for Committee consideration, then we recommend that in all modelled scenarios the effectiveness in terms of a hazard ratio for mortality is capped at 1 (e.g., equivalent to standard of care) to avoid counter-intuitive results where a scenario may be simulated with a treatment reducing hospitalisation but increase mortality.	5. Comment noted. Please see response to your comment #1.4 (Low efficacy scenario) **Hazard ratio of mortality capped at 1:** Based on DG consultation comments, the AG updated its assumption and capped the mortality rate to equal 1 for the low-efficacy scenario. Please see section 3.10 of FDG.

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22	GlaxoSmithKline (Comment 6)	Use of CMDU micro-cost for the administration cost for community treatment We disagree with the Committee's assumption that the CMDU micro-cost, as opposed to an NHS reference cost, is a more accurate reflection of the cost to be borne by the NHS when community treatments are implemented as part of routine NHS practice in 2023. The latest NHS England Commissioning policy (NHS 2022b) explicitly states that the CMDU's will be decommissioned and models of care will be established so recommended community treatments for COVID-19 are administered as part of routine NHS delivery. We do not agree that the true cost to the NHS of delivery of intravenous treatments will be close to £800, and this high cost reflects the resources required to design, establish and staff a new service during the height of the pandemic (which represents a sunk cost). GSK believes that regular NHS reference costs for intravenous administration of treatments will much more accurately reflect the true cost of intravenous community COVID-19 therapies. Alternatively, it may be appropriate to consider the variable cost of each treatment administration by the CMDUs in the most recent months, in effect removing the sunk cost associated at the start of the pandemic with staffing and scaling up the CMDUs.	6. Comment noted. Please see response to your comment #1.5 (Administration costs)
23	Merck Sharp & Dohme (UK) limited (Comment 1)	**Executive summary** Thank you for the opportunity to comment on the appraisal consultation document (ACD). MSD acknowledges the challenge facing NICE: to make a timely, future-proof, endemic-setting recommendation for a high-risk population - that is still being defined - based on limited, yet highly heterogenous early pandemic data from different geographies, variants, vaccination statuses and patient populations. **Unfortunately, the draft guidance is not a sound and suitable basis for guidance to the NHS on COVID-19 treatments.** a) Should nirmatrelvir with ritonavir be the only treatment option recommended in the community setting, some highly vulnerable, high-risk patients will be left without any effective treatment option. The pragmatic methodology employed in this MTA impacts the technologies differently, leading to inconsistent and biased estimates against some, but not all, treatments. Additionally, equality and equity challenges in the UK health system are likely to be amplified, not mitigated, by the current guidance. Not recommending a treatment option for the many patients in the	1a,f,g. **Equality issues**: Comments noted. The committee considered potential equality issues including 'disability – people contraindicated to nirmatrelvir plus ritonavir'. The committee noted the unmet need and equality issues have been partly addressed by recommending sotrovimab, for people (aged 12 years and over) meeting the McInnes defined high-risk of severe COVID-19 criteria and who are contraindicated to nirmatrelvir plus ritonavir (Please see section 3.32 and 3.33) 1b-c,f,g,j,k. **Molnupiravir clinical evidence**. Comments noted. The committee noted that PANORAMIC may have excluded some of the

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		community setting who are contraindicated or have unmanageable drug–drug interactions (DDIs) with the other community-based oral treatment option, leaves some of the highest-risk patients with no community-based treatment option. This includes patients that are older, disabled, or from an ethnic minority background as is described in 2.34 of the ACD. b) MSD's product molnupiravir (Lagevrio) is not recommended in this ACD, despite evidence presented on its clinical and cost effectiveness in the management of COVID-19, particularly in those at highest risk of progression to severe disease. Recent real-world data from Australia, in a population of 27,000 COVID-19 patients aged 70 years and older, report molnupiravir substantially reduced risk of hospitalisation (26%) and risk of death (54%).[1] PBAC has offered to share with NICE what information it has on this dataset (personal communication). c) The inclusion of the PANORAMIC data in this Technology Appraisal (TA) drives this negative decision. While PANORAMIC is a well-designed and well-conducted study, it collected data in a fundamentally different patient population to that of relevance to this TA. Specifically, the patient population in PANORAMIC is not at high-risk of developing severe disease. **PANORAMIC should not be included in this TA either to estimate (background) hospitalisation rates or provide efficacy estimates for molnupiravir**. d) The application of the same high administration costs for molnupiravir and nirmatrelvir with ritonavir in the economic model unnecessarily increases the cost and, therefore, cost-effectiveness of molnupiravir, a treatment that is straightforward to prescribe, is not associated with any DDIs, and could easily be deployed in the primary care setting. In assigning this high cost, the value of molnupiravir is not accurately captured. Equally, the cost of prescribing nirmatrelvir with ritonavir is underestimated due to the time needed to ensure it is not prescribed to patients that are contraindicated or might have drug–drug interactions (DDIs). e) The patient population relevant to this TA were predominantly treated by the COVID Medicines Delivery Units (CMDUs), therefore data and insights from these centres are more appropriate. Applying a hospitalisation rate (2.79%) with the mean efficacy estimate for	highest risk groups that could have powered the study to see benefits in hospitalisation or mortality. The mean-efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were uncertain because of the population differences. The committee noted the results of the UK based OpenSAFELY data, which included a McInnes-defined high-risk population for molnupiravir, support the limited hospitalisation and mortality benefits observed in PANORAMIC and from the overall NMA. The committee noted that any benefit for hospitalisation or mortality is likely to be minimal when the HRs are close to 1, and stronger clinical evidence is needed to justify a difference in relative clinical effects. (Please see section 3.12, 3.16 and 3.19 of FDG) NICE would normally expect companies to approach authors or triallists to access unpublished data rather than NICE seeking this, although on this occasion NICE did communicate with the investigators. The committee considers the OpenSAFELY data relevant for the evaluation because it was reflective of

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		molnupiravir from the meta-analysis excluding PANORAMIC results in an estimated ICER of £[redacted] (Appraisal Committee's [AC]) or £[redacted]/QALY gained versus SoC (company's preferred assumptions; reduced administration costs and mean efficacy only). The cost-effectiveness of molnupiravir versus SoC increases when higher hospitalisation rates are explored based on CMDU expert opinion. [redacted] f) Based on the above analyses, described in more detail below, molnupiravir is cost-effective in a number of plausible scenarios, especially when no alternative treatment options exist for high-risk patients. On this basis, we request the AC reviews its decision and so prevents highly vulnerable patients, including those with disabilities and those from different ethnic backgrounds, losing access to a well-tolerated and effective COVID-19 treatment with a straightforward prescribing and dosing regimen that could be deployed in the primary care setting. **g) Some patients require rapid treatment in the community setting due to clinical considerations including older aged (as example >65years), immunosuppression, diabetes, those with chronic kidney disease (CKD), those receiving treatment for cancer, those vaccinated but not mounting an immune response, and those who are vaccine contraindicated. These high-risk patients may be left without viable treatment options for mild/moderate COVID-19 treatment as per the current draft guidance recommendations.** h) The economic model excludes all social benefits associated with oral treatments administered in the community, as discussed in 3.23 of the ACD. For example, reduced sickness amongst the NHS workforce, avoiding the requirement for patients to travel to the hospital and patient preference for treatment at home. The model fails to accurately cost DDIs associated with nirmatrelvir with ritonavir. It has been clinically validated that prescribing nirmatrelvir with ritonavir safely (taking account of	UK treatment and population setting. (Please see section 3.11) 1d. **Administration costs** Comment noted. The committee considered the differences in administration costs in relation to the net monetary benefit outcomes, noting the uncertainty about future delivery models. (Please see section 3.26 of FDG) 1e. **Hospitalisation rates** Comment noted. The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort and 4% for people contraindicated to nirmatrelvir plus ritonavir. Please see section 3.22 in FDG. 1e,i. **Remit of FDG** Comment noted. The FDG provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as:

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		contraindications and DDIs) would take substantially longer than prescribing molnupiravir. The current model also omits any (rare) DDI events. These omissions disadvantage molnupiravir, which has no known DDIs or contraindications. We disagree that consideration of these factors is outside the NICE Reference Case, as discussed in issue 9 below. i) The draft guidance fails to consider that future variants might be associated with higher hospitalisation rates, which has a considerable impact on cost-effectiveness. The company reports scenarios within the economic model varying hospitalisation rates that are more representative of the high-risk population. These scenarios should be considered in any final NICE guidance to prevent the guidance being redundant. j) MSD has carried out alternative exploratory analyses to ascertain the cost-effectiveness of molnupiravir across a range of different assumptions. The company has demonstrated how realistic deployment costs for molnupiravir impact cost-effectiveness (See Appendix 2). It is clear that the deployment cost applied has a large impact on the cost-effectiveness in alternative scenarios and we advocate for its change prior to issuing any final guidance. k) We therefore urge the AC to reconsider the evidence and make a positive final guidance recommendation for molnupiravir to ensure that high-risk patients can benefit from multiple alternative community treatment options.	•the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or •local or national circumstances of high rates of hospitalisation for COVID-19. For the purposes of this guidance, NICE cannot take into account stock already purchased by the Department of Health and Social Care. 1h. **Uncaptured benefits** Comment noted. The committee considered that some of the uncaptured benefits fall outside of the NICE reference case or there is limited evidence to support them. (Please see section 3.31 of FDG)
24	Merck Sharp & Dohme (UK) limited (Comment 2)	**Clinical evidence considerations** 1: Patients in PANORAMIC are at lower risk of developing severe disease compared with the McInnes high-risk population or the population in the MOVe-OUT RCT. The ACD concludes that the definition for high-risk of progressing to severe disease with COVID-19 presented in the McInnes report should be used to define the relevant patient population for this MTA. The McInnes definition does not include age as a risk factor, despite clear evidence demonstrating increasing risk of hospitalisation and severe disease with increasing age.[2] McInnes is the definition used operationally in the UK in the	2. Comment noted. Please see responses to your previous comment #1b (Molnupiravir clinical evidence)

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		CMDUs to triage the highest-risk patients for treatment. The MTA, in line with usual NICE methods, should only include studies that report data for a similar population at high risk of disease progression, or statistical methods should be used to adjust for the considerable clinical heterogeneity in study populations. Molnupiravir was granted its marketing authorisation based on the results of the MOVe-OUT clinical trial.[3] The inclusion criteria for the PANORAMIC[4] study do not align with either the inclusion criteria for MOVe-OUT or with the marketing authorisation for molnupiravir: inclusion criteria for MOVe-OUT and PANORAMIC are available in Appendix 1. In brief, to be eligible for enrolment into PANORAMIC, a patient had to be aged 50 years or over, or 18 years or over with a specified pre-existing condition. By contrast, presence of a risk factor for progression to severe disease, irrespective of age, was an inclusion criterion for MOVe-OUT, with one factor defined as age of 60 years or over. The difference between the inclusion criteria from the two studies means that patients at lower risk of developing severe COVID-19 were eligible for enrolment in PANORAMIC and could be classified as 'high-risk' patients. The inclusion criterion of "*Judged by recruiting clinician or research nurse to be clinically vulnerable"* is subjective and vague, and allows for the healthcare practitioner to enrol anyone they think might be vulnerable, even if they are not necessarily at high-risk of progressing to severe COVID-19. The consequence of applying the criteria above may result in a population less likely to progress to severe disease and, consequently, an artificially low rate of hospitalisation in both the molnupiravir and standard of care (SoC) groups. • **During the consultation period, MSD contacted UK clinical experts for input, who fed back that those patients at highest risk of progression continued to receive treatment via the CMDUs. Consequently, patients eligible for inclusion in PANORAMIC were at a lower risk of progression than the target population for treatment with molnupiravir. Clinical experts also confirmed that patients not qualifying for treatment via the CMDUs, and therefore a population that is at lower risk of disease progression, were diverted to PANORAMIC for screening and potential enrolment.[5]** Additionally, people randomised to SoC in PANORAMIC were able to obtain molnupiravir and other treatments through the NHS, outside of the study, which confounds the estimates of effect from the SoC group from PANORAMIC, and	

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		likely results in lower rates of hospitalisation and death, both of which contribute to the underestimation of the comparative clinical effectiveness of molnupiravir. In Section 3.14 of the ACD, clinical experts suggested that, given the committee's preferred definition of high-risk, the highest-risk group **is underrepresented** in PANORAMIC, a view which was supported by clinical experts contacted by MSD during the consultation period. Overall, **MSD is extremely concerned that crucial clinical heterogeneity across study populations is not being adequately addressed.** In brief, study key population baseline characteristics for MOVe-OUT[3] and PANORAMIC[4] were; • Mean participant age: 43.7 years (standard deviation 13.7) in MOVe-OUT versus 56.6 years in PANORAMIC; • Proportion of people with one or more comorbidities at risk for progression to severe illness from COVID-19: 99.4% in MOVe-OUT versus 69% in PANORAMIC; • % BMI > 30: ~75% in MOVe-OUT versus ~15% in PANORAMIC • % Diabetic: ~16% across both arms in MOVe-OUT versus ~12% in PANORAMIC • Level of vaccination: 0% in MOVe-OUT versus 99% having received at least one dose of a SARS-CoV-2 in PANORAMIC. While MOVe-OUT patients are younger on average, it is clear that the PANORAMIC study recruited a population that was highly vaccinated and at lower risk of progressing to severe disease, and, based on the timing of the study, was affected by the Omicron variant, which is acknowledged to associated with lower rates of hospitalisation compared with earlier variants. The inclusion of the PANORAMIC trial in the meta-analysis is likely to lead to bias and uncertainty in estimates of comparative effectiveness versus SoC, due to the introduction of additional clinical heterogeneity into the analysis. As noted earlier, the population enrolled in PANORAMIC has a lower risk of progression compared with population from other studies included in the analysis, and, therefore, inclusion of results derived from PANORAMIC are likely to introduce bias against molnupiravir, and underestimate its true clinical effect. Given the recognised	

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		presence of heterogeneity, data were synthesised using a random effects model, and, due to the size of the population enrolled in PANORAMIC, the results from PANORAMIC are likely to have a higher weight in the analysis than results from other studies, which exacerbates the underestimation of the effect of molnupiravir in a population at high risk of progression. Inclusion of results from PANORAMIC in any meta-analysis is likely to increase uncertainty in effect estimates and their generalisability to the target high risk population. It would seem perverse if a negative recommendation were made with respect to molnupiravir largely on the basis of the results from the PANORAMIC trial, given the lack of trial evidence for the other treatments in a highly vaccinated population. Alternatively, all suitable sources of evidence should be incorporated into the NMA as in a typical NICE HTA. MSD is aware of RWE studies from similar geographies to the UK that were conducted during the Omicron variant COVID-19 wave in vaccinated patients more like the McInnes definition of the population at high-risk of developing severe disease. Whilst we acknowledge the limitations of retrospective studies, given the rapidly evolving nature of the clinical data, RWE should be taken into consideration. We enclose this evidence, which is in press or published, in a separate appendix for consideration by the Committee. **Given the aspects described above, MSD considers that results from PANORAMIC are not relevant for the purposes of this appraisal.**	
25	Merck Sharp & Dohme (UK) limited (Comment 3)	2. Additional RWE to PANORAMIC provides critical evidence on the activity of MOV in high-risk patient populations, especially in older patients and those with clinical considerations that may not be able to receive nirmatrelvir with ritonavir. The clinical programme underpinning the effectiveness estimates for molnupiravir is comprehensive, with several clinical studies reporting positive results, as is currently evidenced in the ERG report. By comparison, the efficacy and safety of other agents are predominantly derived from a single RCT. **Evolution of COVID-19 and changes in vaccination rates over time not only impact the assessment of molnupiravir but also all other oral antivirals and monoclonal antibodies; for example, EPIC-HR recruited unvaccinated patients pre-Omicron variant.**	3. Comment noted. Please see responses to your previous comment #1b (Molnupiravir clinical evidence) **Nirmatrelvir plus ritonavir clinical evidence**: For nirmatrelvir plus ritonavir, along with EPIC HR, OpenSAFELY evidence, the committee noted the subgroup analysis from the recent EPIC-SR trial that included people who were vaccinated with at least one risk factor for severe COVID-19. The committee noted that PANORAMIC was also

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		RWE provides additional evidence of the clinical benefit of molnupiravir in treating a broad range of patients with mild-to-moderate COVID-19 both those at low risk of hospitalisation or death and those who are clinically vulnerable and at very high risk of hospitalisation or death due to COVID-19. The pivotal Phase 3 trial, MOVe-OUT, showed that molnupiravir was effective in high-risk, unvaccinated non-hospitalised patients infected with early variants of COVID-19. Given the changing epidemiology of SARS-CoV-2, RWE provides additional useful insights into the clinical efficacy and safety of molnupiravir for treating newer variants. MSD systematically surveyed the literature for reports of RWE studies that include molnupiravir (see Appendix 3 for a tabular summary of RWE studies available as of 29th September 2022). The identified real-world data, collected largely when Omicron was the predominant SARS-CoV-2 variant alongside a range of vaccination rates, provide evidence of the safety and effectiveness of molnupiravir in treating patients across a continuum of risk. Whilst RWE sources may have limitations, they remain important for consideration for COVID-19, which continues to evolve over time. Results from a selection of RWE studies are summarised here. We report the larger, territory wide or national databases, the full list of RWE sources is provided in appendix: • Observational, retrospective assessment of data collected from 19,868 electronic medical records of Clalit Health Services in Israel (Arbel et al 2022[6]), molnupiravir was shown to be associated with a reduced risk of hospitalisation or death in high-risk patients with COVID-19 who were 65 years and older.[6] In this group, the adjusted HR for hospitalisation was 0.55 (95% CI, 0.34 to 0.88). Most patients (92%) in this study had previous COVID-19 immunity (i.e., by vaccination, prior COVID-19 infection, or both) and received molnupiravir during the Omicron wave.[6] • Observational, retrospective cohort study conducted by Wong et al,[7] data from the Hong Kong Hospital Authority were used to identify a territory-wide cohort of non-hospitalised patients with an officially registered diagnosis of SARS-CoV-2 infection during a period in which the Omicron variant was dominant.[7] After propensity score matching, 54,217 patients	recruiting a nirmatrelvir plus ritonavir treatment arm that could answer questions about its effectiveness for people with high risk factors for severe COVID-19 but are not defined in the McInnes high-risk group. (Please see section 3.19 of FDG)

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		(4,983 who received molnupiravir and 49,234 matched controls) were analysed for study outcomes. After matching, the mean age of participants treated with molnupiravir was 71.4 years. Study vaccination rate was ~17%. Molnupiravir use was associated with lower risks of death and in-hospital disease progression.[7] The risk of hospitalisation for molnupiravir-treated patients was similar to the risk in the matched controls (crude incidence rate of 107.6 vs 104.0 per 100,000 person-days, respectively: HR 0.98 [95% CI 0.89 to 1.06]. However, treatment with molnupiravir was associated with a lower risk of all-cause mortality (crude incidence rate of 17.9 vs. 22.1 per 100,000 person-days, respectively: HR 0.76 [95% CI 0.61 to 0.95]).[7] ○ An evaluation of the clinical effectiveness of molnupiravir (by the same authors) in patients in Hong Kong who were hospitalised due to their high risk of progression to severe disease showed that molnupiravir was associated with a lower risk of death compared with matched controls (HR: 0.48 [95% CI 0.40 to 0.59]).[8] It should be noted that the mean age after propensity score matching in the molnupiravir arm was 80.7 years. • In a retrospective cohort study conducted by Bruno et al[9] in southern Italy, 719 high-risk patients received treatment for COVID-19 during a period when Omicron and subvariants were dominant.[9] Of the trial population, 554 patients received molnupiravir whereas 165 patients received nirmatrelvir and ritonavir – 93% of the total trial population had been fully vaccinated. The mean age for molnupiravir was 73 years, whereas for nirmatrelvir and ritonavir mean age was 62 years. Overall, 43 all-cause hospitalisations (5.9%) and 13 (1.8%) deaths were observed at 30 days. No differences between the two antivirals were observed. Both antivirals helped to limit hospitalisation and deaths at 30 days among patients who were at high-risk of disease progression in the period when Omicron was dominant, and most of the population was vaccinated. Amongst others, age ≥75 years was associated with higher risk for hospitalisation. • A retrospective study conducted in Israel by Najjar-Debbiny et al[10] examined the effectiveness of molnupiravir in patients who were at high-risk for severe COVID-19 and had no contraindications for molnupiravir use.[10] Overall 2,661 molnupiravir patients were propensity score matched to 2,661 controls. The composite outcome was progression to severe COVID-19 or COVID-19 specific mortality. Molnupiravir was associated with a nonsignificant reduced risk of the composite outcome (HR, 0.83	

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		[95% CI, 0.57 to 1.21]). However, subgroup analyses showed that molnupiravir was associated with a significant decrease in the risk of the composite outcome in older patients (HR: 0.54 [95% CI, 0.34 to 0.86]), females (HR: 0.41 [95% CI, 0.22 to 0.77]), and in patients with inadequate COVID-19 vaccination (HR: 0.45 [95% CI:0.25 to 0.82]); the vaccination status in the study was ~77%.[10] Authors report that adequate vaccination was associated with significant decrease in number of events for all examined outcomes. • A retrospective study, conducted by Flisiak *et al.* 2022,[11] assessed the efficacy of molnupiravir in patients hospitalised for COVID-19 in a real-world clinical practice during the wave of Omicron infections. Of the 203 patients that received molnupiravir, 9.9% died during the 28-day follow up compared with 16.3% of the 387 patients that did not receive anti-viral treatment (p=0.03). The reduction in 28-day mortality was particularly evident in the population of patients over 80 years of age treated in the first 5 days of the disease (14.6% vs 35.2%, p=0.016).[11] Data are not available on the vaccination status of participants included in the study. • MSD is aware of the Australia Victoria Government dataset that is being prepared for publication and may provide a valuable source of evidence for the use of molnupiravir in the real-world setting. Top-line results have been reported by the authors who note that the risk of hospitalisation reduced by 26% and the risk of death reduced by 54% for molnupiravir-treated patients in patients over 70 years of age.[1] MSD kindly requests NICE utilises its relationship with the PBAC in Australia, who we understand have access to some of this data, to source this large and relevant dataset. [redacted] These RW studies consistently report positive effectiveness of molnupiravir with evidence of benefit in higher risk populations (including older ages and unvaccinated patients). Interesting routes requiring further research also emerge: patients hospitalised after molnupiravir treatment require less intensive treatment and a measurable benefit in rapid treatment with an antiviral.	

Comment number	Organisation name	Stakeholder comment	NICE Response
		The rapid evolution of the COVID-19 pandemic has made it necessary to consider data from randomized-controlled trials (RCTs) **and** RWE studies to understand the true efficacy of COVID-19 antiviral treatments and the populations with greatest potential to benefit. These studies vary in inclusion/exclusion criteria (e.g., vaccination status), outcomes, and predominant circulating variant, which makes simple cross-trial comparisons of reported efficacy results challenging and baseline hospitalisation rates is not appropriate as it would not account for such differences. An internal MSD study by Maas *et al*. 2022[12] used a multivariate logistic regression model of influential factors (developed based on the MOVe-OUT study) to predict the baseline event rates for hospitalization/death in populations from nine recently published studies given the COVID-19 evolution under the assumption that alternative RWE sources can be used to carry out such adjustments on the current clinical literature (abstract submitted to ECCMID 2023 for publication and shared in confidence). The analysis demonstrated that baseline rates of hospitalisation or death were highest in studies involving unvaccinated populations and carried out pre-Omicron variant. The analysis also showed variations in baseline hospitalisation risk across RCTs, with the MOVe-OUT trial enrolling the highest risk population, with a predicted mean event rate of [redacted], while the UK PANORAMIC study population was associated with the lowest baseline event rate (predicted mean: [redacted]) based on the different adjustments conducted. The baseline event rates for studies conducted in vaccinated participants, while the Omicron variant was the predominant variant, were much lower compared to studies of unvaccinated participants conducted pre-Omicron with alternative adjustments and models providing a mean range of baseline hospitalisation rates across the different studies included in the analysis . Notably, **in RWE studies, higher risk patients tended to receive molnupiravir, while lower risk patients tended to receive nirmatrelvir with ritonavir or SoC (Figure 4).** Clinical characteristics, such as patient risk factors, vaccination status, and virus variant, had a substantial impact on hospitalisation rate or death. The data presented add further support to the company's position that it is inappropriate to use the PANORAMIC trial alongside the other RCT evidence to model the clinical effectiveness of molnupiravir within the economic assessment	

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		(i.e., the meta-analysed treatment effects), without further consideration of underlying risk and how this impacts the cost-effectiveness results. **See Figure 3 in MSD DG consultation comments.** ▌ The RWE described above offers additional evidence of the clinical benefit of molnupiravir that is generalisable in the Omicron variant across a range of populations and vaccination rates, which could be of relevance in those with inadequate immune response. However, the unconventional MTA process means that these additional, potentially relevant, studies have not been included, however, results from the PANORAMIC study *have* been included, despite the population heterogeneity with MOVe-OUT and the McInnes population highlighted under Issue 1 above. Molnupiravir's comprehensive evidence base, compared to that of other treatments in the community setting, has not been taken into account as a strength in this appraisal process and instead the inclusion of data from PANORAMIC for a low-risk, vaccinated population exposed to the Omicron variant, unfairly penalises the treatment. MSD is aware that the clinical effectiveness of nirmatrelvir with ritonavir is currently being assessed within the PANORAMIC trial as noted in the draft guidance. It is unclear from the ACD when or how the results for nirmatrelvir with ritonavir will be incorporated into clinical and cost effectiveness analyses? MSD requests that NICE transparently states how it plans to revisit any guidance following the release of the PANORAMIC data for nirmatrelvir with ritonavir. We urge the Committee to consider the totality of the evidence presented above which is strongly supportive of the effectiveness of molnupiravir in vaccinated, Omicron-infected, **high-risk patients.** **Additional RWE supports the effectiveness of molnupiravir in high-risk patient populations, especially older patients and those with clinical considerations who may not be able to receive nirmatrelvir with ritonavir, due to contraindication or potential DDIs, and patients requiring rapid treatment in the community setting. MSD reiterates its request for the Committee to consider the additional evidence presented. Only at that stage can it be certain that any final guidance issued by NICE may continue to remain relevant for the NHS.**	

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		We note section 3.6 in the ACD states, “the committee considered a single definition of high risk should be used because of the model limitations. Additional functionality would be required to make differential subgroup recommendations and this would not be practical or proportionate to the decision problem”. It is not true to say additional functionality would be required to make subgroup recommendations, all that is needed is an estimate of the background hospitalisation (and mortality rate) for the relevant subgroup. The consequence of not considering subgroups, which is apparent in this draft guidance, is that high-risk populations, including those with relevant protected characteristics around race and disability, are left without any treatment option. We request the AC reconsider if this situation is proportionate.	
26	Merck Sharp & Dohme (UK) limited (Comment 4)	A significant number of patients will be unable to receive treatment for COVID-19 due to drug-drug interactions and contraindications. Their impact is excluded from the economic evaluation **A significant number of high-risk patients are ineligible for treatment with nirmatrelvir plus ritonavir, due to the potential for DDIs and contraindications with existing treatments for co-morbid conditions. As no alternative treatments have been recommended for use in the community, these patients will have no access to treatment for COVID-19. DDIs should be included in the economic model. DDIs have an impact on the cost-effectiveness of interventions that is currently omitted.** In the ACD, nirmatrelvir plus ritonavir is the only COVID-19 treatment recommended for use in the community setting. Ritonavir (in the nirmatrelvir and ritonavir combination) is a potent CYP38 inhibitor and interactions with other medicines may lead to severe, life-threatening, or fatal events.[13] Contraindications for nirmatrelvir plus ritonavir include severe renal and hepatic impairment. Furthermore, ritonavir is known to have interactions with many treatments used in the management of other conditions, including interactions with anticoagulants, anticonvulsants and antiarrhythmics, which are common treatments for the comorbid conditions the presence of which defines a high-risk patient.	4.Comment noted. Please see responses to your comment 1a (Equality issues) and 1d (Administration costs)

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		A UK clinical expert consulted by MSD fed back that approximately 20% of patients could be contraindicated to nirmatrelvir plus ritonavir and will therefore require access to alternative treatment options. MSD therefore explored various scenarios using age as a proxy for increasing severity and assuming that patients with severe renal and hepatic impairment are at higher-risk of progressing to severe disease with COVID-19. Simply adjusting the model starting age to 65 with a 2.79% hospitalisation rate using MSD's preferred assumptions resulted in an ICER of £[redacted]For patients aged 70 or older the ICER was £[redacted]. It should be noted that the background hospitalisation rates in these patients is likely to be higher than the 2.79% and alternative values informed by expert opinion or clinical literature (such as Vo et al 2022) only improve the cost-effectiveness of molnupiravir in this patient population with ICERs between £[redacted] and £[redacted] depending the efficacy selection and hospitalisation input explored; refer to full cost-effectiveness results provided by MSD in confidential appendix). Several analyses have been conducted exploring the potential risks of administering a ritonavir-containing COVID-19 treatment, which are discussed in further detail below: • In an analysis of the Optum claims database of 1.2 million US patients diagnosed with COVID-19 from 1st January 2020 to 30th June 2021,[14] it was estimated that approximately 43% of all COVID-19 patients were receiving at least one concomitant medication that had a potential contraindication to or major DDI with ritonavir-containing COVID-19 treatment. The prevalence of potential DDIs increased in high-risk populations for severe illness from COVID-19, including patients >60 years of age (62%), those with diabetes (72%), with any type of cancer (62%), with chronic kidney disease stage 3–5 (74%), or residing in a long-term care facility (68%).[14] • A similar analysis conducted with data derived from the 2015–2019 National Health and Nutrition Examination Surveys database[15] estimated that 29.3% of all US adults had a potential contraindication or major DDI with a ritonavir-containing COVID-19 treatment.[15] The prevalence rose to 60% among those aged at least 60 years, 78% among individuals with diabetes, and 88% among those with serious heart conditions. Thus, a	

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		vast number of high-risk patients will be without an effective COVID-19 treatment if only nirmatrelvir plus ritonavir is approved.[15] • An analysis of the Pharmaceutical Benefits Scheme 10% sample (PBS10) claims data found that over 40% of the Australian adult population were at risk of potential DDIs that would be classified as major or contraindicated with ritonavir-containing treatment.[16] Patients at higher risk for severe COVID-19 symptoms had the highest prevalence of contraindications or major potential DDIs. These were highest in patients with cancer (79%), dementia and/or Alzheimer's (77.2%), and diabetes (73.8%). The study further demonstrates patients with the highest risk of developing severe COVID-19 symptoms, and therefore most likely to require hospitalisation, will be without an effective COVID-19 treatment if only nirmatrelvir with ritonavir is recommended.[16] • A retrospective analysis was conducted using the statutory health insurance (SHI) claim data from 2019 in database of Gesundheitsforen Leipzig GmbH (Germany) (abstract submitted to the DOAK conference for publication and share in confidence). Contraindicated medications and medications being subject to physician's decision were defined according to either SmPC or Mikus 2022. The study showed that combined potential DDI among those using ritonavir-containing regimen for contraindicated medications and those requiring a physician's decision was 56.0% according to SmPC, and 44.3% according to Mikus's approach. • A cohort study conducted by Hoertel et al (2022)[17] examined the prevalence of contraindications to nirmatrelvir with ritonavir in patients hospitalised with COVID-19. A review of the health records of 62,525 patients identified that 14.6% had a medical contraindication to nirmatrelvir plus ritonavir. Rate of contraindications increased to 26.9% in patients aged over 65 years and to over 37.0% in people with comorbidities, which included diseases of the skin and subcutaneous tissue (45.5%), neoplasms (38.2%) and diseases of the nervous system (39.4%).[17] Section 3.24 in the ACD acknowledges that the current recommendations may exclude some people in certain risk groups who are included in the marketing authorisation and who have a disability. People with disabilities are more likely to be taking a medicine in the list of nirmatrelvir plus ritonavir contraindications.	

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		These patients are already at increased risk for progression to severe COVID-19, therefore not recommending an alternative COVID-19 treatment unfairly discriminates against people with a high unmet need for an effective treatment. The same section also highlights that people from ethnic minority family backgrounds are more likely to be diagnosed with COVID-19 and have a higher risk of dying from COVID-19 than the white British population (black people: HR 1.71; 95% CI, 1.44 to 2.02: Asian people: HR 1.62; 95% CI, 1.43 to 1.82).[18] Furthermore, the ACD acknowledges that the prevalence of hepatic and renal impairments is high in people from ethnic minority family backgrounds. Nirmatrelvir plus ritonavir is contraindicated in patients with severe hepatic and renal impairments.[19] Offering no alternative COVID-19 treatment for non-hospitalised patients indirectly discriminates against patients from an ethnic minority family background. These patients are already at an increased risk of suffering fatal COVID-19 and are now being denied access to effective COVID-19 treatments. There is compelling evidence in the scientific literature that highlights the implications of DDIs in optimal treatment selection for specific patient groups, and these concerns are also supported by clinicians whom MSD engaged during the appraisal consultation process. The evidence demonstrates that, in some patient groups, the risk of DDIs is considerable due to the nature of their conditions. Interruption of regular treatment schedules for some comorbid conditions to facilitate treatment for COVID-19 with nirmatrelvir with ritonavir is considered clinically inappropriate, especially as there are existing COVID-19 treatments that may be prescribed concomitantly with treatments for comorbid conditions, such as molnupiravir. With regards to the economic evaluation, before prescribing nirmatrelvir plus ritonavir, a full medication review is required to evaluate potential for DDIs. As such, administration costs for nirmatrelvir plus ritonavir are likely to be higher than other comparators but this is not reflected at all in the economic analyses run to date. For example, the cost of a pharmacist per hour is valued at £352.49,[20, 21] which underscores that administration costs could rapidly accumulate should only ritonavir-based treatment be recommended. Additional costs associated with DDIs include GP and pharmacist costs, as well as hospital visits. DDIs complicate the ability of the pharmacist to easily prescribe	

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		additional medication due to the requirement for a full medication review, which is resource intense. If patients in the UK can be treated within the community with molnupiravir, an easy-to-administer drug with no known DDIs, then considerable time and resource use is saved compared with the use of other community drugs for high-risk patients with COVID-19. The sensitivity analysis provided by the Committee demonstrates 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 hospitalisation admission proportion increase in the standard of care arm. Figure 23 in the Committee papers shows that, as the hospitalisation risk increases, the ICER for molnupiravir reduces. As such, the likelihood of molnupiravir being a cost-effective treatment for people with disabilities or from ethnic minority family backgrounds is increased, as these groups have an increased risk of hospitalisation. For example, a study carried out by Imperial College London (April 2022) has identified people with long-term conditions, such as severe mental illness and learning disabilities, as the groups with the highest risk of hospitalisation.[22] Furthermore, as there are no known DDIs or contraindications associated with the use of molnupiravir, making it an ideal alternative treatment for high-risk patients ineligible to receive nirmatrelvir plus ritonavir. To avoid excluding a significant number of high-risk patients from COVID-19 treatment, in particular people with disabilities and people from ethnic minority family backgrounds, the Committee needs to address the significant unmet need for an effective alternative agent that can be quickly administered in the community for patient groups with various clinical considerations at high risk of progressing to severe disease which may require urgent care in the community setting. **It is clear that from the evidence above that the impact of DDIs is important and relevant and should be considered formally in the appraisal process to avoid disadvantaging any patient groups indirectly.** **Unlike its comparators, molnupiravir has no known drug-drug interactions and the full cost-effectiveness implications of this have not been explored.**	

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		Currently the cost-effectiveness of molnupiravir is underestimated significantly, especially for patient groups that cannot receive alternatives recommended within the draft guidance.	
27	Merck Sharp & Dohme (UK) limited (Comment 5)	**The current evidence synthesis methodology is flawed. Using low-efficacy estimates for molnupiravir is both inappropriate and disadvantageous.** **MSD has serious concerns regarding the approach to the evidence synthesis and its ability to inform decision making. There are key differences across studies that have not been adjusted for and that may affect the validity of the results considered by the AC. MSD conducted some additional analyses that attempt to quantify the impact of study differences and adjust trial outcomes to demonstrate the likely impact of differences on the estimates of clinical and cost effectiveness of molnupiravir.** Due to the limited time available, a pragmatic approach was adopted by the EAG to identify and collate information on COVID-19 for non-hospitalised patients to provide evidence for decision-making. The estimates of comparative effectiveness presented in Table 5 (p31) of the EAG report were derived from the two living systematic reviews (COVID-NMA initiative and the metaEvidence initiative). The COVID-NMA initiative was used as a third-party source to identify relevant trials and synthesise data from these trials. The EAG report does not list the source trial data included in the synthesis and does specify which trials are included in the synthesis for patients at risk of hospitalisation. Most of the studies included in the evidence synthesis were conducted in an unvaccinated population and pre-Omicron, with the exception of the PANORAMIC study, the data from which became available a few working days before the ACM. Of treatments under consideration within PANORAMIC and the MTA, only results for molnupiravir results have read out to date. However, we understand that whilst nirmatrelvir with ritonavir is undergoing assessment, it will be some time before results will be available, particularly given the slower than expected recruitment of the study to date. In contrast to the other pivotal RCTs included in the review, as noted earlier, the **PANORAMIC study recruited a highly vaccinated population at a low risk of progressing to severe disease and affected by the Omicron variant (see**	5. Comments noted. Please see responses to your previous comment #1b (Molnupiravir clinical evidence) and #3 (nirmatrelvir plus ritonavir clinical evidence) 5a. **Statement on pooling PANORAMIC results:** In the FDG the statement has been updated to 'the mean-efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were uncertain because of the population differences' **5b.EAG report source trial data**: The data is publicly available from the COVID-NMA website. The details of all the trials informing the meta-analysis have been provided in the appendix Table 1 of the EAG report. 5c. **Low efficacy scenario**: Comment noted. The committee considered that low efficacy scenarios represented an attempt to address some aspects of uncertainty in the absence of alternative methods to model the uncertainty. At DG consultation, consultees highlighted that a probabilistic sensitivity analysis would be a better way to capture the uncertainty. The committee noted that

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		Issue 1 above). Despite the high level of clinical heterogeneity identified when comparing PANORAMIC with other included studies, results from PANORAMIC were synthesised with those from other trials identified from the COVID-NMA initiative, in effect "adjusting" the relative treatment effect reported from the other pivotal RCTs to that of an "less risk, Omicron exposed, highly vaccinated population". **It should be noted that no comparable evidence in a highly vaccinated population was considered with respect to any of the other treatments under consideration and no attempts were made to adjust the other data in any other way.** In the draft ACD, the Committee also noted that: *"the mean efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were likely to overestimate the benefits of molnupiravir."* This is factually incorrect, and we request it is corrected to "*the mean efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were likely to* ***underestimate*** *the benefits of molnupiravir.* ***This is because PANORAMIC recruited a population that is generally perceived to be at lower risk for progression to severe disease if left untreated"*** The estimates of relative effectiveness from the PANORAMIC trial are likely to be biased due to patients in the usual care arm receiving molnupiravir and other treatments through the NHS, as commented on by the authors of the PANORAMIC trial: "*Participants randomised to molnupiravir would not have received additional molnupiravir through the NHS; however, those randomised to usual care may have received molnupiravir through the NHS and this was recorded in the online diary".* MSD is concerned about the preference for considering the low-efficacy estimates from the evidence synthesis to inform decision making. **Use of the low efficacy estimate does not capture the effectiveness of molnupiravir in the real-world setting and disproportionately disadvantaged against molnupiravir.** Furthermore, inclusion of the results from PANORAMIC disproportionately disadvantages against molnupiravir because of the lower rate of hospitalisation derived from a population at lower risk of progression, which leads to an underestimation of the clinical effect of molnupiravir in its target population.	the heterogeneity in the trial populations and the generalisability issues across the trials made the uncertainty challenging to parameterise. Therefore, the appropriate type of uncertainty would not have been captured in the probabilistic sensitivity analysis. Please see section 3.10 in FDG.

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		There is no reason to believe that the confidence interval (CI), which is used to generate the low efficacy scenario from the meta-analysis represents, a reasonable estimate of the efficacy in the contemporary population, and it should be clearly noted that a 95% CI is an arbitrary level. Further, the lower limit of the 95% CI estimates should be viewed with extreme pessimism. **For these reasons MSD does not believe that the low efficacy values should be considered by the Committee when evaluating the cost-effectiveness of treatments in the non-hospitalised setting.** Specific to the evidence synthesis, the estimated QALYs from the cost-effectiveness model, based on evidence synthesis results are presented (from Erratum dated 25/10/22). As demonstrated, there is a high degree of uncertainty in both the comparability of results from different studies and the relevance of the study results to a contemporary population given that the studies evaluated patients from an unvaccinated population and did not include patients infected with the Omicron variant. **As a result, any judgement as to the ranking of molnupiravir relative to nirmatrelvir with ritonavir is highly uncertain.** These uncertainties notwithstanding, molnupiravir was estimated to be the second most effective treatment. The mean estimated QALYs were 0.03 less than nirmatrelvir with ritonavir, which was recommended in the draft guidance. MSD has extracted the forest plots from the living COVID-NMA to demonstrate the inappropriateness of ranking treatments (Figures 2 and 3); molnupiravir's assessment included a larger number of studies, which informs the point estimate, including the PANORAMIC study (Butler et al 2022[4]). This is not the case for EPIC-HR informing the evaluation of nirmatrelvir with ritonavir with effect size estimates extracted from a single RCT. Multiple studies and the evolution of COVID-19 would contribute to the upper level estimate of molnupiravir's effectiveness crossing the line of no difference. However, as explained, this is not fully reflective or relevant because the analysis below includes a lower risk population, which biases the results.	

		See Figure 4 in MSD DG consultation comments: Forest plot from COVID-NMA for meta-analysis of RCTs evaluating molnupiravir **Figure 3** *in MSD DG consultation comments:*: **Forest plot from COVID-NMA for analysis of RCT evaluating nirmatrelvir with ritonavir** Table 4 *in MSD DG consultation comments:*: **Extract from Table 21 of updated AG report (Erratum dated 25/10/22)** As recommended in a recent publication by Thom *et al.* (2022),[23] decision-making should not be based on deterministic analysis due to the uncertainty in model parameters. Basing the final recommendations on probabilistic sensitivity analysis would better capture the uncertainty in certain model parameters, such as efficacy values, as well as future-proofing the guidance. **Assuming low efficacy estimates for molnupiravir is both inappropriate and disadvantageous considering the extensive RCT and RWE evidence base available for molnupiravir, in contrast to all other agents under assessment.** The AC may continue to consider conservative assumptions in efficacy estimates for other agents to account for their limited evidence base when informing final recommendations. The current methods bring severe implications in the validity of the comparative effectiveness estimates used for molnupiravir's assessment. The impact of clinical heterogeneity is not captured, and attempts have not been made to adjust the results to account for the differences. To do this adequately, a full assessment of uncertainty, primarily based on clinical heterogeneity in the patient population and on the disparity across the studies in other factors (i.e., standard of care, variant type, pandemic development) would be required rather than on pure statistical heterogeneity from an aggregate level meta-analysis, where selected studies are pooled together without any adjustment. **Simply pooling the results of these studies to inform the decision making is therefore flawed.** Given these aspects MSD strongly urges the Committee to only **consider the results of the meta-analysis <u>excluding</u> the PANORAMIC trial versus SoC, as these will provide the least biased estimates of comparative effectiveness versus SoC as suggested by clinical experts.** A more robust meta-analysis could alternatively be performed if the PANORAMIC research team made available the patient level data to the EAG for the purposes of identifying the "true	

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		high-risk" sub-group population to ensure a more robust basis for evidence synthesis before drawing conclusions for decision making. Given information available, we would expect this to be a small proportion of the PANORAMIC study population. Adjustments to the remaining clinical evidence should also be carried out to reflect the ongoing evolution of clinical evidence base.	
28	Merck Sharp & Dohme (UK) limited (Comment 6)	Alternative hospitalisation rates need exploring. **Hospitalisation rates were extensively discussed at the ACM, and different sources were cited as proxies of the true background hospitalisation rate for patients who are at high risk of progressing to severe disease. It is also acknowledged within the ACD that the PANORAMIC hospitalisation rate of 0.77% could be an underestimation for the target population at 'high-risk'.** In Section 3.6 of the ACD, the Committee concluded that the definition of high-risk in the McInnes report is the most robust. Using the DISCOVER-NOW database[24] interim analysis and McInnes high-risk population definition results in a hospitalisation rate of 2.79%.[25] Given the Committee's preferred definition of "high-risk", the hospitalisation rate should be sourced from data using the high-risk definition for consistency. In Section 3.14 of the ACD, clinical experts suggested that, given the Committee's preferred definition of high-risk, the highest-risk group may have been under-represented in the PANORAMIC trial given that the hospitalisation rate was 0.77%, which is significantly lower than all the other reported estimates: 2.79% for the original estimate used by the EAG for their base case, 1.45% in the OPENSAFELY study,[26] and 18.4% in the Shields *et al.* 2022 publication.[27] Despite acknowledging that the hospitalisation rate from PANORAMIC is likely to be an underestimation of the true rate for high-risk patients, the Committee presented scenario analyses in Section 3.20 of the ACD utilising the low, likely underestimated, hospitalisation rate. Additionally, the Committee states that the results for molnupiravir are over NICE's £30,000 per QALY willingness-to-pay threshold. However, there is no acknowledgement that scenario analysis using the low-efficacy measure and 0.77% hospitalisation rate generates an ICER for nirmatrelvir plus ritonavir that is also over the standard willingness-to-pay threshold at £60,415 per QALY gained, with nirmatrelvir plus ritonavir being recommended as a treatment option in the ACD.	6.Comment noted. Please see response to your comment 1e (Hospitalisation rates) Clinical experts were present at both ACM1 and ACM2 and were given the opportunity to provide their opinion on the hospitalisation rates.

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		MSD engaged with clinical experts and patient organisations during the consultation period to collect more insights around the appropriateness of the parameters applied in the economic model. Experts and patient organisation representatives **agreed that the PANORAMIC baseline hospitalisation rate does not reflect the patients at true high risk of progressing to severe disease. Experts note that COVID-19 continues to evolve, and it is unclear how future variants will affect patients.** One clinical expert closely affiliated with a CMDU provided further insights noting that as: "*a minimum, a 3%-5% hospitalisation rate is realistic for true high-risk patients who had an immune response with COVID-19 vaccination. But this rate could perhaps increase to 7% or even 8% for those who do not mount an adequate immune response after COVID-19 vaccination. To put this into perspective, from the 28% treated at a CMDU, approximately 20% of patients do not mount an immune response.*" Including patients with a lower risk for progression to severe COVID-19 than in the identified target population (such as those included in PANORAMIC) will translate into a lower rate of hospitalisation and rate of mortality. Any decisions made using parameters from a trial population unreflective of the target population will lead to a spurious final recommendation. Considering that the hospitalisation rate parameter is a key model driver, MSD asks that a full systematic review is conducted to capture all randomised and non-randomised data sources, in line with the NICE evaluation methods, **in the correct high-risk of severe disease population**. Consulting clinical experts would also generate and/or validate more accurate rate of hospitalisation for high-risk patients. MSD has run some additional analyses using the hospitalisation rates provided by clinical experts, alongside some estimates reported in the clinical literature (please see in Appendix 2). The analyses reflect comments that PANORAMIC underestimates the true hospitalisation rate and illustrates the impact this parameter has on the ICER. MSD has also run alternative scenarios to ascertain what hospitalisation rates result in ICERs below £30,000/QALY for molnupiravir versus SoC. These analyses demonstrate that the hospitalisation rate needs to be between [redacted] depending on the assumptions feeing into the economic	

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		analysis. Importantly, these analyses validate the clinical expert values for hospitalisation (*"range of 3% to 5% as minimum and perhaps a 7%-8% for some patient groups)*". MSD's analyses demonstrate the importance of exploring alternative hospitalisation rates for all interventions, given the uncertainty in disease evolution over time, as supported by expert feedback. **MSD asks that the Committee takes into consideration the expert insights and a range of estimates around rate of hospitalisation for its final guidance to ensure future proofing of the recommendations.**	
29	Merck Sharp & Dohme (UK) limited (Comment 7)	Unjustified administration cost for oral antiviral treatments: Once delivery of oral antivirals is moved to the primary care setting, in the future, the current deployment costs for oral therapies (£410) will reduce substantially. Molnupiravir is easy to prescribe, with no known DDIs, which means that deployment costs for most patients should proxy those of community NHS prescription plus postage costs for timely treatment delivery. Under these considerations, the application of a £410 administration cost for oral antiviral treatments is unjustified and should be removed or, at minimum, reduced to align with the cost of prescribing drugs in the community. MSD acknowledges that a percentage of patients may still require a more formal review, based on clinical expert discussions held during the appraisal process and, therefore, has adjusted deployment costs to reflect true routine commissioning reality. We note that the draft guidance page 27 states; **"***NHS England provided Covid Medicines Delivery Unit (CMDU) deployment costs for the administration of oral antivirals (£410) and neutralising monoclonal antibodies (£820). Some companies disagreed with using CMDU deployment costs because these include costs based in secondary care.* ***However, future delivery is anticipated to be in primary care, which would reduce these costs. The NHS England representative explained that the delivery of service is subject to change. In future, integrated care boards will be responsible for treatment delivery currently done by the CMDUs****"*. It was also noted that costs were calculated before implementation of nirmatrelvir plus ritonavir as an additional antiviral treatment.	7.Comment noted. Please see response to your comment #1d (Administration costs)

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		Nirmatrelvir plus ritonavir is expected to increase resource use because of the expected requirements to assess contraindications. We therefore request that deployment costs applied to this agent are proportionally adjusted to reflect clinical reality in line with emerging literature on this subject. Section 3.18 of the ACD explains the EAG's rationale for including an administration cost for oral COVID-19 treatments. MSD disagrees with the Committee's decision to include a £410 administration cost for oral COVID-19 treatments for the following reasons: • The Position Statement from the CMDU, included in the committee papers, highlights the difficulty CMDUs participating in the costing exercise encountered in estimating the staff time spent on administration, triage, and treatment. As such, the estimated administration cost is uncertain and has the potential to include the cost of staff time spent on both triage and treatment. • The £410 administration cost applied in the economic analysis includes deployment costs based in secondary care. The ACD suggests that "*future delivery may be in primary care*", which would likely reduce deployment costs. Molnupiravir is administered in the community as an outpatient treatment, therefore, including secondary care deployment costs in the CMDU's oral administration cost estimate will unnecessarily inflate the administration cost for primary care treatments. Comparing the CMDU's estimated administration cost for oral treatments with the NHS prescription charge highlights the disparity between the costs. A £410 administration cost is approximately equivalent to three hours of GP time (£140 per hour GMS activity[20]), which is high for an oral drug with no contraindications. Furthermore, the PSSRU 2021 reported a prescription cost per consultation as £33.10, which is considerably lower than the £410 administration cost applied in the model.[20] The cost of £33.10 is more appropriate for molnupiravir, because the risk of contraindications is understood to be minimal.[14] • Furthermore, MSD has engaged with clinical experts to understand if CMDUs (or their future transformation) could still be used to deploy access of antivirals in specific patient populations (primarily those with polypharmacy due to comorbidities). Experts noted that between **7% and**	

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		8% (maximum value of 10% reported used) of patients that are at high risk of progressing to severe disease and may therefore require COVID-19 therapeutics will need a more detailed assessment due to DDIs and comorbidities. For the purposes of this assessment, we used the maximum value of 10% that would require a complex assessment in similar facility of the CMDU. Therefore, the Committee considered an alternative cost of £41.00 for molnupiravir alone, 10% of the £410 administration cost used in the economic analysis. The administration costs for nirmatrelvir with ritonavir should differ to account for the higher assessment time required to ascertain patient fitness based on DDIs. The rapidly changing nature of the pandemic and the speed at which CMDUs were established meant that the structure and resourcing needs of the CMDUs evolved with the progression of the pandemic. The Position Statement explained how deployment costs have continued to change throughout the pandemic. As the treatment pathway becomes established and patient needs are more predictable, administration costs for oral COVID treatments are likely to fall due to increased efficiency when administering treatments within the CMDU. In the ACD, a representative from NHS England explained how the delivery of the service is subject to change with integrated care boards responsible for treatment delivery currently done by the CMDU. To future-proof the guidance, MSD believes the best approach would be to either exclude administration costs for oral treatments or adjust them accordingly as outlined above, to ensure estimates used in the economic model have face validity. In Appendix 2, MSD have run some additional analyses which include a DDI cost for nirmatrelvir/ritonavir and the elimination of administration costs for an oral drug in the community. Applying these assumptions results in total discounted costs of [redacted] and total discounted QALYs of [redacted] for molnupiravir and an overall ICER of [redacted] for molnupiravir vs SoC. This is compared to an overall ICER of £10,251 for nirmatrelvir/ritonavir vs SoC (MSD has applied costs for DDIs in its preferred assumptions). **Using alternative plausible administration costs results in improved estimates of cost-effectiveness for molnupiravir versus SoC.**	

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30	Merck Sharp & Dohme (UK) limited (Comment 8)	Omissions from the economic model: It is also worth noting that other aspects from PANORAMIC in addition to the hospitalisation rate that benefit molnupiravir are currently not factored in the economic assessment. For example, the PANORAMIC study demonstrates a significant improvement in the time to resolution of symptoms for patients treated with molnupiravir. The median time to first recovery was 9 days in molnupiravir and 15 days in usual care, resulting in an estimated benefit of 4.2 days with molnupiravir treatment. Therefore, a faster return to health will result in a greater incremental QALY for patients treated with molnupiravir compared to usual care. • Additionally, reduced healthcare resource use is associated with molnupiravir. Of the patients in the PANORAMIC study, 19.6% of those receiving molnupiravir contacted a GP, compared with 23.7% receiving usual care, which leads to reduced costs with use of molnupiravir **Whilst hospitalisation rates for SoC have been included from PANORAMIC, other relevant endpoints, such as time to recovery and health care resource use, have not been included in the assessment by the EAG. It can therefore be concluded that the cost-effectiveness of molnupiravir is currently underestimated within the current economic model.**	8.Comment noted. The committee considered that relative treatment effect, and reduced hospitalisation and mortality rates are key drivers of benefit, but acknowledged that the model was not sensitive to other benefits of treatment like faster resolution of symptoms. The committee considered the model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19. The committee acknowledged that in the PANORAMIC trial results for molnupiravir, there was a significant difference in the secondary endpoint of time to self-reported recovery. (Please see section 3.19 and 3.21 of FDG)
31	Merck Sharp & Dohme (UK) limited (Comment 9)	**Uncaptured clinical and societal value of molnupiravir:** **MSD continues to remain concerned with the current technology appraisal process and the evaluation framework followed for COVID-19 therapeutics. The rigidity of the current framework means that clinical and societal value are not captured for antivirals, including molnupiravir, with a resulting negative impact on the cost-effectiveness analyses.** Some aspects of additional value could had been easily introduced without requiring excessive model structure changes. We note that section 3.23 in the ACD discusses elements of uncaptured value including, for example, transmission to healthcare professionals and concludes these either fall out of the reference case or there is limited evidence to support them. We disagree that these fall outside of the reference case. While it is generally understood that the current NICE evaluation framework may be	9.Comment noted. Please see response to your comment #1h (Uncaptured benefit)

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		restrictive in capturing wider societal benefits, these factors have been discussed extensively on a number of occasions: • Recent anti-microbial assessments (cefiderocol and ceftazimide/avibactam for severe drug-resistant, gram-negative bacteria);[28] • Other antiviral HTAs (notably in Hepatitis C [TA430,[29] TA499,[30] TA507;[31] focusing on latest TAs] and Influenza [TA158[32] and TA168[33]]); • Direct societal and economic impact to the NHS of sickness in the NHS workforce. Drawing from the examples listed above, MSD restates that areas of uncaptured value relevant for decision-making are excluded from this MTA. This includes some elements of transmission, diversity of products and insurance (antimicrobial assessments)[25,26] and transmission (hepatitis-C appraisals (TA507,[31] TA499[30])). **Relevance for COVID-19:** During the appraisal committee meeting, extensive time was dedicated to discussing the effectiveness of technologies under consideration across different COVID-19 variants. We welcome the Committee's apparent conclusions that AVs are more likely to maintain their effectiveness over time. MSD considers that the Committee's deliberations on the above matter attempts to capture qualitatively the following "STEDI" aspects of the antimicrobial assessment framework that would enable to capturing of wider health benefits: • spectrum of action (antibiotics specific); • transmission disruption (applicable to COVID); • enablement value for the NHS (applicable to COVID); • diversity of products (applicable to COVID); • insurance value (applicable to COVID). With regards to the COVID-19 therapeutics appraisal, the EAG model and assessment report exclude all social benefits associated with approving oral treatments that can be administered in the community. These include reduced	

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		sickness amongst the NHS workforce, avoiding the requirement for patients to travel to the hospital and patient preference for treatment at home. Due to the patient-facing nature of the role, front-line healthcare workers are at a higher risk of contracting COVID-19 than the general public, which will result in significant costs to the health service through staff absenteeism and, consequently, delayed or cancelled treatments. Such costs would be reduced by preventing hospitalisation in high-risk patients with COVID-19, which would, therefore, result in the reduction of transmission to front-line healthcare workers. As a treatment that is delivered entirely in the community, and that has been shown to reduce rate of hospitalisation compare with placebo, molnupiravir can reduce the exposure of the NHS workforce to COVID-19.[3] The reduction in transmission to key healthcare workers, a key benefit of molnupiravir, is not considered in the economic model. **MSD continues to advocate that such aspects should be formally modelled as part of the ongoing MTA or at least be explored in scenario analyses considering their relevance, although we acknowledge that some restructure in the economic model may be necessary to capture the aspects outlined above.**	
32	Pfizer (Comment 1)	**Restriction of the eligible population despite cost-effectiveness in a broader population** Pfizer are disappointed that NICE have chosen to restrict the definition of high risk, effectively removing from consideration a large group of patients who could benefit from treatment (outlined in Appendix 1), particularly given the Committee conclusion that this restriction could indirectly discriminate against patients with disability, such as those with severe and profound learning disability. This is despite evidence of clinical and cost-effectiveness of Paxlovid in a broader population of patients. In this response we address this issue by discussing the following: a) The inappropriateness of using the McInness report definition of highest risk to define a high-risk population b) Retained high risk population trends in the era of the Omicron SARS-Cov-2 variant (Comment 2)	**1a-b**. Comments noted. **Highest-risk and high-risk group:** At ACM2, the committee noted the draft guidance consultation comments highlighted the need for separate 'high risk' and 'highest risk' groups, or a separate high-risk group contraindicated to nirmatrelvir plus ritonavir. The committee saw examples on how the risk group could be split based on Patel et al. 2022. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. The committee did not see additional

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		c) The use of age in defining a population at high risk of severe COVID-19 in a robust and equitable way (Comment 3) d) Hospitalisation rates adopted in the model by the committee do not align with the considered population, we therefore propose alternative estimate sources (Comment 4) e) Perform further cost effectiveness analysis using alternative hospitalisation rates (Comment 9). The appraisal consultation document (ACD) states that subgroups should be considered separately because considering a mixed group of risk definitions disadvantages the highest risk groups. It is unclear why this should be the case, as availability of treatments for all high-risk patients will ensure that the highest risk groups will also receive treatment. Use of the McInnes report to define the eligible population is of particular concern given the stated objectives of this work are not aligned to the objectives of the NICE assessment. The McInnes report sought to define those patients who remain at the very highest risk of severe COVID-19 despite full adherence with community-wide public health measures including vaccination.[1] This is in contrast to defining all those who are at high risk of adverse COVID-19 outcomes that could hence benefit from treatment with Paxlovid®, which should be the remit of this assessment. The very highest risk population as defined by the McInnes report is in effect a subgroup of the population at high risk of severe COVID-19. A clear distinction between high and highest risk needs to be made as was done by in the study by Patel et al., 2022[2] in which they calculated the hospitalisation rate for the for the McInnes report subpopulation. As a result, within the ACD, all references to the "high risk" definition from the McInnes report should more accurately be termed "highest risk". This conclusion is supported by international guidance,[3] where the definition of "high risk" broadly aligns with the PANORAMIC study,[4] which should be the definition considered in this guidance. The ACD states that the committee was concerned that making a recommendation based on age might cause inequality, given that age is a protected characteristic. While we acknowledge the challenge in defining an age threshold, we disagree that doing so is a source of inequality. The Joint Committee on Vaccination and Immunisation (JCVI) routinely recommends access to vaccinations based on age as an eligibility criterion and this includes access to the COVID-19 vaccine. The JCVI state that for the 2022 autumn booster	evidence to justify splitting the high-risk group. **McInnes definition:** The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected. (Please see section 3.4 to 3.7 of FDG) **1c. Age:** Comment noted. The committee acknowledged that age is a risk factor for progression to severe COVID 19. The committee considered that the relationship between age and comorbidities can be important in explaining risk of severe disease. The committee also noted that additional evidence is needed to model age over 70 years as an independent subgroup for the mild COVID-19 setting. The

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		programme,[5] the primary objective is to augment immunity in those at higher risk from COVID-19 and thereby optimise protection against severe COVID-19, specifically hospitalisation and death, over winter 2022 to 2023. Those at higher risk are defined as: • residents in a care home for older adults and staff working in care homes for older adults • frontline health and social care workers • all adults aged 50 years and over • persons aged 5 to 49 years in a clinical risk group, as set out in the Green Book, chapter 14a, tables 3 and 4[6] • persons aged 5 to 49 years who are household contacts of people with immunosuppression • persons aged 16 to 49 years who are carers, as set out in the Green Book, chapter 14a, table 3[6] We agree with NICE that staging recommendations across different subgroups would introduce additional uncertainty. However, restricting the criteria applied in the community setting to only those at the absolute highest risk deprives patient groups at risk of progression to severe disease of effective treatment. We are not aware of any clinical or cost-effectiveness rationale to exclude these patients from receiving treatment and believe this decision goes against the scientific evidence[7] and expert opinions shared in the company submission (CS) and at the appraisal committee meeting (ACM). **See Table 5 - High- and highest-risk conditions criteria in Pfizer DG consultation comments**	committee concluded that the McInnes report's definition of high risk included the most robust evidence of people who have a high risk for progressing to severe COVID-19, and this did not include age as an independent risk factor.
33	Pfizer (Comment 2)	**Evidence to support high risk population in the era of Omicron** The Appraisal Committee has requested additional evidence to support a broader definition of high risk, specifically evidence in a vaccinated population with the Omicron variant. Pfizer has presented this evidence below and on this basis request that the Appraisal Committee re-consider the restriction of the eligible population. The ACD notes the following: "The committee concluded that more evidence is needed on the impact of age to justify including it as an independent factor that	2. Comment noted. Please also see response to your earlier comment #1a-c. For inclusion of additional subgroups the committee noted additional functionality, clinical or cost inputs and treatment-effectiveness assumptions would be required to make differential subgroup recommendations and this

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		increases risk at similar levels to other comorbidities defined in the McInnes report. This should include evidence, adjusted for comorbidities, from a vaccinated population with the Omicron variant." We are unclear as to why this evidence needs to achieve this specific criterion to be considered valid. The McInnes report was published in May 2022 and is predominantly based on evidence published during 2021[1], particularly QCOVID3, which is based on data available to June 2021.[8] As a result, the conclusions from the McInnes report are based on evidence from time periods where the Alpha and Delta variants were dominant in the UK.[9,10] Although it is likely that the conclusions from the McInnes report remain relevant to the "highest risk" population, it is important to note the time period and associated dominant variants contributing to this evidence base. As such, it is unclear why the Committee considered this to be the most robust definition when later evidence is available to support the inclusion of broader patient groups within the high-risk category (see Omicron based evidence in Appendix 2).[11-13] As previously highlighted, the living risk prediction algorithm QCOVID has demonstrated the impact of an increasing age on the risk of COVID-19 death and hospitalisation in England.[14] The algorithm has been externally validated[15] and further validated via real world evidence studies in Wales and Scotland.[16,17] In addition to QCOVID, there is a substantial UK and international evidence base supporting age as an independent risk factor for hospitalisation and mortality,[18-22] detailed in the CS. At the core of the McInnes report is a subset of conditions identified as high risk for severe COVID-19 based on QCOVID3, with additional data from the advisory group evaluating additional data from the ISARIC Coronavirus Clinical Characterisation Consortium (ISIRAC 4C)[13] report. Additional literature and expert opinion were used to provide further granularity allowing for identification of a very highest risk subgroup. In our CS evidence, from an evaluation of QCOVID4 risk algorithm[23] (commissioned by the UK's Department of Health and Social Care), we used data from the Omicron wave, as well as the number of vaccination doses and prior SARS-CoV-2 infection, to identify individuals at highest levels of absolute risk for targeted interventions more accurately than the 'conditions-based' approach adopted by NHS Digital based on relative risk of a list of medical conditions. We also provided evidence from literature showing a clear increased risk of severe COVID-19 for conditions included in the PANORAMIC study, as well as a clear independent correlation between age and risk of severe COVID-19. The	would not be practical or aligned with the decision problem. (Please see section 3.7 in FDG) The committee said the evidence for inclusion of age in the model should include: age-adjusted hospitalisation and mortality rates for the untreated population and relative treatment effects for the intervention. (Please see section 3.6 in FDG)

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		independent clinical experts who contributed to the ACM discussion, agreed with this assessment citing similar evidence.[24] In its evidence-based resource for healthcare professionals, the Center for Disease Control and Prevention (CDC) includes age as a risk factor for severe COVID-19 outcomes, going as far to say "Age remains the strongest risk factor".[3] High risk populations included in the PANORAMIC study are also listed by CDC in its summary of conditions with evidence for higher risk for severe COVID-19 outcomes, including asthma, COPD, diabetes, learning disabilities, heart conditions, and obesity (BMI ≥ 30 kg/m^2).[3] The CDC defines higher risk for severe COVID-19 outcomes as an underlying medical condition or risk factor that has a published meta-analysis or systematic review or having completed the CDC systematic review process.[25] The evidence the CDC provide[26] could be used to supplement or as an alternative to the McInnes report for defining high risk populations. Similarly, age is a key criterion in the definition of higher risk applied in the UK for the 2022 autumn booster programme.[5,6] This advice notes that those patients over the age of 65 years have by far the highest risk, and the risk increases with age. As a result, patients are further prioritised for vaccination on the basis of age: 1. Residents in a care home for older adults or staff working in care homes for older adults 2. Frontline health and social care workers and all those 80 years of age and over 3. All those 75 years of age and over 4. All those 70 years of age and over or individuals aged 16 to 69 in a high-risk group 5. All those 65 years of age and over 6. Adults aged 16 to 65 years in an at-risk group 7. All those 60 years of age and over 8. All those 55 years of age and over 9. All those 50 years of age and over	

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34	Pfizer (Comment 3)	**Age as a robust and equitable definition of high risk** While age is an independent risk factor for severe COVID-19 outcomes,[7,27] pre-existing conditions are also independently correlated to severe COVID-19 outcomes. In addition, the total number of underlying medical conditions (multi-morbidities) was a strong risk factor of severe COVID-19 illness (see See Figure **5**).[28,29] Even in the Omicron era, older age, frailty and multimorbidity remain significant risk factors for a worse clinical outcome.[11-13,29,30] Guidance from the McInnes report focused on a few specific pre-existing conditions in isolation and did not account for the cumulative absolute risk associated with multiple co-morbidities, age, prior infection, vaccination status or the new variants. **See Figure 5 in Pfizer's DG consultation comments. Risk ratio (95% CI) of death, invasive mechanical ventilation (IMV), and admission to intensive care unit (ICU), by the number of underlying medical conditions among adults hospitalised with COVID-19 in the Premier Healthcare Database Special COVID-19 Release.** Each panel contains the results of a single generalized linear model with Poisson distribution and log link function, adjusted for age group, sex, race/ethnicity, payer type, hospital urbanicity, US Census region of hospital, admission month, and admission month squared as controls. Patients who died without ICU care or IMV were excluded from the sample when estimating the model with the outcome of ICU care or IMV, respectively. Source: Kompaniyets et al. (2021)[28] It is well documented that age is positively correlated with the prevalence of co-morbidities,[31,32] as well as the number of conditions an individual has (multi-morbidities).[32-35] In 2015, it was estimated that over half (54.0%) of the population aged 65+ in England had two or more diseases. When stratified by age, multi-morbidity increases with age: from 45.7% for those aged 65–74 to 68.7% for those aged 85+.[33] Another study looking at British civil servants at Whitehall in London estimated that the prevalence of multi-morbidity (≥2 chronic diseases) was 6.6% (655/9937) at age 55 and 31.7% (2464/7783) at age 70.[33] Multi-morbidity is common, socially patterned, and associated with increased health service utilisation.[35] A Clinical Practice Research Datalink (CPRD) study of adults ages	3. Comment noted. Please see responses to your earlier comment 1c.

Comment number	Organisation name	Stakeholder comment	NICE Response
		18+ in England found that greater socioeconomic deprivation was associated with significantly higher levels of multi-morbidity — 30.0% in the quintile with the greatest levels of deprivation versus 25.8% in that with the lowest (see See Figure **6** below).[35] **See Figure 6 in Pfizer's DG consultation comments.** ***Prevalence of multimorbidity by age and socioeconomic status. A1 is the quintile with the least socioeconomic deprivation, 5 is that with the greatest.*** Source: Cassell et al. (2018)[35] An eligibility criterion that includes an age threshold allows for the equitable inclusion of patients with not only individual pre-existing high risk conditions but also those with cumulative absolute risk associated with multiple co-morbidities and age which places them at high risk of severe COVID-19 or COVID-19 related death. In Comment 9, we present results from scenario analysis that in combination with additional data from PANORAMIC would allow the committee to determine an age inclusion criterion using cost-effectiveness analysis. This is similar to the approach taken by the JCVI in their recommendation for the 2022 autumn booster programme,[5] where the primary objective is to augment immunity in those at higher risk from COVID-19 and thereby optimise protection against severe COVID-19, specifically hospitalisation and death, over winter 2022 to 2023.	
35	Pfizer (Comment 4)	**Hospitalisation rates adopted in the model by the committee do not align with the considered population** We believe that the hospitalisation rates applied in the model (0.77% derived from PANORAMIC) are an underestimate and do not represent all the at-risk population groups, since it excludes the highest risk population. The associated cost-effectiveness results should therefore be considered overly conservative. A retrospective cohort study of non-hospitalised patients who received early treatment for, or were diagnosed with, COVID-19 between 1 December 2021 and 31 May 2022, used data from the Discover dataset in north-west London and included patients who were high risk or highest risk (see See Table **5**) and treated with sotrovimab, nirmatrelvir/ritonavir or molnupiravir, or were untreated. This study by Patel et al. 2022 which provided the 2.8% hospitalisation rate estimate	4. **Hospitalisation rates:** Comments noted. The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort and 4% for people contraindicated to nirmatrelvir plus ritonavir. (Please see section 3.22 in FDG) The committee also considered the mean- and low-efficacy scenarios using

Comment number	Organisation name	Stakeholder comment	NICE Response
		for the highest risk population also contains data on the hospitalisation rate (2.1%) for a high-risk population treated with Molnupiravir as defined in See Table **5**. This population was made up of individuals with no highest risk conditions (45.7%), 1 highest risk condition (37.2%) and 2 highest risk conditions (17.0%). Considering these patients were treated, a 2.1% hospitalisation rate would be a conservative estimate for a high-risk population. In light of the limited availability of data to inform the baseline hospitalisation rates, mortality rates and mean age in the community of patients at high risk of progression to severe Covid-19 between the current estimates from the McInness report population (0.8%) and the PANORAMIC trial estimate (2.8%), we propose that NICE obtain these estimates from the PANORAMIC study investigators: stratification of the PANORAMIC population based on their risk criteria or age at study admission would allow NICE and the evidence assessment group (EAG) to explore scenarios aligned to a variety of risk definitions to identify the optimal population in which Paxlovid is cost-effective. We believe this would be the best approach for defining the true patient group for which treatments are cost effective, rather than having to restrict to just the highest risk patients using the McInnes criteria, which excludes patients that would likely benefit from treatment. The PANORAMIC data should be used to explore cost-effectiveness using modified PANORAMIC eligibility criterion, considering all aged 18+ with at least one risk conditions as defined in PANORAMIC study and incrementally one of the following: • all aged 55+ • all aged 60+ • all aged 65+ • all aged 70+ • all aged 75+ etc • excluding an age threshold **While these data would provide additional inputs for the cost-effectiveness model, they would still underestimate the true hospitalisation rates since the population in the PANORAMIC trial excludes the highest risk group.**	a hospitalisation rate of 0.77% from PANORAMIC which more closely approximated the marketing authorisation population for nirmatrelvir plus ritonavir. NICE would normally expect companies to approach authors or triallists to access unpublished data rather than NICE seeking this. However, on this occasion, NICE communicated with the PANORAMIC investigators. (Please see section 3.28 in FDG)
36	Pfizer (Comment 5)	**The administration costs applied in the EAG model are an overestimate compared to real-world costs**	5. Comment noted. **Administration costs:**

Comment number	Organisation name	Stakeholder comment	NICE Response
		The future delivery of treatments will be in a primary care setting and therefore we believe that applying the COVID-19 Medicine Delivery Unit (CMDU) deployment costs (£410) for Paxlovid is an overestimation compared to the likely real-world/business as usual costs once final guidance is implemented. Furthermore, the cost calculation included cost elements not appropriate for a primary care delivery model for antivirals for example clinical consumables, stationery, room hire, office equipment and multiple staff costs. While these might be relevant in accessing the costs of setting up and running a CMDU (which do not have permanent structures), they do not reflect costs associated with routine delivery of an oral treatment in primary care. Based on current systems, the dispensing of Paxlovid may involve an e-consultation or telephone tirage involving a medical clinical review to ensure suitability of treatment and a pharmacy pick up or delivery service. We suggest two alternate costing scenarios based on possible real world administration scenarios: • To model the administration process for Paxlovid for the average patient in primary care, we assume that clinical medical review, prescribing and dispensing will require a maximum of one hour of time (allowing for triage and clinical medical review) from a band 8a pharmacist or prescribing nurse: £75 based on Personal Social Services Research Unit (PSSRU) costs.[36] • An alternative scenario to administration costing representing the more complex medical review required for care home patients should also be considered for a portion of the eligible population. PSSRU review for this scenario found that "the average cost per resident of the multi-professional medication review intervention was £117".[36] This scenario represents the most complex medical review process and is considered as the upper limit for oral antiviral administration cost. This has been applied in the cost effectiveness analysis presented in Comment 9, See Figure **8**	The committee acknowledged the different administration costs provided during draft guidance consultation. The committee considered the differences in administration costs in relation to the net monetary benefit outcomes, noting the uncertainty about future delivery models. The views of the companies, clinical experts, patient/carer representatives and the public surrounding this issue were considered by committee when formulating its recommendations (Please see section 3.26).
37	Pfizer (Comment 6)	**Manageability of Paxlovid contraindications and interactions** The ACD quotes clinical expert advice that there are many contraindications for Paxlovid (nirmatrelvir plus ritonavir), including severe renal and hepatic impairment, and interactions with many common treatments. However, it is worth	6. Comment noted. Please see response to your comment #5 (Administration costs)

Comment number	Organisation name	Stakeholder comment	NICE Response
		noting that the majority of these contraindications align with the profile for ritonavir,[37-39] which is an extremely well-characterised antiviral therapy, first receiving marketing authorisation in the EU in 1996.[40] Although usage has reduced over the following decades, ritonavir remains part of regimens recommended in the 2022 BHIVA guidelines.[41] In this context, clinicians are familiar with assessing contraindications and conducting drug interaction assessments for ritonavir-boosted therapies. Further, there are publicly available resources to help support clinicians in assessing the drug interactions,[42,43] reducing the time that will be required during prescribing. As a result, the admin cost we propose in comment 5 would be factoring in the time associated with drug interaction assessment.	
38	Pfizer (Comment 7)	**Inappropriateness of the low-efficacy scenarios for Paxlovid despite clear evidence of effectiveness in vaccinated individuals and the omicron variant from real-world evidence (RWE)** Recent large RWE studies (see Appendix 2) on the effectiveness of Paxlovid during the omicron period in vaccinated patients,[44-64] is supportive of the efficacy of Paxlovid demonstrated in the EPIC-HR study (this also informs Paxlovid effectiveness estimates in the EAG's model). Paxlovid is effective in a variety of real-world settings with varying standards of care, proportions of people with COVID-19 vaccinations, and varied levels of population immunity derived through natural infection. The numerous RWE studies demonstrate the robust protection offered by Paxlovid in the current setting of Omicron dominance and within a high population seroprevalence. Therefore, we believe the use of the low efficacy scenario in the model for decision making is not supported by clinical evidence. Combining these low efficacy estimates with the hospitalisation rates from PANORAMIC is overly conservative given the available RWE (see Appendix 2) and the evidence included in the CS. We believe this demonstrates that the 'mean efficacy' scenario applied in the model should be considered the lower bound for Paxlovid clinical effectiveness during NICE decision making. The lower efficacy scenario is not supported by any clinical evidence we are aware of and is likely an underestimate of Paxlovid's effectiveness in both vaccinated and unvaccinated populations and during the Omicron period.	7. Comment noted. **Nirmatrelvir plus ritonavir clinical effectiveness:** Committee noted the observational evidence and the trial evidence. Committee still considered there to be substantial uncertainty with the EPIC-HR trial data because of generalisability concerns with the mean-efficacy estimate. Therefore, the committee considered the range between the mean- and lower-efficacy estimates for nirmatrelvir plus ritonavir from the trial to be more suited to the current endemic setting, despite the limitations with this approach. (Please see section 3.11, 3.12 and 3.19 of FDG)

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39	Pfizer (Comment 8)	**Hospitalisation costs used in the EAG model are currently underestimated** While the EAG has taken onboard the need to use an alternative set of HRG codes (DZ11 Lobar, Atypical or Viral Pneumonia) in relation to the COVID-19 hospitalisation costs, an error was made in hospitalisation cost calculation resulting in an underestimation. Hospitalisation costs are crucial in this analysis as hospitalisation costs and hospitalisation rates are coupled on their impact on the incremental cost-effectiveness ratio (ICER). The current approach is underestimating hospitalisation costs. The issues with the current approach are 2-fold: 1. Use of DZ19H - DZ19N (Other Respiratory Disorders) for non-elective (1-2 days) costs is inappropriate since COVID-19 has an average length of admission of 11 days.[65] 2. Non-critical care NHS reference costs were used as cost per day when they are actually costs per finished consultancy episode (FCE). The numbers of FCEs per admission need to be accounted for. COVID-19 specific HRG codes are now available in the NHS reference costs file under HRG code subchapter DX. However, they are not split by level of organ support of severity which limits how they can be mapped to the ordinal scales. Using the Adult HRG codes are DX01A, DX11A and DX21A, the weighted average costs per FCE is £5,027. Accounting for the average number of FCEs per admission (2.29 FCEs) and length of stay (11 days) the cost per day admitted to non-critical care ward would be £1,044. This is much higher than the current estimates of £563 and £828 for ordinal scales 4 and 5. Using an alternative set of HRG codes (DZ11) allows for stratification of costs by severity to match the ordinal scales in the EAG model. After accounting for the number of FCEs per admission and length of stay, the estimates of £732.20 and £1124.13 for ordinal scales 4 and 5. We proposed using these estimates (DZ11 based) in the cost-effectiveness analysis. The impact of doing so is presented in our analysis in Comment 9, See Figure **8**. In Appendix 3, we provide further explanation of issues and solutions on the current approach.	8.Comment noted. **Hospitalisation costs:** The AG agreed with the changes suggested and updated the costs. The committee acknowledged the changes implemented by the AG and agreed with the AG's final approach. (Please see section 3.27 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
40	Pfizer (Comment 9)	**Additional scenario analysis** Using the EAG model, we performed cost-effectiveness analysis of Paxlovid at different baseline hospitalisation rates ranging from 0.77% (Panoramic population estimate) to 2.79% (Patel et al.[2] - McInnes population estimates). This analysis demonstrates that Paxlovid would remain cost effective when broadening the recommended population, the restricted 'highest risk' cohort. Furthermore, an update of the admin costs and hospitalisation costs show that Paxlovid is cost effective across all considered hospitalisation rates when using a mean efficacy for Paxlovid. All model inputs were aligned with that used by the EAG to inform the revised EAG report, with the exception of mortality rate and the average age in the community setting, which was aligned with PANORAMIC. We find that Paxlovid remains cost-effective at £30,000/ quality-adjusted life year (QALY) at baseline hospitalisation rates of 1.45% (low efficacy), 0.89% (mean efficacy), or 0.78% (high efficacy), see See Figure **7**. As noted above, the low efficacy scenario is inappropriate, particularly in combination with reduced hospitalisation rates. Despite this, Paxlovid remained cost-effective across all scenarios at plausible, conservative hospitalisation rates. When taking into account the updated admin costs and correcting the hospitalisation costs, Paxlovid remains cost-effective at £30,000/QALY at baseline hospitalisation rates of 1.10% (low efficacy), 0.77% (mean efficacy and high efficacy), as shown in See Figure **8**. **See Figure 7 in Pfizer DG consultation comments. Cost-effectiveness of Paxlovid at different baseline hospitalisation rates** **See Figure 8 in Pfizer DG consultation comments. Cost-effectiveness of Paxlovid when considering updated admin costs and hospitalisation rates. Updated inputs include and admin cost of £117 and hospitalisation costs from the HRG codes DZ11, of £732.20 and £1124.13 for ordinal scales 4 and 5.**	9.Comment noted. Please see response to your comment #4 (hospitalisation rate), #5 (administration costs) and #7 (Nirmatrelvir plus ritonavir clinical effectiveness) for committee's recommendations. **Committee conclusions for nirmatrelvir plus ritonavir:** Based on the committee's preferred assumptions, it considered that nirmatrelvir plus ritonavir was likely a cost-effective use of NHS resources compared with standard care, for people with high risk of severe COVID 19, as defined by the McInnes criteria. The committee also considered the mean- and low-efficacy scenarios using a hospitalisation rate of 0.77% from PANORAMIC which more closely approximated the marketing authorisation population for nirmatrelvir plus ritonavir. The ICERs were above £20,000 per QALY gained and nirmatrelvir plus ritonavir was likely not a cost-effective use of NHS resources in this broader lower risk population. (Please see section 3.28 of the FDG)

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		The above analysis demonstrates that even in the pessimistic lower efficacy scenario (which is not aligned with the evidence in comment 7), Paxlovid is cost effective at hospitalisation rates below 2.79%,[2] which is aligned with the highest risk population defined from the McInnes report. Therefore, when broadening the recommended population beyond this 'highest risk' cohort, Paxlovid would still remain cost effective.	
41	Pfizer (Comment 10)	**Additional benefits of treatment that have not been captured in the ICER** Clinical experts have stated that the economic model should capture additional clinical benefits beyond hospitalisation and mortality. However, the committee concluded that it had not been presented with strong evidence that the health benefits of Paxlovid had been inadequately captured and therefore that the health utility gained was misrepresented. Pfizer is disappointed with this conclusion and presents herein evidence that describes these additional benefits. In summary: • It is extremely likely that the reduction in SARS-CoV-2 viral load and the acceleration of negative RT-PCR respiratory SARS-CoV-2 conversion observed with Paxlovid treatment will reduce virus transmission in both the community and hospital setting. Reduced transmission will improve quality of life for the population, reduce NHS costs and protect patients at high risk of COVID-19. Impact on viral load is within the scope of this assessment; however, the economic model does not reflect this benefit, overestimating the ICER. • Reduced transmission in the hospital setting has the added benefit of reducing NHS staff absences, supporting them in providing care to non-COVID-19 patients. The economic model does not capture the potential harm associated with additional staffing pressures on the NHS, particularly during winter months. • Early evidence suggests that Paxlovid reduces development of long COVID, improving patient quality of life and reducing NHS costs. While this evidence is not yet definitive, future updates of this guidance should aim to include this value. **Virological outcomes and value of reduced transmission** Virological outcomes are within the scope of the current assessment.[66] Further, these outcomes are a key endpoint for many virologic diseases, with impacts on clinical outcomes and disease transmission for economic models in other	10. Comments noted. **Uncaptured benefits:** The committee considered that some of the uncaptured benefits fall outside of the NICE reference case or there is limited evidence to support them. (Please see section 3.31 of FDG)

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		indications,[67] particularly for chronic diseases in order to assess impact of treatment on long-term outcomes. Hence, it can be considered well within the scope of the NICE reference case. Paxlovid had a significant impact on viral load in EPIC-HR,[68] and has also demonstrated reduced time to negative RT-PCR test in a real-world cohort study.[45] While the association between virological outcomes and transmission or infectiousness is not fully characterised, published evidence shows that viral load is associated with transmission[69,70] while negative respiratory RT-PCR test is a strong indicator of non-infectiousness.[71] Taken together, this evidence strongly suggests that Paxlovid reduces virus transmission. The Appraisal Committee noted that community treatments may not limit transmission of the virus, because it mostly spreads when people are asymptomatic. However, this is not fully aligned with current evidence. Guidance from the World Health Organisation agrees that infected people appear to be most infectious just before they develop symptoms but notes that infectiousness continues into the early stages of illness and that people who develop severe disease can be infectious for longer.[72] Further, UK evidence up to March 2021 suggests that around 65% of patients continue to shed virus beyond five days following symptom onset and around 24% of patients shed virus beyond seven days.[73] This is supported by recent, non-peer-reviewed evidence assessing populations where the Omicron variant is dominant.[74,75] Given that there is no longer a legal requirement to isolate following a positive COVID-19 test, improvements in these virological outcomes may have a significant impact on onward transmission. Taking into consideration the limited timescale of the present assessment and the limited evidence base, a pragmatic approach is suggested, similar to those used in the recent assessment of novel antimicrobials.[76,77] However, full assessment of the impact of viral load and transmission in the economic model would be recommended for future assessments of COVID-19 therapies. **Transmission to healthcare professionals** As noted in the ACD, Paxlovid use is associated with a significant reduction in hospitalisations in patients infected with COVID-19 at high risk of adverse outcomes. A reduction in the number of COVID-19 patients requiring treatment in the hospital setting would be reasonably expected to reduce the risk of virus transmission to healthcare professionals, even in the context of lower rates of	

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		transmission in symptomatic patients. This would have beneficial impacts on healthcare professionals individually and also for the NHS more broadly. **Impact on incidence and duration of long COVID** The NICE reference case specifies that all health and cost outcomes should be included in the assessment.[78] Given the cost impact and quality of life decrement experienced by patients with long COVID, the impact of treatment on incidence and duration of long COVID can be considered a vital element of the NICE assessment. Early, non-peer-reviewed real world evidence suggests that use of Paxlovid in line with the licensed indication reduces the risk of long COVID regardless of vaccination status and history of prior infection,[79] indicating that this is a potential benefit not captured in the economic model. The EAG model assumes that 10% of patients in the non-hospital setting would have long COVID, regardless of treatment or subsequent outcomes. While this is a valid simplifying assumption currently, in the context of limited evidence for the Omicron variant, there is likely to be additional data generated in the future that should allow inclusion in the economic model.	
42	Roche (Comment 1)	We appreciate the Committee's efforts in producing this complex guidance and would like the NICE to consider two points: 1. Clarifying further within the document the reasons behind the negative recommendation for casirivimab/imdevimab, as currently it seems contradictory *"Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?"* We ask to review the statement on page 5 **Why the committee made these recommendations**, it is written: *"Casirivimab plus imdevimab (...) are not recommended because the likely cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources."* This is in contrast with section *3.22 pg. 31* **Cost-effectiveness estimates Hospital settings with supplemental oxygen**: *"For the low efficacy scenario, casirivimab plus imdevimab was cheaper and less effective than standard care. In the mean-efficacy scenario, the ICER for casirivimab plus imdevimab compared with standard care was below £20,000 per QALY gained."*	1. Comment noted. The FDG have addressed the issues raised. Mild COVID-19 setting: 'Casirivimab plus imdevimab, molnupiravir and tixagevimab plus cilgavimab are not recommended because they are unlikely to be effective at treating COVID-19 and it is not possible to reliably estimate their cost effectiveness.' Severe COVID-19 setting: 'Casirivimab plus imdevimab and remdesivir are not recommended because they are unlikely to be effective at treating severe COVID-19

Comment number	Organisation name	Stakeholder comment	NICE Response
		We understand that We understand that the effectiveness of neutralising monoclonal antibodies is variant dependent and agree with the generalisability concerns of this analysis, expressed in section 3.10, pg. 18 Generalisability to the Omicron variant: "The committee recognised that the neutralising monoclonal antibodies had shown effectiveness against previous variants. However, it considered that the generalisability concerns in relation to Omicron were too substantial to ignore". This sentiment is also reflected elsewhere in the document, including in 3.11 and 3.12, pages 19-22 **Relative treatment effect**, where the results for casirivimab/imdevimab based on the studies underpinning the current marketing authorisation are not discussed. Given the above, we believe the reason behind a negative recommendation is the generalisability concerns of this analysis due to the lack of / uncertainty of effectiveness in the current omicron variant, not the cost-effectiveness estimates. This interpretation is also in line with NICE's press release (1). It would be pertinent for this to be clarified and the statement on page 5 removed for the recommendation rational to be clear. https://www.nice.org.uk/news/article/nice-recommends-3-treatments-for-covid-19-in-draft-guidance	and it is not possible to reliably estimate their cost effectiveness.' Please see section 1 of FDG
43	Roche (Comment 2)	2. How to rapidly review this recommendation, should monoclonal antibodies be needed by patients in the future, with evolving COVID-19 variants, evidence and label updates *"Are the provisional recommendations sound and a suitable basis for guidance to the NHS? "* Given the evolving nature of the virus, the evidence and the linked marketing authorisations, we believe that the production of this guidance document has to go hand in hand with a clear plan on how to review it in future. The German G-BA decided to address this by giving separate recommendations for variants against which casirivimab/Imdevimab did not have enough efficacy, versus variants where it is proven effective, where it is recommended (2). Alternatively, we welcome the publication of a clear and simple process to update this guidance at the same time as the guidance becomes effective and invite the	2. Comment noted. NICE has announced it is developing a new rapid update process to maintain these recommendations. Please also note 'This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in

Comment number	Organisation name	Stakeholder comment	NICE Response
		Committee to highlight this potentially time sensitive need within this draft guidance. Should the need for these treatments emerge, the lack of a clear and fast process for reviewing the guidance could put UK patients, the health system and all the stakeholders involved at a disadvantage. (1) https://www.g-ba.de/downloads/39-261-5649/2022-10-06_AM-RL-XII_Casirivimab-Imdevimab_D-810_BAnz.pdf	a different way to that set out in section 1 of the guidance in situations such as: • the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or • local or national circumstances of high rates of hospitalisation for COVID-19.'

Abbreviations: ACM2, Second appraisal committee meeting; DG, Draft guidance; FDG, Final draft guidance

Comments received from consultees (all other consultees excluding companies)

Comment number	Organisation name	Stakeholder comment	NICE Response
1	Action for Pulmonary Fibrosis (Comment 1)	**Relevant evidence** 1.1Although evidence has been provided in the Draft Guidance for each drug, the impact of removing them on the 500,000 immune compromised people in UK does not seem to have been fully considered. Many people, including solid organ transplant patients, will no longer have access to any anti-virals or antibody treatments, if the recommendations go ahead. The only one left on the list (Nirmatrelvir plus ritonavir - Paxlovid), cannot be taken by most transplant patients because it interferes negatively with the immune-suppressant drugs we take. This would mean increased costs of hospitalisation for some of these patients, using up both stretched and precious NHS resources. We suggest that the committee re-examines its recommendations and assesses the implications for all the different categories of people who are immune suppressed and ensures that each category of immune suppressed patient will have access to at least one effective anti-covid therapy. So, in our view, the question that should have been asked was: • what is the most cost-effective COVID-19 treatment that can be provided for each of the different categories of immune suppressed patient?	1.1 Comment noted. Sotrovimab has been recommended for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 in FDG) 1.2 Comment noted. Patient experts were present at ACM1 and ACM2. The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website. The views of the companies, clinical experts, patient/carer representatives, the public and NHS England surrounding this issue were considered by committee at the second meeting when formulating its recommendations.

Comment number	Organisation name	Stakeholder comment	NICE Response
		not • What is the most cost-effective therapy for the NHS to use, given limited resources? 1.2We notice that there was no patient representative on the Evaluation Committee. This issue might have been considered earlier, if there had been.	
2	Action for Pulmonary Fibrosis (Comment 2)	**Clinical and cost effectiveness** We think the committee's cost effectiveness analysis should have taken account of the money the NHS has invested to date in the 500,000 immune compromised people. A lung transplant patient, for example, has probably cost the NHS £150-200K. As considerable public money, time and expertise has already been invested, it seems short-sighted to deny immune suppressed people COVID-19 therapies. In our view, providing the drugs would be a cost-effective way of protecting the NHS's overall investment in the nation's health, though there are ethical considerations. A broader benefit-cost analysis is needed.	2. Comment noted. The economic model is modelling a high-risk cohort and not individual subgroups. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. The committee did not see additional evidence to justify splitting the high-risk group. (Please see section 3.4 to 3.7 of FDG) The committee however explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir. To explore cost effectiveness for people contraindicated to nirmatrelvir plus ritonavir the committee looked at a scenario in which the hospitalisation rate was set to 4.00%. For sotrovimab assuming the efficacy was between mean and low efficacy and with a lower administration cost (£410, equivalent to the cost used for providing an oral antiviral), the ICER

Comment number	Organisation name	Stakeholder comment	NICE Response
			was within the range normally considered an acceptable use of NHS resources. (Please see section 3.28 of FDG)
3	Action for Pulmonary Fibrosis (Comment 3)	**Impact of shielding on mental health** We are surprised that the document makes no mention of the fact that many immune suppressed people are still shielding with serious impacts on mental health. These social costs should have been included in the analysis. For example, I am immune suppressed following a lung transplant. Since March 2020, I have only once been into a building other than my house and the hospital. When Covid therapies became available in December 2021, I felt I had a 'safety net' and was happy for friends to visit after taking a lateral flow test first. But, if these guidelines are approved, I would have to revert to full shielding since Paxlovid is contra-indicated for me and no other COVID-19 therapy will be available to me. **These guidelines, if implemented, would put tens of thousands of people, like me, back into full lock-down, with significant impacts on mental health.** In the draft section, there is a section on 'Equality Issues' but you seem to play down the fact that the 500,000 immune suppressed people are a minority who need special attention. In our view, your recommendations do not adequately address our needs. Please reconsider.	3.Comment noted. The committee noted the 'value of treatment options available as insurance for people who are shielding' is a potential uncaptured benefit. The committee considered the advice in section 6.2.36 of NICE's manual on health technology evaluations. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained. Please also see the response to your comment #2 where the committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option.

Comment number	Organisation name	Stakeholder comment	NICE Response
4	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 1)	We are concerned that by limiting options for treatment, the current NICE decision does not allow for patient choice; multiple options are always preferred. This decision is removing access to treatments that patients value.	1. Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option. (Please see section 3.28 of FDG)
5	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 2)	We disagree with the application of the PANORAMIC trial to calculate baseline hospitalisation risk. Omicron may have a lower hospitalisation rate, but the PANORAMIC trial did not include those with the highest risk of hospitalisation and death due to COVID-19, like blood cancer patients and recent stem cell transplant recipients. Patients with blood cancers were given access to treatments through rapid commissioning agreement outside of the PANORAMIC trial. Many people at the highest risk of COVID-19 do not mount a sufficient response to vaccination and should be considered unvaccinated. There were no unvaccinated people in the PANORAMIC trial. Therefore we believe the hospitalisation rates in the PANORAMIC trial do not accurately reflect the hospitalisation rates that would be observed in people with high risk of COVID-19.	2. Comment noted. The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort and 4% for people contraindicated to nirmatrelvir plus ritonavir. The committee also considered a hospitalisation rate of 0.77% from PANORAMIC which more closely approximated the marketing authorisation population for nirmatrelvir plus ritonavir. (Please see section 3.22 and 3.28 of FDG)
6	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 3)	We welcome the approval of Paxlovid, but are concerned about contraindications. Paxlovid on its own is not a sufficient option for blood cancer patients. Many of the contraindications and drug interactions will limit access to the treatment within the high risk group. We consider a failure to account for this group of patients to be both unfair and unreasonable.	3.Comment noted. Please see response to your comment #1. Sotrovimab has now been recommended as an alternative treatment for people with contraindications to nirmatrelvir plus ritonavir. (Please see section 3.28 of FDG)

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		The contraindication due to renal failure could limit myeloma patient access. Myeloma and its treatments can damage the kidneys, and reduced kidney function is common in myeloma. Half of myeloma patients experience serious kidney problems. They are more common at diagnosis and relapse when the level of immunosuppression is highest because patients have active myeloma and are starting treatment. 10% of these myeloma patients develop chronic dialysis-dependent kidney disease. Relevant drug interactions for Paxlovid for people with blood cancer: <u>Contraindicated:</u> ● Venetoclax - used for active treatment in Chronic Lymphocytic Leukaemia, Small Lymphocytic Lymphoma and Acute Myeloid Leukaemia. <u>'May not mix':</u> Haematology should be contacted for patients on the following treatments, in regards to rationalising treatments and considering COVID-19 risk. ● Dasatinib – active treatment for Chronic Myeloid Leukaemia. ● Nilotinib - active treatment for Chronic Myeloid Leukaemia. ● Vincristine – active treatment for Acute Lymphoblastic Leukaemia and Hodgkins disease. ● Vinblastine – active treatment for Acute Lymphoblastic Leukaemia, Non Hodgkins Lymphoma and Hodgkins disease. ● Ibrutinib – active treatment for Chronic Lymphocytic Leukaemia and other B-cells disorders. ● Ivosidenib – new active treatment for Acute Myeloid Leukaemia. ● Anticoagulants – as a whole are often used as patients with haematological malignancies can be predisposed to clots	

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		due to Central Venous Lines commonly used and deranged bloods at diagnosis (particularly Acute Leukaemia patients)and treatment with immunomodulatory drugs (e.g. lenalidomide). ● Anti-fungal treatments and prevention – Itraconazole and Voriconazole, particularly prescribed to those having intensive chemotherapy, stem sell transplants and CAR-T cell therapy. Steroids – dexamethasone and prednisolone are commonly used in anti-myeloma combination treatments	
7	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 4)	NICE considered the significant number of treatments contraindicated by Paxlovid, yet failed to provide an alternative treatment option for this patient group. They justified this decision by claiming that no other treatment was cost-effective in the whole high risk population. However, it is both unfair and unreasonable for NICE to come to this conclusion without separately modelling which treatments would be cost-effective in the subgroup of patients who would be ineligible for Paxlovid. This blood cancer patient subgroup will likely have a higher risk from COVID-19, and higher hospitalisation rate, because they are likely to be on active cancer treatment and/or other immunosuppressive therapies. NICE must therefore calculate the cost-effectiveness of community treatments solely for this smaller, higher-risk patient group, in order to conclude whether alternative treatments for these patients are cost-effective.	4.Comment noted. The economic model is modelling a high-risk cohort and not individual subgroups. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. The committee did not see additional evidence to justify splitting the high-risk group. (Please see section 3.4 to 3.7 of FDG) The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir. To explore cost effectiveness for people contraindicated to nirmatrelvir plus ritonavir the committee looked at a scenario in which the hospitalisation rate was set to 4.00%. For sotrovimab assuming the efficacy was between mean and low efficacy and with a lower administration cost (£410, equivalent to the cost used for providing an oral antiviral), the ICER was within the range normally considered an

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			acceptable use of NHS resources. (Please see section 3.28 of FDG)
8	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 5)	As well as clinical contraindications, there may be other reasons why patients cannot have particular treatments. These include socio-economic reasons and personal circumstances, such as whether they have access to transport or practical support for potential side effects. It is unfair and unreasonable that NICE has not explained how its decision making impacts on those people who cannot have treatments for non-medical reasons and what their options would be.	5.Comment noted. Please see response to your comment #1 and #3.
9	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 6)	The decision to recommend only Paxlovid in the community setting has resulted in only one mode of administration for COVID-19 community treatments. The Living with Leukaemia survey (2017) by Leukaemia Care shows how patients often have a preference on delivery of treatment, but the preference depends on their circumstances and is therefore not universal. As such it is important that options and choices are made available for all patients.	6.Comment noted. Please see response to your comment #1 and #3
10	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 7)	It is unfair and unreasonable not to consider the impact of fewer treatment options on the mental wellbeing, quality of life and economic activity of those who are affected by this decision. Our submission and further conversations with patients show that this will impact people's quality of life. Some blood cancer patients are still shielding and we have heard from patients that this decision will lead to some deciding to further reduce their contact with others.	7. Comment noted. The committee noted the 'value of treatment options available as insurance for people who are shielding' is a potential uncaptured benefit. The committee considered the advice in section 6.2.36 of NICE's manual on health technology evaluations. The

Comment number	Organisation name	Stakeholder comment	NICE Response
			committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained. However, the committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option. Please see response to your comment #1 and #3
11	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 8)	Drug interactions need to be carefully monitored and managed. This has the potential to impact patients, their families and clinical practice. Patients and their families have the added anxiety of looking for and noticing any change in side effects due to increased toxicity from drug interactions or choosing between COVID-19 treatment and disease-related treatments. For example, patients recovering after a stem cell transplant and on preventative anti-fungal treatments would be forced to choose between either stopping that treatment or foregoing the one COVID-19 treatment available in the community. Monitoring and managing drug interactions impacts clinical and pharmacy capacity. It takes longer to prescribe treatments with multiple interactions, and more clinical staff need to be notified and consulted on treatment decisions. This complexity could also cause	8.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option. Please see response to your comment #1 and #3

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		service delays and lead to patients missing out on treatment due to the narrow window for treatment after testing positive for COVID-19.	
12	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 9)	It is unreasonable not to consider the serious clinical and cost impacts caused by pausing the above active cancer treatments in order to take Paxlovid, and the benefits in this area that other treatments offer.	9.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option. Please see response to your comment #1 and #3
13	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 10)	Removing existing options for immunocompromised individuals will add to existing anxiety and concerns around COVID-19. It is unreasonable to expect patients who are on treatments that are contraindicated by Paxlovid to choose between returning to isolation, or waiting for their COVID-19 infection to progress to such severity that they are hospitalised. As a CLL patient explained to Blood Cancer UK: “Due to my cancer drug regime I cannot have Paxlovid. I considered the two treatments I could have as a safety net in case I caught Covid; by offering only Paxlovid that net has been removed completely. I cannot contemplate stopping my cancer treatment so the only option for me is to completely isolate myself again…As I am a self-employed contractor I will no longer be able to fulfil the requirements of my contract and so will lose my income. It is unfair and unacceptable that I am being asked to risk catching Covid with no treatment option or to give up my livelihood and subject me to the high levels of anxiety due to loss of income, no available treatments, and the mental effects on me and my family from reentering complete isolation.”	10. Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option. Please see response to your comment #1, #3 and #7

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14	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 11)	NICE must take the uncertain and evolving nature of the virus's epidemiology into consideration, and place more weight in its model on higher hospitalisation rates. We feel the current interpretation is unreasonable in light of the available evidence. In doing so, treatments may prove to be more cost-effective.	11.Comment noted. This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as: • the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or • local or national circumstances of high rates of hospitalisation for COVID-19. The committee considered a wide range of hospitalisation rates based on the recent and most evidence data sources. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort and 4% for

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			people contraindicated to nirmatrelvir plus ritonavir. Please see section 3.22 in FDG.
15	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 12)	It is unreasonable for NICE to acknowledge uncertainty, but use hospitalisation rates based off of the Omicron variant, when hospitalisations rates would vary with different SARS-CoV-2 variants. Future variants may be more pathological and lead to more severe disease, therefore potentially leading to higher rates of hospitalisation. The current cost-effectiveness analysis is based on hospitalisations rates of variants which are mild.	12.Comment noted. Please see response to your comment #11.
16	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 13)	It is unfair and unreasonable for NICE not to explain why it favours the advice of WHO and FDA over other clinical advice for sotrovimab.	13.Comment noted. **Sotrovimab clinical evidence:** The committee acknowledged that observational OpenSAFELY evidence supported the clinical efficacy seen in COMET-ICE but was mindful not to make conclusions about relative treatment effect solely based on non-randomised evidence. The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing subvariants. The committee considered there was not enough evidence from COMET-ICE to

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			consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.12,3.16,3.18-3.19 of FDG)
17	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 14)	We welcome the McInnes report definition of high risk as covering most people with blood cancers, but NICE guidance must ensure those who have been previously left out are included, such as those not undergoing active treatment for T cell blood cancers and chronic lymphocytic leukaemia.	14.Comment noted. **McInnes definition:** The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected. (Please see section 3.4 to 3.7 of FDG)
18	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support	It is unfair and unreasonable that NICE has not set out the specific reasons why it has approved Paxlovid over the other treatments. If NICE is accepting "significant uncertainty" in some circumstances, regarding data, efficacy and changing variants, it should be clearer why it hasn't in others. It appears that NICE has accepted uncertainty of data where it reduces cost-effectiveness, but not where it doesn't, however the rationale behind this is not given.	15.Comment noted. Please see section 3.28 of FDG for a complete overview of the rationale for why nirmatrelvir plus ritonavir and sotrovimab

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	(Comment 15)		were recommended in the mild COVID-19 setting and the remaining technologies were not.
19	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support (Comment 16)	NICE has acknowledged that antivirals and anti-inflammatories are least likely to be impacted by evolving variants.Clinical experts consulted by Leukaemia Care have also seen improvement in symptom severity when using remedesivir, so we urge NICE to re-evaluate the usage of this treatment, as well as all others in this context.	16.Comment noted. **Remdesivir recommendations:** In the mild COVID-19 setting the committee concluded that remdesivir is not a cost-effective use of NHS resources. (Please see section 3.28 of FDG) NICE expects its advisory bodies to use their scientific and clinical judgement in deciding whether the available evidence is sufficient to provide a basis for recommending or rejecting particular clinical or public health measures (Social Value Judgements; 'Principles for the development of NICE guidance', principle 1). Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide

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			sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 4 and 5). In the severe COVID-19 and supplemental oxygen setting the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG)
20	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support	Having only one treatment available risks leaving these vulnerable blood cancer patients subject to supply issues, leaving even those eligible for Paxlovid with no options at all. We urge NICE to consider the impact of their decision on this.	17.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and

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	(Comment 17)		was therefore able to recommend sotrovimab as an alternative treatment option. Please see response to your comment #1, #3 and #7
21	British Infection Association (Comment 1)	**a)1.2 Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who:** **• are having systemic corticosteroids and** **• need supplemental oxygen or mechanical ventilation.** *This recommendation suggests that everyone with COVID-19 might be eligible for tocilizumab which is neither evidence-based nor safe. At present there is a very small subgroup of patients hospitalised with COVID-19 who warrant COVID-specific treatment, but often a low threshold for Emergency/Acute medicine doctors to give steroids (who on reflection do not have a covid pneumonitis but other reasons for their oxygen need), and this risks overtreating. The recommendation should narrow down the recommendation to meet RECOVERY and REMAPCAP criteria… evidence of covid pneumonitis plus CRP >75 or within short timeframe of respiratory support.* **b)1.5 Molnupiravir is not recommended, within its marketing authorisation, for treating mild to moderate confirmed COVID-19 in adults who have at least 1 risk factor for developing severe COVID-19.**	1a. Comment noted. NICE can only recommend treatments within their marketing authorisation in Great Britain. The SMPC states that tocilizumab is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. The exact wording from the SMPC is also used in the guidance. Link to SMPC: https://www.medicines.org.uk/emc/product/6673/smpc 1b. Comment noted. The recommendation for molnupiravir has now been updated to avoid confusion. The committee made the decision because molnupiravir has limited effectiveness at treating mild COVID-19 compared with standard care because it does not reduce hospitalisation

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		This is poorly worded. It might be read as suggesting that it is recommended in patients who do not have at least 1 risk factor. *Also – the data to support use of molnupiravir is from the PANORAMIC study which showed no benefit in terms of hard outcomes (hospitalisation/death) and only in terms of symptom duration in a non-blinded study. If the recommendations evolve after consultation and revert to the current system of availability of alternatives to Paxlovid where contraindicated, it is quite unclear why this has translated into an ongoing recommendation ahead of sotrovimab for those with much higher risk factors (eg CEV), despite OPENSAFELY data suggesting a clear benefit of sotro over molnu for both BA1 and BA2.* *c)* ***1.6*** **Remdesivir is not recommended, within its marketing authorisation, for treating COVID-19 in:** **• people aged at least 4 weeks and weighing at least 3 kg with pneumonia who need supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation) at start of treatment** **• young people weighing at least 40 kg and adults who do not need supplemental oxygen and have an increased risk for progression to severe COVID-19.** *This is poorly worded. It suggests that remdesivir might be recommended in those aged less than 4 weeks or weighing less than 3kg or in young people weighing less than 40kg or in people who do not have an increased risk of progression etc….* *This removes the only antiviral other than Paxlovid (often contraindicated due to co-morbidities/drugs) for a severely immunocompromised patient hospitalised with COVID and not*	and mortality rates. The committee said sotrovimab is likely to be effective at treating mild COVID-19 compared with standard care but some of the evidence is uncertain. The cost-effectiveness estimates for sotrovimab are also within what NICE considers an acceptable use of NHS resources, but only for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. So, sotrovimab is recommended in this group. (Please see section 1.4 of FDG) This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as:

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		requiring oxygen, despite often a significant impact of ongoing viral replication on their health, and an obvious benefit in such a sick patient in bringing viral replication under control among the other elements of their care. A patient with a haematological malignancy would be a typical example. *Given the statement about remdesivir, If the recommendations evolve after consultation and revert to the current system of availability of alternatives to Paxlovid where contraindicated, it is quite unclear why this has translated into an ongoing recommendation ahead of sotrovimab for those with much higher risk factors (eg CEV), despite much published data demonstrating the high rate of relapse in severely antibody deficient states.* Eg Treatment of chronic or relapsing COVID-19 in immunodeficiency - PubMed (nih.gov) and Shields AM, Burns SO, Savic S, Richter AG; UK PIN COVID-19 Consortium. COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. J Allergy Clin Immunol. 2021 Mar;147(3):870-875.e1. doi: 10.1016/j.jaci.2020.12.620. Epub 2020 Dec 15. And comment in Persistent SARS-CoV-2 infection: the urgent need for access to treatment and trials - PubMed (nih.gov) **d)1.7 Sotrovimab is not recommended, within its marketing authorisation, for treating symptomatic acute COVID-19 in people aged 12 years and over and weighing at least 40 kg who:** **• do not need oxygen supplementation and** **• have an increased risk for progression to severe COVID-19.** *We have previously expressed in publications (Lancet letter, emails, OPENSAFELY preprint)*	• the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or • local or national circumstances of high rates of hospitalisation for COVID-19. 1c. Comment noted. **Remdesivir recommendation:** The recommendation for remdesivir has now been updated to avoid confusion. The committee was aware that the AG presented ICERs for remdesivir in severe COVID-19 setting without supplemental oxygen. However, the committee did not consider that this setting was within the marketing authorisation for remdesivir in Great Britain (Please see section 2 of FDG). It had separately considered remdesivir for people with mild COVID-19 who do not need supplemental oxygen and who have an increased risk of progression to severe COVID-19 (Please see section 3.28 of FDG).

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		*[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01938-9/fulltext; **https://doi.org/10.1101/2022.05.22.22275417**] the arguments in favour of maintaining sotro for CEV patients who cannot have Pax, arguing that the in vitro data DOES support ongoing efficacy against BA.2 and that (in OPENSAFELY supplementary table) the benefit of sotro over molnu is maintained in BA2 era.* **e)1.9 People may be offered treatment from supplies already purchased by the Department of Health and Social Care before this guidance was published under the existing interim clinical commissioning policies, if clinicians consider it an appropriate option for people with COVID-19.** *This is confusing – either NICE think these are appropriate medications or they do not. How might clinicians consider them appropriate options if NICE believe that they are not? If the decision is purely and simply a cost-effectiveness decision, then this should be made clear but would require a great deal more health economic analysis for example to determine the cost effectiveness of 2nd line treatment in a very high risk patient (eg someone on rituximab) for whom Paxlovid is contraindicated.* *There is a significant risk of inequity of access here to say that someone on certain drugs and without renal impairment do deserve treatment whereas others who have renal impairment and/or happen to be on other contra-indicating drugs (cardiovascular drugs, transplant drugs, anticoagulation, etc) do not.*	In the mild COVID-19 setting the committee concluded that remdesivir is not a cost-effective use of NHS resources. (Please see section 3.28 of FDG) NICE expects its advisory bodies to use their scientific and clinical judgement in deciding whether the available evidence is sufficient to provide a basis for recommending or rejecting particular clinical or public health measures (Social Value Judgements; 'Principles for the development of NICE guidance', principle 1). Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 4 and 5). In the severe COVID-19 and supplemental oxygen setting the committee concluded there

Comment number	Organisation name	Stakeholder comment	NICE Response
		f)3.4 The clinical experts gave examples of additional considerations around how high-risk groups are affected differently: • **They cited the OPENSAFELY cohort analysis study that assessed the risk of severe COVID-19 in people with immune-mediated inflammatory diseases. This showed that people with inflammatory diseases who are having systemic therapies had similar rates of hospitalisation and death as people having targeted therapies, except for rituximab. The committee considered the different risk of progressing to severe COVID-19 may be related to which immunosuppressant drugs are taken, but the relationship may be complex and differ in other disease areas.** *Unfortunately this distinction wrt rituximab does not seem to have translated to a recognition of the significant risk associated with COVID in patients on this drug (or with other reasons for severe antibody deficiency such as primary or secondary IgG deficiency) and so with no access to drugs other than Paxlovid despite a significant proportion potentially having contraindications to Paxlovid.* **g)3.7 Current clinical management of COVID-19 in people who have a high risk for progressing to severe COVID-19 includes treatments available through an NHS interim commissioning policy (see section 3.3). As of June 2022, the policy recommendations are as follows:** **• first-line treatment: nirmatrelvir plus ritonavir (antiviral) or sotrovimab (a neutralising monoclonal antibody)** **• second-line treatment: remdesivir (antiviral)** **• third-line treatment: molnupiravir (antiviral)**	was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG) **d)** Comment noted. **Sotrovimab clinical evidence:** The committee acknowledged that observational OpenSAFELY evidence supported the clinical efficacy seen in COMET-ICE but was mindful not to make conclusions about relative treatment effect solely based on non-randomised evidence. The committee said considerable uncertainty remained in the clinical efficacy estimates

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		• combination treatment with a neutralising monoclonal antibody and an antiviral is not routinely recommended. *This is actually not correct. See https://www.england.nhs.uk/coronavirus/interim-clinical-commissioning-policy-antivirals-or-neutralising-monoclonal-antibodies-in-the-treatment-of-hospital-onset-covid which does not include molnupiravir.* **h) 3.8** **…..The clinical experts considered that antivirals may have a limited role for people in hospital with COVID-19 because their mechanism of action focuses on blocking viral replication rather than controlling inflammation.** *Of course this may be a reasonable view from the perspective of biological plausibility, however RECOVERY clearly demonstrated a benefit of anti-SARSCOV2 nMAB (Ronapreve) in a subgroup of patients hospitalised with COVID-19 who were seronegative… and meta-analyses have demonstrated a benefit of remdesivir. So the biological plausibility is not enough to stand alone in a statement in a NICE guideline; Moreover if there is an argument to be made about biological plausibility it should by definition tgake account of the fact that a significant patient subgroup (those who are immunocompromised) have a biologically plausible reason why stopping viral replication may contribute to a better outcome from the downstream effects. This statement risks inequity of recognition of this subgroup as a population deserving clinical management that takes account of their different host response*	because of the in vitro evidence showing reduced neutralisation against the prevailing subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.12,3.16,3.18-3.19 of FDG) To explore cost effectiveness for people contraindicated to nirmatrelvir plus ritonavir the committee looked at a scenario in which the hospitalisation rate was set to 4.00%. For sotrovimab assuming the efficacy was between mean and low efficacy and with a lower administration cost (£410, equivalent to the cost used for providing an oral antiviral), the ICER was within the range normally considered an acceptable use of NHS resources. (Please see section 3.28 of FDG) e) The statement regarding supplies already purchased by the Department of Health and

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		i) 3.10 • **Anti-inflammatories (baricitinib, tocilizumab): Most evidence on these was generated during the earliest waves of the pandemic. Although later circulating variants have substantially lower mortality than earlier variants, the committee considered the relative benefit of treatments largely generalisable to later waves. This is because the mechanism of action regulates hyperinflammation, which it did not consider specific to a particular variant.** *What is the basis for this view? It is entirely without an evidence base. There is every reason to consider that the hyperinflammation may be less pronounced and less responsive to anti-inflammatories with a less virulent variant or in a vaccinated host. If such views are considered worthy of justification for use of anti-inflammatories in omicron era (ie not subject to NICE cost-effectiveness calculations done for omicron outcomes) then non-cost-effectiveness arguments should be used to provide access to antivirals.* • **• Antivirals (molnupiravir, nirmatrelvir plus ritonavir, remdesivir): Most evidence on these was generated before later circulating variants. This is except for evidence on molnupiravir from PANORAMIC that recruited participants while the Omicron variant was circulating. The committee noted that some observational data supported efficacy of antivirals against later variants, but noted that these were not considered in a systematic approach.**	Social Care has now been removed. Regarding comment on 'significant risk of inequity of access' please also see response to your comment #1d. f) Please see response to your comment #1d. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option. g) Comment noted. The most up to date interim commissioning policy had been referenced at the time of ACM1, this was further updated in November 2022. Please see section 3.8 of FDG for the update. h) Comment noted. The statement has been removed from the FDG. Please also see response to your comment #1c (remdesivir recommendation) Regarding Casirivimab plus imdevimab (Ronapreve) which is a neutralising monoclonal antibody - taking account of in vitro study

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		There is a systematic approach which is the use of data linkage cohorts such as OPENSAFELY to explore outcomes of patients receiving current antiviral therapy. While this is not an RCT it is unfair to say that it is not systematic. The capacity for RCTs to answer this question is minimal given current hospitalisation rates and changing variants so systematic observational data carefully analysed and reviewed should be considered a better determinant than committee consensus. **• Neutralising monoclonal antibodies (casirivimab plus imdevimab, sotrovimab, tixagevimab plus cilgavimab): The committee recognised that these treatments bind to spike proteins that may change with each new variant. Therefore, neutralising monoclonal antibodies may lose the ability to neutralise the virus over time. This could create uncertainty in any assessment of generalisability of response from previous clinical trials and clinical efficacy estimates… etc etc** *We have argued in this article* WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed - The Lancet why the existing data does NOT support the argument that sotro is ineffective against BA2 (nor in fact does the Crick data make a specific argument for a higher dose), and if anything emerging evidence suggests better efficacy against even newer variants. *j)* **3.12 Remdesivir** **"…..The committee considered that remdesivir's mechanism of action may not fit the stated treatment aims. This is because**	differences, clinical expert conclusions and the framework (Please see sections 3.14 to 3.16 of FDG) the committee concluded that casirivimab plus imdevimab was unlikely to retain sufficient neutralisation activity against most variants circulating at the time of this evaluation. Also, this was the most useful estimate of effect against future variants. The committee noted substantial uncertainty with the relative treatment effects of casirivimab plus imdevimab. The committee concluded casirivimab plus imdevimab has limited and uncertain clinical effectiveness in terms of reducing hospitalisation or mortality rates and therefore the ICERs were considered very uncertain (Please see section 3.17). i) Comment noted. **Remdesivir and tocilizumab comparison:** Please see the detailed discussion on remdesivir and tocilizumab's clinical evidence base in section 3.20 of the FDG. The clinical evidence base for tocilizumab is stronger and UK hospital

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		antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation…" *See comments above – while this was an early hypothesis, and no doubt applies to a majority of patients, this should not be allowed as a statement in an evidence-based policy document given that (a) meta-analysis has shown an overall benefit of remdesivir in hospitalised patients (b) RECOVERY showed a mortality benefit of REGNCOV in a subgroup with negative serology (c) controlling viral replication in heavily immunocompromised patients is a key part of management and follows as plausible a biological process as one arguing that in immunocompetent patients antiviral therapy is ineffective. Remsdesivir is currently the ONLY antiviral that can be used in hospital settings for immunosuppressed patients hospitalised FOR Covid, and the idea that for example a BMT or CarT or rituximab-treated patient with no antibodies (and contraindications to Paxlovid or ineligible as being hospitalised FOR Covid) with ongoing symptomatic viral replication should not be able to access antivirals is rather perverse in taking a key part of management of infection out of the armamentarium.* *k)* **3.13 economic model** *In general it is unclear how cost effectiveness models take account of the consequences of SARSCOV2 infection in heavily immunocompromised patients* *l)* **3.20 non-hospital treatments** *I also have concerns as to whether the specifics around eg 3 hospital visits with associated transport costs (for remdesivir), as well as the high chance of relapse in antibody deficient patients warranting*	setting specific which reduces the uncertainty in the relative treatment effect of tocilizumab versus standard care. **Observational evidence:** Regarding observational evidence (Please see section 3.11 of FDG). The committee acknowledged that the analysis of OpenSAFELY was done well and made efforts to account for confounding bias when possible. The analysis was done in a dynamic environment with changing treatment practices and linkages with various data sources which can increase risk of confounding bias. The committee was willing to accept the OpenSAFELY data on relative treatment effectiveness as supplementary evidence to the trial evidence and for modelling estimates for hospitalisation rates. The committee cautioned against solely relying on non-randomised evidence when making conclusions on treatment effect. **In vitro evidence**

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		repeat treatment as they would have a high rate of relapse, been adequately costed *m)* **3.24 Equality issues** *Inequity due to "pushy" articulate patients demanding a local solution vs others accepting NHSE policy decision.* *It seems completely inequitable that, for example, a patient meeting CMDU criteria for Paxlovid and falling into a very high risk group, would have it explained to him/her that they would qualify for treatment in terms of reduction in poor outcomes, but then in the course of the telephone consult be told that they cannot have it (and therefore any other treatment) because they happen to be on eg clopidogrel, or carbamazepine, or tacrolimus, or have an eGFR <30. How can that be equitable? There is also a risk that, in the absence of alternatives, the prescriber gives the medication anyway and risks serious adverse events due to the interaction*	The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. The advisory group included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG. j. Please see responses to your comments above: • #1c (Remdesivir recommendation), • #1h (Statement on mechanism of action has been removed) and

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			• #1i (Remdesivir and tocilizumab comparison) k. Comment noted. The economic model is modelling a McInnes defined high-risk group cohort and not individual subgroups within the cohort. **Highest-risk and high-risk group:** At ACM2, the committee noted the draft guidance consultation comments highlighted the need for separate 'high risk' and 'highest risk' groups, or a separate high-risk group contraindicated to nirmatrelvir plus ritonavir. The committee saw examples on how the risk group could be split based on Patel et al. 2022. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. The committee did not see additional evidence to justify splitting the high-risk group. (Please see section 3.4 to 3.7 of FDG) For inclusion of additional subgroups the committee noted additional functionality, clinical or cost inputs and treatment-effectiveness assumptions would be required to make differential subgroup recommendations and this would not be practical or aligned with the decision problem. (Please see section 3.7 in FDG) l. Comment noted. The committee understood that there in future higher QALY gains or cost

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			savings could be captured if the model includes the additional uncaptured benefit of treatments. The committee considered that some of these benefits fall outside of the NICE reference case or there is limited evidence to support them. (Please see section 3.31 of FDG) m. Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option to help reduce the current equality issues. Discussion on all equality issues have been included in section 3.32 of FDG.
22	British Infection Association (Comment 2)	a) Overall general point- I am surprised Remdesivir is not authorised within the hospital setting only. I agree it's not cost effective to bring outpatients in for it but our antivirals in hospital are very limited in the first 10 days of disease and I would imagine it may have a cost effective role then- as it was only considered across the whole time frame of disease this may have been missed- I would think it should be for particular subgroups though such as those who are immunosuppressed and unable to take paxlovid- I appreciate some of them also would be unable to take Remdesivir b) Otherwise the recommendations make sense and align with current practice and other guidelines- except that we	2.Comments noted. Please see individual responses below: a. Regarding remdesivir recommendations please see response to your comment #1c and j b. NICE have made recommendations within the marketing authorisation for all technologies being evaluated.

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		currently give steroids and baricitinib together and then only tocilizumab if the CRP is high- there is no mention of such stratification here. c) Section 1.1 p3 the link is to as defined in the independent advisory group report commissioned by the Department of Health and Social Care. However- this is a cumbersome link and not a simple table- there should be a user friendly table e.g. in the appendices and it should be clear that this evidence basis was in unvaccinated populations so may overestimate the benefit to an individual vaccinated patient with a normal immune system d) 1.4 • Casirivimab plus imdevimab is not recommended, within its marketing authorisation, for treating acute COVID-19 in adults. • Worth adding except in the extremely rare scenario of proven delta infection? People with COVID-19 who have a high risk for progression to severe COVID-19 are offered treatments to stop their symptoms worsening. e) P4 “Usually, people would be offered nirmatrelvir plus ritonavir, sotrovimab, remdesivir or molnupiravir.” Should read People with COVID-19 who have a high risk for progression to severe COVID-19 and are not currently requiring oxygen are offered treatments to stop their symptoms worsening. f) P20	c) The source of the McInnes high-risk definition is linked to the complete report to allow stakeholders to understand all the assumptions behind the high-risk criteria. d) The committee have made recommendations for casirivimab plus imdevimab based on currently circulating Omicron variants. (Please see section 1 – Recommendations in FDG) Please note this final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as: • the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or

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		Molnupiravir: The committee noted that published PANORAMIC results (Butler et al. 2022) Isn't this still a pre-print? For all 'publications' cited this should be made clear g) P23 • The AG assumed that 100% of people in the hospital setting and 10% in the non-hospital setting would have long COVID • This is simply incorrect- 100% of people in the hospital setting definitely do not develop long COVID. Why did the committee not model this on a more realistic estimate such as 25% or similar? h) P25 • recurrent Clostridium difficile infection - needs italics	• local or national circumstances of high rates of hospitalisation for COVID-19. e) Statement has been amended. NICE have made recommendations within the marketing authorisation in Great Britain for all technologies being evaluated. f) The pre-print has now been published. g) The AG have made a conservative assumption for long COVID in the absence of more appropriate data sources. h) Italics have now been added.
23	British Infection Association (Comment 3)	Decision not to recommend sotrovimab – whilst understandable in economic terms – leaves a major problem with all solid organ transplant patients due to issues of drug interaction +/- stage 4/5 CKD with Paxlovid. Hence unless there is some change in guidance around potentially stopping/reducing calcineurin inhibitors or reducing Paxlovid dose further in severe CKD – nothing will be available for this group who are currently at highest risk of severe COVID (as per Agrawal U, et al. Lancet 400. October 15, 2022: DOI:https://doi.org/10.1016/S0140-6736(22)01656-7) – 10 -20 times risk, whereas most other groups in McInnes list were no more than 5x increased risk.	3.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option.

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24	British Infection Association (Comment 4)	Thanks you for asking me to provide comments on this draft NICE guidance, which is now out for consultation. I have read the document in its entirely and my comments would be as follows: a) <u>GENERAL</u> · It is welcome that NICE is now reviewing the use of drugs for the treatment of COVID-19 in the systematic manner used of other drugs, adopting a cost-effectiveness approach. During the early stages of the pandemic there was a very understandable rush to try to get new drugs to clinicians in the NHS as quickly as possible. Whilst this was in many ways welcome, it has also led to a lot of debate and confusion– particularly given the fact that the original trials for these drugs were largely performed in the pre-Omicron era. · It is also welcome that the NICE guidance, when published, will hopefully result in a significantly simplified approach to therapeutics for COVID-19. I think most of our clinical colleagues (including some in ID and Micro!) are simply lost in the complexity of the multiple CAS alerts/ UK Interim Clinical Commissioning Policy (UK-ICCP) documents etc etc. that have been pinged out over the last couple of years. Despite laudable attempts to summarise guidance within some simplified UK-ICCP 'Clinical Guide' flow diagrams, it all remains far too complicated for busy front of hospital staff to follow and adherence to the guidance is therefore poor. Simplified guidance, with a more limited range of therapies that we all have some confidence actually work(!), is very desirable. · Publication of the NICE guidance MUST go hand in hand with withdrawal of the UK-ICCP guidance and flow diagrams, so as not to just cause further confusion	4a. Thank you for your comments on the DG. 4b.Comment noted. The committee have taken the entirety of the clinical and cost-effectiveness evidence into consideration when making its recommendations. Section 1 'Why the committee made these recommendations' have been updated to address this comment. We have now made clear distinctions between the mild COVID-19 setting which includes community and hospital onset COVID-19 with high-risk of disease severity. All technologies are being evaluated within their marketing authorisations in Great Britain. The decision problem for mild COVID-19 setting is only evaluating the population who are within the McInnes high-risk defined group. As such there is only one 'high-risk' group being evaluated for the mild COVID-19 setting. Please see section 3.7 and 3.8 of FDG for further details.

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		· In my view he summary Recommendations (Section 1) are sensible and sound, and would tie in with what I would see as an appropriate way forward based on my own knowledge of the literature along with my own clinical experience of managing COVID-19 b) SPECIFIC · At times I found it difficult to follow whether the discussion in the document (e.g in the ICER discussions) relates to ALL patients, or just to 'highest risk' patients. This could/ should be clarified as far as possible · The Table in the Conclusion section (page 35) is over-simplified and, because of that, actually misleading/ confusing. Specifically, it does not really tie in with the guidance in the Recommendations section (Section 1), and completely fails to address the question of ALL patients vs highest risk patients. Thus surely we will still be recommending Paxlovid (nirmatrelvir plus ritonavir) to symptomatic 'highest risk' patients who are in hospital but who do not have a requirement for supplemental oxygen? Why would this not happen if this is something that would be getting offered if they were still in a non-hospital setting?? · Remdesivir: I think it is appropriate to see the role of this drug demoted, for the reasons described in the document. There should however probably be a clearer separation between the 2 different indications and treatment protocols that are currently in place for Remdesivir: § 5-day course for unwell patients on oxygen and dexamethasone: I have never been in any way convinced that Remdesivir confers	**Sotrovimab clinical evidence:** The committee acknowledged that observational OpenSAFELY evidence supported the clinical efficacy seen in COMET-ICE but was mindful not to make conclusions about relative treatment effect solely based on non-randomised evidence. The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing subvariants. (Please see section 3.12,3.16,3.18-3.19 of FDG)

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		any therapeutic benefit in this situation. Indeed, locally we took it out of our local prescribing guideline, only to reluctantly add it back in so as not to cause confusion following the roll-out of the UK-ICCP 'clinical guide' flow diagrams. So glad to see it go – which is a view shared by my ID Consultant colleagues § 3-day course, on an outpatient basis, for 'highest risk' patients with mild/ mod symps, to prevent deterioration and hospital admission: There is better (but not great) data to support use in this scenario. However, the data is pre-Omicron, Remdesivir is expensive and attending daily for an IV infusion is very challenging (esp when you need to consider weekend provision of IV infusions). In practice, we have not used Remdesivir in this fashion at all, due to all the logistical challenges posed. So again – glad to see it dropped from the guidance § I have no doubt that Gilead will challenge the position taken by NICE on Remdesivir use. This challenge should be resisted with the cost-effectiveness data and what I believe is a strong clinical consensus opinion · Sotrovimab (+ other nMABs): The in vitro data does not support use. I really do not understand why we are still advocating the use of Sotrovimab at present – we wouldn't use any other antimicrobial drug that in vitro testing shows is	

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		ineffective Locally, we have just agreed to drop the use of Sotrovimab, based on the Sept 2022 WHO updated guidance. So in my view it is appropriate to see it dropped by NICE as well. However, again I suspect we may well see a drug company challenge here – as well as possibly from patient groups.	
25	British Infection Association (Comment 5)	It must be acknowledged that the shifting standards of care, vaccination status of the population, and differing circulating variants have made any assessments and conclusions difficult for the committee, and they should be congratulated for their work to date. Though many of the conclusions and assumptions are reasonable and correct, there are some areas of internal disagreement within the consultation document and some vital data that has not been fully accounted for. a) In terms of the general background, it is important to point out that future variants of concern could well be more virulent (in terms of causing hospitalisation and death) than the current omicron variant. Though a pathogen over time is likely to decrease in pathogenicity, this is often over decades or longer and the next major variant of concern is perhaps as likely to be more rather than less virulent. Also the evolutionary pressure resulting in new variants is based on immune responses to the spike protein, which is not the target of the antivirals being assessed. There is no evidence that current variants have any significantly altered sensitivity to these antivirals (in fact some evidence to the contrary (e.g. Vangeel L et al. *bioRxiv* 2021. DOI: 10.1101/2021.12.27.474275), and it would not be expected that future variants are likely to have altered susceptibility. I	5a. This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a

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		therefore disagree that '…the evidence of antivirals is uncertain for newer variants. It therefore considered a broader range of efficacy estimates to account for the uncertainty…' (section 3.10). b) For tocilizumab use in those requiring oxygen who are hospitalised, the RECOVERY trial - a major contributor to the evidence – only utilised this therapy in those with a C-reactive protein level exceeding 75. It is puzzling that this has not been significantly commented on, and that conclusions utilising this data have been extrapolated to those with lower C-reactive protein levels. c) It is disappointing that marketing authorisation seems to be required for an assessment (for example with baricitinib). The data is available, and the decision and timing of seeking authorisation have many other contributing factors. Such a decision (i.e. not providing a judgement) may be a policy of NICE but could well deny individuals access to an efficacious therapy, and therefore should be reconsidered. Similar could be expressed for the use of altered dosing of neutralising monoclonal antibody therapy, e.g. for tixagevimab/cilgavimab – for which there is currently data on efficacy against several prevalent omicron strains e.g. BA.4/5 (see https://covdb.stanford.edu/page/susceptibility-data) and there is therefore a risk in taking the position that '…the committee considered it reasonable to extend the likelihood of reduced efficacy to tixagevimab and cilgavimab.' (section 3.10) – each neutralising antibody differs from others and a broad generalisation has been shown to be invalid against earlier variants (as shown by data used to establish the Stanford	different way to that set out in section 1 of the guidance in situations such as: • the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or • local or national circumstances of high rates of hospitalisation for COVID-19. 5b. NICE can only recommend treatments within their marketing authorisation. The SMPC states that tocilizumab is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. The exact wording from the SMPC is also used in the guidance. Link to SMPC: https://www.medicines.org.uk/emc/product/6673/smpc 5c. NICE cannot provide guidance on technologies without marketing authorisation in Great Britain as the risk-benefit profile of these treatments have not been assessed by the

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		algorithms: https://covdb.stanford.edu/page/susceptibility-data). d) The most fundamental areas where the committee should reconsider are based on the judgements on remdesivir therapy. There seems to be an assumption accepted by the panel that antivirals have limited efficacy and a limited role in those hospitalised requiring oxygen (as stated in section 3.8, and in section 3.12 – 'Remdesivir's mechanism of action may not fit the stated treatment aims.'). Though it is true that the pathogenetic mechanisms shift during COVID-19 from being predominately virus-mediated to being predominately inflammation-based there is significant overlap with both processes being responsible for disease in a large proportion of individuals. It is important to note that many of those hospitalised have on-going active viral replication (as demonstrated by cytopathic effects), and such active viral infection may persist for a significant period (e.g reference: Folgueria MD, *et al. Clin Microbiol Infect* 2021; 27:886–891) and, more importantly, there is a significant amount of efficacy data demonstrated for this product in this hospitalised setting (for example ACTT-1, final SOLIDARITY results, and significant real-World data (such as Olender SA et al. CROI. 2021; Olender SA et al. *Clin Infect Dis*. 2021;73:e4166–e4174; Garibaldi BT et al. *JAMA Netw Open*. 2021;4:e213071; Go A et al. ASM. 2021; Arch B et al. *MedRxiv*. 2021. DOI: 10.1101/2021.06.18.21259072; Joo EJ et al. *J Korean Med Sci.* 2021;36:e83; Chokkalingam AP et al. ASM. 2021; Mozaffari E et al. ASM. 2021; Mozaffari E et al. CROI. 2021; Garcia-Vidal C et al. *Lancet Reg Health Eur*. 2021;3:100041; Garcia-Vidal C et al. *Rev Esp Quimioter*.	Medicines and Healthcare Regulatory products Agency (MHRA). **Baricitinib:** As such as of 7 December 2022 Eli Lilly have withdrawn its application for an extension to the marketing authorisation for baricitinib in the treatment of people in hospital with COVID-19. (Link to EMA: https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/olumiant) **Tixagevimab plus cilgavimab** Taking account of the trial evidence generalisability concerns the committee concluded the clinical effectiveness of tixagevimab plus cilgavimab is highly uncertain in terms of reducing hospitalisation or mortality rates. (Please see section 3.12 to 3.17 in FDG) Based on committee conclusions, tixagevimab plus cilgavimab is not recommended because it is unlikely to be effective at treating COVID-19

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		2021;34:136–40; Mozaffari E et al. EFIM. 2021; Wong CKH et al. *Clin Infect Dis.* 2021. DOI: 10.1093/cid/ciab728; Mehta RM et al. *Int J Infect Dis.* 2021;106:71–7.). Other points in more detail: e) It is unclear why Nirmatrelvir/ritonavir in the community is judged by its ability to reduce progression, whilst Remdesivir is seemingly judged by survival benefit (section 3.11), when the primary endpoint was similarly prevention of hospitalisation and all-cause mortality at 1 month. f) Section 3.12 states that the use of Remdesivir '…is not as clearly defined' in the hospital setting – but it is quite clear from ACTT-1, the final SOLIDARITY results and a wealth of real-World data that a consistent mortality benefit is seen in those requiring oxygen support. g) It is unclear why the large randomised SOLIDARITY trial's final results are not fully considered but rather '…the value of including this information is uncertain' (Section 3.12) - when data on the other products were similarly impacted (as acknowledged by the report on page 5) by trials performed prior to the emergence of omicron and largely in unvaccinated populations. Consistency in assessment is required from the panel. h)There is also a contradiction where there is acknowledgement earlier in the report that '… clinical experts said a hierarchical flow of treatments is followed in the hospital and recommending one treatment over another is challenging' (section 3.8), but then section 3.22 states that '… Remdesivir was dominated by cheaper and more	and it is not possible to reliably estimate their cost effectiveness. (Please see section 1 in FDG) 5d. Following DG consultation comments the statement on remdesivir's mechanism of action has been removed. 5e. For mild COVID-19 setting these clinical endpoints were considered in the AG model: • relative risk of hospitalisation or death • relative risk of all-cause mortality at 28 days. Therefore the same endpoints were considered for nirmatrelvir/ritonavir and remdesivir for the mild COVID-19 setting. The severe COVID-19 setting included these clinical endpoints in the AG model: • hazard ratio of time to death • hazard ratio of time to discharge

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		clinically effective treatments'. These other treatments being cited have a completely different mechanism of action, and there is data on the additive benefit of Remdesivir therapy in combination with immune modulation (e.g. RECOVERY Collaborative Group et al. *MedRxiv*. 2022. DOI: 10.1101/2022.03.02.22271623). i) As a minor point, it is worth re-phrasing that not all the antivirals are oral (as specified in section 3.7) – as Remdesivir is intra-venous.	• relative risk of clinical improvement at 28 days. (Please see section 3.10 of FDG and 3.12 to 3.20 of FDG for the clinical evidence considerations for all technologies evaluated) 5f) The statement was made by clinical experts at ACM1. It should be noted remdesivir and all other technologies are being evaluated within their marketing authorisation in Great Britain. 5g) Comment noted. For the second committee meeting, the company provided NMA with SOLIDARITY was considered by committee. (Please see section 3.10 of FDG). 5h) At ACM2 committee only considered a pairwise analysis of all ICERs versus standard care 5i) The statement has been updated following stakeholder comments

Comment number	Organisation name	Stakeholder comment	NICE Response
26	British Infection Association (Comment 6)	a) Has all of the relevant evidence been taken into account? This Consultation has not given enough weightage to clinical effectiveness evidence as much as it has laid emphasis on cost rather than even cost effectiveness as the evidence on cost-effectiveness too is quite skewed and confounded by looking at data across the entire pandemic timeline where the different variants that evolved have been so different from each other, and also from the original strain. If cost effectiveness is studied as a distinct time period for the current omicron post-origin era, that will instruct more accurately the ICERs of antivirals including Remdesivir quite early on in the presentation and especially in unvaccinated and/or immunosuppressed patients. However, there is a lot of data on clinical effectiveness of remdesivir in low oxygen requirement conditions; and even in those not needing oxygen which needs to be considered and I am not sure that this current appraisal document has. **Real-World Effectiveness of Remdesivir in Adults Hospitalized With Coronavirus Disease 2019 (COVID-19): A Retrospective, Multicenter Comparative Effectiveness Study** *Clinical Infectious Diseases*, Volume 75, Issue 1, 1 July 2022, Pages e516–e524, https://doi.org/10.1093/cid/ciab1035 A recent metanalysis: **Remdesivir for the treatment of patients hospitalized with COVID-19 receiving supplemental oxygen: a targeted literature review and meta-analysis** ***Scientific Reports*** **volume 12, Article number: 9622 (2022)** **https://www.nature.com/articles/s41598-022-13680-6** b) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	6a/b. Regarding remdesivir recommendations please see response to your comment #1c and j 6c/g. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option. Please also see response to your comment #1f. 6d-e. The economic model is modelling a McInnes defined high-risk group cohort and not individual subgroups within the cohort. Please also see response to your comment #1k. 6f. Please refer to AG report for the detailed costs included in the model. Alongside treatment costs, hospitalisation and long COVID costs have also been included. Please see section 3.31 in FDG which lists uncaptured benefits not considered where some of these benefits fall outside of the NICE reference case or there is limited evidence to support them.

Comment number	Organisation name	Stakeholder comment	NICE Response
		The cost effectiveness analysis is skewed on the grounds that most of the data is drawn across different covid variants cycles, and more often than not the 'time-to-initiation' of therapy with some antiviral agents (esp remdesivir) has been broad with therapy instituted too late. The narrowing down to low flow oxygen indication happened quite late in the pandemic cycle in terms of mortality rates time line graphs. The committee had made the argument that in this omicron era, the recommendation cannot be generalised, which could in fact suggest that the QALYs/ICER may be better in the Omicron/post-Omicron era if remdesivir is started early. Furthermore, there are 3 important practical points to consider: c) What is the antiviral option when paxlovid is ruled out due to its myriad of drug-drug interactions? d) Have the committee considered data or would it ask for data / literature need on how cost effectiveness [ICER/QALYs] and clinical effectiveness for the Remdesivir, sotrovimab, evusheld would be distinctly improved for those with failed immune function [immunosuppressed] and/or failed to take any SARS-CoV-2 vaccines or have been ineligible for it. e) Has the committee looked at readmission rates in those immunosuppressed if not given adjuvant monoclonal antibodies [sotrovimab or evusheld]; or can there be a recommendation to look for evidence of that? f) Are the recommendations sound and a suitable basis for guidance to the NHS?	6g. Please see an overview of equality issues considered by the committee in section 3.32 of FDG

Comment number	Organisation name	Stakeholder comment	NICE Response
		The recommendation prevaricate mainly towards the cost of medications and it has not been a proper cost effectiveness analysis. As such, these recommendations will lead to poorer outcomes and standard of care for covid-19 in NHS. g) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? There is no perceived discrimination against individuals with protected characteristics. However, as highlighted above, the options for immunosuppressed individuals will be sub-optimal if depending on the SARS-CoV-2 variant in circulation, monoclonal antibodies such as sotrovimab or evusheld are withheld from being available.	
27	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 1)	**General comment:** This document recommends against use of any specific treatments in the context of acute COVID for those under 18 years of age without adequate discussion of the available data in this age range or acknowledgement of the impact this may have in the rare instances when severe disease may occur in this age group. There appears to be very limited consideration of the needs of individuals under 18 years in this guidance. Notable exclusions from the stakeholder list include RCPCH and BPAIIG, two organisations which have provided rapid, inclusive, multidisciplinary, evidence-based guidance on the management of COVID in children throughout the pandemic. There are significant differences in the frequency of severe disease, in disease phenotype and in risk factors for severity between adult	**1.** Comment noted. Based on stakeholder consultation comments, at ACM2 a paediatric clinical expert was present and the committee heard from the expert about the impact of COVID-19 on younger people (aged 18 years or less). The FDG has included the clinical expert and paediatric patient organisation perspectives

Comment number	Organisation name	Stakeholder comment	NICE Response
		and paediatric COVID, although there is clearly a spectrum of disease manifestations between birth and young adult. Despite the rarity of severe disease in children, significant efforts have been made to provide robust observational data and to include children and young people in studies relating to treatment safety, pK and efficacy. This does not appear to have been taken in to account in this guidance. We request that the needs of those under 18 years of age are specifically taken in to account and discussed more thoroughly for each agent listed in this guideline taking in to account the well recognised differences between adult and paediatric disease and the comparative availability of licensed agents.	where possible (section 3.1,3.5,3.32 and 3.33 of FDG). The initial failure to include paediatric organisations from the stakeholder list was an oversight. However, during the scoping phase we do ask respondents to let us know if we have missed any important organisations from the stakeholder list, and did not receive any comments relating to paediatric organisations.
28	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 2)	1.1 Nirmatrelvir plus ritonavir is recommended as an option for treating COVID-19 in adults, only if they: - do not need supplemental oxygen for COVID-19 and - have an increased risk for progression to severe COVID-19, as defined in the independent advisory group report commissioned by the Department of Health and Social Care. Comment – no additional considerations for children as not licensed in this age group although it should be noted that any recommendation for use of this agent in adults but not in those under 18 years of age automatically discriminates against those individuals. Adolescent (>40kg >12 years) COVID disease phenotype (especially in those with obesity and risk factors associated with severe disease in adult populations) is very similar to that of young adults and by extrapolation agents with proven efficacy could be recommended in those age groups if/when licensed. PK and safety studies for children >6yrs of age are underway and this drug has received emergency authorisation in the USA, where observational data will shortly be published.	2. Comment noted. Nirmatrelvir plus ritonavir does not currently have marketing authorisation in Great Britain for younger people (aged 18 years or less). In the mild COVID-19 setting the committee has recommended sotrovimab for people for whom nirmatrelvir plus ritonavir is unsuitable. Sotrovimab's marketing authorisation in Great Britain includes adolescents (aged 12 years and over), so this would be an option for them, if they have a high-risk of progression to severe COVID-19 as defined by the McInnes report.

Comment number	Organisation name	Stakeholder comment	NICE Response
29	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 3)	1.2 Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who: - are having systemic corticosteroids and - need supplemental oxygen or mechanical ventilation. Tocilizumab is only recommended if the company provides it according to the commercial arrangement (see section 2). Comment – Patients under 18 years of age were included in the RECOVERY trial which demonstrated efficacy of tocilizumab. Although rare it is reasonable to extrapolate that CYP experiencing the hyperinflammatory phase of COVID may benefit from tocilizimab as has been demonstrated in adult studies. Consideration should be made for inclusion of individuals under 18 years in this recommendation. There is extensive safety and dosing data for use of tocilizumab for other indications in children.	3. Comment noted. Tocilizumab does not currently have marketing authorisation in Great Britain for younger people (aged 18 years or less). For younger children the only option in this setting is remdesivir. However, the ICERs were very high and not considered a cost-effective use of NHS resources. By only recommending tocilizumab in the severe COVID-19 setting there is a risk of indirectly discriminating against children and young people. However, the alternative treatments had substantially higher ICERs and were not considered a cost-effective use of NHS resources. NICE expects its advisory bodies to use their scientific and clinical judgement in deciding whether the available evidence is sufficient to provide a basis for recommending or rejecting particular clinical or public health measures (Social Value Judgements; 'Principles for the development of NICE guidance', principle 1). Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 4 and 5).

Comment number	Organisation name	Stakeholder comment	NICE Response
30	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 4)	1.3 Baricitinib is recommended as an option for treating COVID-19 in adults, subject to it receiving a marketing authorisation in Great Britain for this indication. Comment – Patients under 18 years of age were included in the RECOVERY trial which demonstrated efficacy of baricitinib. Although rare it is reasonable to extrapolate that CYP with COVID may benefit from baricitinib as has been demonstrated in adult studies. Consideration should be made for inclusion of individuals under 18 years, >40kg in this recommendation. Safety and dosing data for use of baricitinib for other indications in children are available.	**4**. As of 7 December 2022 Eli Lilly have withdrawn its application for an extension to the marketing authorisation for baricitinib in the treatment of people in hospital with COVID-19. (Link to EMA: https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/olumiant) NICE cannot make any recommendations for treatments without a marketing authorisation in Great Britain.
31	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 5)	1.4 Casirivimab plus imdevimab is not recommended, within its marketing authorisation, for treating acute COVID-19 in adults Comments – There is no mention of those under 18 years of age in this recommendation. This product is licensed for use in the treatment of COVID in adolescents and therefore a consideration of whether this agent should or should not be used in the adolescent age range (in which oral antiviral agents are not licensed) is warranted.	5. In the mild and severe COVID-19 setting casirivimab plus imdevimab is not recommended because it is unlikely to be effective at treating severe COVID-19 and it is not possible to reliably estimate its cost effectiveness.
32	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 6)	1.5 Molnupiravir is not recommended, within its marketing authorisation, for treating mild to moderate confirmed COVID-19 in adults who have at least 1 risk factor for developing severe COVID-19. Comment – no additional considerations for children as not licensed in this age group although it should be noted that any recommendation for use of this agent in adults but not in those under	6. Molnupiravir is not recommended because it is unlikely to be effective at treating COVID-19 and it is not possible to reliably estimate its cost

Comment number	Organisation name	Stakeholder comment	NICE Response
		18 years of age automatically discriminates against those individuals. Adolescent (>40kg >12 years) COVID disease phenotype (especially in those with obesity and risk factors associated with severe disease in adult populations) is very similar to that of young adults and by extrapolation agents with proven efficacy could be recommended in those age groups if/when licensed.	effectiveness. Please also see response to comment #2
33	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 7)	1.6 Remdesivir (RDV) is not recommended, within its marketing authorisation, for treating COVID-19 in: - people aged at least 4 weeks and weighing at least 3 kg with pneumonia who need supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation) at start of treatment - young people weighing at least 40 kg and adults who do not need supplemental oxygen and have an increased risk for progression to severe COVID-19. Comment – Reassuring safety and pK data is available from well designed clinical trials for remdesivir in those under 18 years of age. In addition, carefully reported observational data is also available. It is licensed for pre-hospital treatment in the adolescent age range and for hospitalised patients down to very young ages. In the under 12 age range this is the only licensed treatment available. Furthermore the disease phenotype in younger children is more of an acute viral syndrome (similar to other acute viral respiratory infections) rather than the hyperinflammatory process observed in older age groups. Efficacious antiviral agents are therefore likely to play more of a role than anti-inflammatory agents in this age range. In addition RDV is licensed for outpatient treatment of high risk individuals with symptomatic COVID, based on trial data which included adolescents. In the absence of a license for oral antivirals this is the only antiviral option for non-hospitalised children and young people with COVID as well as those with hospital onset early disease in those hospitalised for different reasons.	**7. Comment noted.** In the severe COVID-19 and supplemental oxygen setting the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG). Please also see response to your comment #3.

Comment number	Organisation name	Stakeholder comment	NICE Response
		These considerations do not appear to have been adequately discussed or taken in to account when making this recommendation which could be considered discriminatory against this age group.	
34	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 8)	1.7 Sotrovimab is not recommended, within its marketing authorisation, for treating symptomatic acute COVID-19 in people aged 12 years and over and weighing at least 40 kg who: - do not need oxygen supplementation and - have an increased risk for progression to severe COVID-19. Comment – in the absence of a license for the oral antiviral therapies licensed for adults, sotrovimab is one of only 2 options available for treatment of non-hospitalised individuals under the age of 18 years with symptomatic COVID at risk of hospitalisation (the other being remdesivir which requires 3 daily doses of IV administration). Sotrovimab requires only 1 infusion and there are well established processes for providing this to those eligible (along with accumulating safety and tolerability data). Although there is some doubt about efficacy of sotrovimab for newer variants or in the context of natural or vaccine induced immunity, there is still evidence available that would support its use, especially if oral antiviral agents are not an option. The limited options available to those 18 years does not appear to have been taken in to account in this recommendation.	8. Comment noted. In the mild COVID-19 setting the committee has recommended sotrovimab for people for whom nirmatrelvir plus ritonavir is unsuitable. Sotrovimab's marketing authorisation in Great Britain includes adolescents (aged 12 years and over), so this would be an option for them, if they have a high-risk of progression to severe COVID-19 as defined by the McInnes report.
35	British Paediatric Allergy Infection and Immunity Group (BPAIIG) (Comment 9)	1.8 COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The role of tixagevimab and cilgavimab for pre-exposure prophylaxis in CYP peri-transplant/ or significant immunosuppression (eg induction chemotherapy) should be considered. PK, Safety and efficacy studies are underway in the UK for children and young people between the ages of 28 days and 18 years.	**9.** Comment noted. Tixagevimab and cilgavimab does not have marketing authorisation in Great Britain in younger people (18 years or less). Please see response to your comment #1 and #8.

Comment number	Organisation name	Stakeholder comment	NICE Response
		It is noteworthy that the trials that these recommendations are based on predominantly included unvaccinated adults, the majority of whom were not immunocompromised. The current population who is at risk/ vulnerable to severe disease and death, for whom these recommendations are key, are largely immunocompromised through underlying disease and treatments, and are often unable to respond effectively to vaccinations for the same reasons. Emerging data specific to these cohorts is crucial for informing NICE guidance. In particular, monoclonals, including tixagevimab plus cilgavimab, are likely to play a greater role in those unable to mount an appropriate antibody response. The children who are unwell with COVID, or at risk of severe disease are either those with significant immunocompromise, for whom even small benefits from monoclonals may be relevant, or are susceptible to viraemic pneumonitis and have limited reserve (those with complex neurodisability), for whom anti-virals are likely to be play a crucial role. These considerations should be part of this document.	
36	British Thoracic Society (Comment 1)	We are concerned that this guideline provides for 1x antiviral preparation (Paxlovid) only, in non-hospitalised patients at high risk of progression. This is a drug with several CIs including liver and renal disease, and numerous drug interactions – including with several 'essential' or high risk medications which may be challenging to stop or replace during the treatment period. We would expect to see some analysis of the % of immunocompromised patients who would be ineligible for treatment with Paxlovid – this would seem key to a decision about providing this single antiviral treatment only.	1.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option. (Please see section 1 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
37	British Thoracic Society (Comment 2)	We are concerned that this guideline will provide anti-inflammatory therapy only, with tocilizumab or baricitinib, for hospitalised patients requiring oxygen, with no antiviral or neutralising mAb provision. - Thresholds for admission vary, and we are increasingly seeing patients with early disease but a high comorbidity burden (particularly the elderly) being admitted to hospital +/- oxygen requirements. One would hypothesise a role for antivirals in this patient group - There is likely a transition period, even in those with more severe disease, who have both ongoing viral replication and a growing inflammatory response. There is likely a role for both antiviral and anti-inflammatory treatment in this patient group. - This approach makes no provision for immunocompromised patients / those with persistent viral PCR positivity who are admitted to hospital unwell, with failure to clear the virus – this is a growing proportion of our (extended) hospital admissions in whom antiviral treatment is essential.	2.Comment noted. 'Casirivimab plus imdevimab and remdesivir are not recommended because they are unlikely to be effective at treating severe COVID-19 and it is not possible to reliably estimate their cost effectiveness.' Please see section 1 of FDG Remdesivir does not currently have marketing authorisation in Great Britain for people who do not need supplemental oxygen unless they are at increased risk of severe COVID-19. NICE can only evaluate remdesivir within its current marketing authorisation in Great Britain. (Please see section 2.4 of FDG) NICE has recommended two treatment options (nirmatrelvir plus ritonavir and sotrovimab) for people who do not need supplemental oxygen and who are at an increased risk of severe COVID-19 based on McInnes high-risk definition. Please see section 1 of FDG.

Comment number	Organisation name	Stakeholder comment	NICE Response
			In the severe COVID-19 and supplemental oxygen setting the committee concluded there was insufficient evidence for remdesivir to show meaningful difference in mortality benefit compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG)
38	British Thoracic Society (Comment 3)	There is repeated concern expressed that there is limited data for the efficacy of remdesivir – perhaps in relation to limited data about use in vaccinated groups / Omicron (p21/22). We wonder if this has led to inappropriate under weighting of data from the SOLIDARITY study. Whilst we understand the concern about efficacy across strains, it is not clear why remdesivir would be less effective in a vaccinated cohort – hospitalisation with evidence of PCR positivity presumably reflects viral replication +/- host inflammatory response, irrespective of vaccination status. It would be helpful if this concern could be justified / supported by some data.	3. Comment noted. The company provided NMA which included SOLIDARITY was considered by committee at ACM2. (Please see section 3.10 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
39	British Thoracic Society (Comment 4)	We have some questions about the assumptions made within the model re. long Covid – - The analysis seems to conflate complications of an ITU admission amongst hospitalised patients, with the experience of long-Covid. I believe these are two distinct sequalae of Covid disease, with different types of care required, different duration of illness, and affecting different Covid patient groups. I'm not sure one set of utility values can be applied across these conditions. Perhaps related to this - the assumptions made on p23 re. the proportion of hospitalised / non-hospitalised patients experiencing long-covid do not feel quite right. Is there data to support this? Clinical experience suggests that there is a poor correlation between disease severity and the incidence / severity of long-Covid with a high burden of disease seen amongst non-hospitalised individuals who had relatively 'mild' initial disease.	4.Comment noted. Based on stakeholder comments during DG consultation the AG updated the long COVID cost and duration. The best source of evidence for long COVID available at the time of evaluation was used. (Please see section 3.21, 3.24 and 3.25 of the FDG)
40	British Transplantation Society (BTS) (Comment 1)	The British Transplantation Society is concerned that the recommendation, as currently phrased, may imply that solid organ transplant patients do not benefit from treatment with sotrovimab in the community (data not available to support this position).	1.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
41	British Transplantation Society (BTS) (Comment 2)	The consultation does not include a recent publication of factors associated with severe infection in the UK following an extended vaccine course, including an additional booster[1]. The study found that solid organ transplant recipients remained at highest relative risk of severe infection, which is an important consideration as the key driver in the economic models was the baseline rate of hospitalisation. Data is now also available showing a significant proportion of kidney transplant recipients fail to have detectable serological or cellular responses, even after 4-doses of COVID-19 vaccines[2]. The OCTAVE data, referenced in the consultation, contains minimal immunogenicity data on solid organ transplant recipients[3]. Solid organ transplant (SOT) recipients have been able to receive community treatment for COVID-19 following infection. This treatment option will be removed, if this guidance is ratified, and the alternative Paxlovid is not recommended for people with severe renal or hepatic impairment and is contraindicated with concurrent use of immunosuppression medications (CYP3A metabolic pathway). Therefore, both patients on the transplant wait list and transplant recipients, will not have access to antiviral treatment, despite being the population at highest risk. The consultation references data by the Crick Institute and OpenSAFFELY group, which supports continued access to sotrovimab for transplant recipients, until evidence suggests the agent no longer has clinical effectiveness[4,5]. The data from the OpenSAFELY group, also supports the benefit of sotrovimab over molnupiravir[6](pre-print). It should be noted that the PANORAMIC Study only reported outcome data on 127 SOT recipients, of whom all were eligible for concurrent monoclonal antibody therapy, and therefore will not be readily applicable to inform ongoing management in this population[7]. Access to community treatment has provided an additional layer of protection for SOT recipients, who are aware that vaccination may not provide as much protection as in the general population. Our patient	2.Comment noted. **Sotrovimab's clinical effectiveness**: The committee considered the COMET-ICE trial evidence, alongside the in vitro and OpenSAFELY observational evidence for sotrovimab. The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing BQ.1 and BQ.1.1 subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.19 in FDG) **In vitro evidence** The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in

Comment number	Organisation name	Stakeholder comment	NICE Response
		representatives have already raised concerns and removal of access to community treatment will increase anxiety still further within this population- exacerbating health inequalities. The higher prevalence of lower socio-economic status and ethnic minorities in both the organ failure and SOT recipient populations has been well described, and this guidance will exacerbate those differences.	vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. The advisory group included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. (Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG) Please also see response to your comment #1
42	Cardiothoracic Transplant Patient Group (Under the governance of the Organ Donation and Transplantation Directorate at NHS Blood and Transplant) Response formally approved at Cardiothoracic Transplant Patient	The Cardiothoracic Transplant Patient Group is concerned that the preliminary recommendations could have an adverse impact on those individuals whose life is sustained with a donor heart and / or lung. That the preliminary recommendations will discriminate against this group. In section 3.24 the committee noted that nirmatrelvir plus ritonavir would not be a viable option for some patient groups due to the contraindication for concomitant use. This would apply to all heart and / or lung transplant recipients due to their immunosuppressant drug regimes. The Cardiothoracic Transplant Patient Group recognise that the committee acknowledged this issue and considered alternative treatments (such as Sotrovimab) but concluded that they "had	1.Comment noted. **Sotrovimab recommendation:** The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir

Comment number	Organisation name	Stakeholder comment	NICE Response
	Group Meeting on 7 December 2022 (Comment 1)	substantially higher Incremental Cost Effectiveness Ratios and were not considered a cost-effective use of NHS resources". The Cardiothoracic Transplant Patient Group would like to formally raise concerns that the Incremental Cost Effectiveness Ratios have been calculated for the McInnes defined high risk patient group and suggest these figures should be calculated for the subgroups of heart and lung transplant. During such an exercise the following considerations should be taken into account; • The lack of viability of nirmatrelvir plus ritonavir for this patient group • The very high Covid severe disease risk with heart and lung transplant patients. This is exemplified by the latest Covid 19 mortality figures published by NHS Blood and Transplant (monthly-report-on-covid-19-nhsbt-16-march-2022.pdf (windows.net)), which shows mortality rates of 15.5% and 7.5% for lung and heart transplant respectively. The Cardiothoracic Transplant Patient Group was pleased to note that in 3.25 the committee stated that "in theory it would be willing to accept an Incremental Cost Effectiveness Ratios slightly more than what is usually acceptable if it addressed such health inequalities (people with protected characteristics disproportionately)". In summary, the Cardiothoracic Transplant Patient Group appreciate that the committee has considered the potential for the guidance to discriminate against people with certain disabilities. However, it does not believe that the committee has specifically analysed the impact of the draft guidance on heart and / or lung transplant patients to be confident that this patient group is not being discriminated against.	plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) **Hospitalisation rates:** The committee considered a wide range of hospitalisation rates including the 15.9% by Shields et al. 2022. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort and 4% for people contraindicated to nirmatrelvir plus ritonavir. Please see section 3.22 in FDG.

Comment number	Organisation name	Stakeholder comment	NICE Response
43	Cardiothoracic Transplant Patient Group (Under the governance of the Organ Donation and Transplantation Directorate at NHS Blood and Transplant) Response formally approved at Cardiothoracic Transplant Patient Group Meeting on 7 December 2022 (Comment 2)	The Cardiothoracic Transplant Group would like to raise concerns that the hospitalisation rates used for calculating the Incremental Cost Effectiveness Ratios, are a likely significant underestimate of actual rates experienced by heart and / or lung recipients. The maximum rate used for calculating the ICERs was 2.79% (DISCOVER-NOW). However, Shields et al. 2022 report 18.4% for people with primary or secondary immunodeficiency and known Covid mortality rates for lung and heart transplant recipients are 15.5% and 7.5% respectively (monthly-report-on-covid-19-nhsbt-16-march-2022.pdf (windows.net)). The Cardiothoracic Transplant Patient Group acknowledge that the committee recognised the uncertainty around hospitalisation rates for some patient groups, citing transplant recipients as an example. However, the Cardiothoracic Patient Transplant Group do not consider that the committee have investigated the available evidence in sufficient detail to assure itself that the draft guidance would not cause discrimination to people with a protected characteristic. It is difficult to conclude that 2.79% is a sufficient hospitalisation rate ceiling for a patient group with known publicly available mortality figures of 15.5% and 7.5% (monthly-report-on-covid-19-nhsbt-16-march-2022.pdf (windows.net)) In summary the Cardiothoracic Transplant Patient Group consider that the hospitalisation rates selected for the Incremental Cost Effectiveness Ratios will almost certainly have discriminated against those individuals whose life is sustained with a donated heart and / or lung.	2.Comment noted. Please see response to your comment #1 (hospitalisation rates followed by sotrovimab recommendation)
44	Cardiothoracic Transplant Patient Group (Under the governance of the Organ Donation and	The Cardiothoracic Transplant Patient Group is concerned that the committee may have not received all relevant evidence relevant to cardiothoracic transplant recipients due to the lack of stakeholder inclusion and engagement from the cardiothoracic transplant patient and clinical communities. The extensive list of patient carer groups included most disease types within the Independent Advisory Group defined list of highest risk patients. However, apart from Pulmonary	3.Comment noted. Prior to ACM2, the committee was given the opportunity to review the stakeholder consultation comments including

Comment number	Organisation name	Stakeholder comment	NICE Response
	Transplantation Directorate at NHS Blood and Transplant) Response formally approved at Cardiothoracic Transplant Patient Group Meeting on 7 December 2022 (Comment 3)	Fibrosis no other patient carer group relating to cardiothoracic transplant was involved.	'The Cardiothoracic Transplant Patient Group' comments.
45	Cardiothoracic Transplant Patient Group (Under the governance of the Organ Donation and Transplantation Directorate at NHS Blood and Transplant) Response formally approved at Cardiothoracic Transplant Patient Group Meeting on 7 December 2022 (Comment 4)	The Cardiothoracic Transplant Patient Group are concerned that the time allocated to the External Advisory Group was insufficient for them to consider the impacts on individuals with certain protected characteristics such as those whose life is sustained by a donor heart and / or lung. The External Advisory Group Assessment report specifically highlights this issue in 1.4.5 stating, "Due to time constraints, the only subgrouping considered was related to whether oxygen was required upon admission to hospital entry… The External Advisory Group is aware that other possible criteria for selecting subgroups includes but are not limited to age; immune system competence; comorbidities; seroprevalence; vaccination status; and the predominant SAR-CoV-2 variant but did not have time to explore the impact of these characteristics." The consequence has been that the preliminary recommendations are only based on hospitalisation rate data from PANORAMIC or DISCOVER-NOW which the Cardiothoracic Transplant Patient Group believe is a significant underestimate of the actual rates for their patient population. The preliminary recommendations will have an adverse impact on people with a donor heart and / or lung.	4.Comment noted. At ACM2, the committee noted the draft guidance consultation comments highlighted the need for separate 'high risk' and 'highest risk' groups, or a separate high-risk group contraindicated to nirmatrelvir plus ritonavir. The committee saw examples on how the risk group could be split based on Patel et al. 2022. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. The committee did not

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			see additional evidence to justify splitting the high-risk group. (Please see section 3.4 to 3.7 of FDG) For inclusion of additional subgroups the committee noted additional functionality, clinical or cost inputs and treatment-effectiveness assumptions would be required to make differential subgroup recommendations and this would not be practical or aligned with the decision problem. (Please see section 3.7 in FDG) Please also see response to your comment #1 where a committee considered a contraindicated to nirmatrelvir plus ritonavir group in their recommendations and alternative hospitalisation rates.
46	Cardiothoracic Transplant Patient Group (Under the governance of the Organ Donation and	The Cardiothoracic Transplant Patient Group believe that the preliminary recommendations are not sound and suitable guidance to the NHS as they remove many treatment options for heart and lung transplant recipients. The primary recommendation of nirmatrelvir plus ritonavir is known to be clinically unsuitable for this patient group.	5.Comment noted. Please see response to your comment #1 (Sotrovimab recommendation)

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	Transplantation Directorate at NHS Blood and Transplant) Response formally approved at Cardiothoracic Transplant Patient Group Meeting on 7 December 2022 (Comment 5)		
47	Cardiothoracic Transplant Patient Group (Under the governance of the Organ Donation and Transplantation Directorate at NHS Blood and Transplant) Response formally approved at Cardiothoracic Transplant Patient Group Meeting on 7 December 2022 (Comment 6)	The Cardiothoracic Transplant Patient Group would like to highlight new evidence to the Appraisal Committee. An observational study published in the BMJ (BMJ 2022;379:e071932) comparing the effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community suggested, "sotrovimab was associated with a lower risk of severe covid-19 outcomes than molnupiravir, including in those patients who were fully vaccinated".	6.Comment noted. **Sotrovimab's clinical effectiveness**: The committee considered the COMET-ICE trial evidence, alongside the in vitro and OpenSAFELY observational evidence for sotrovimab. The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing BQ.1 and BQ.1.1 subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to

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			consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.19 in FDG) **In vitro evidence** The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. The advisory group included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. (Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG)
48	Faculty of Pharmaceutical Medicine (Comment 1)	a) This draft guidance, if implemented, would result in the majority of the population of the UK being unable to access treatment for symptomatic COVID illness. This will particularly impact vulnerable individuals, who have been targeted by JCVI for receipt of vaccination boosters by virtue	1a. Comment noted. **Sotrovimab recommendation:**

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		of their disease susceptibility and risk of more severe outcomes. b) In addition, this guidance stands in contrast to similar recommendations for the use of antiviral treatment for influenza, which provides access to treatment for the identical same group of patients that are recommended for free influenza vaccination (https://www.nice.org.uk/guidance/ta168). The committee might wish to consider whether the differences in recommendations for the management of two, now quite similar, respiratory viral diseases is justifiable and explicable to prescribing healthcare professionals. Many of the general population are at risk of more severe outcomes from both COVID and influenza based on age (>65) or comorbidities (chronic cardiac disease, diabetes, chronic respiratory disease, chronic renal disease, chronic neurological conditions), which are conditions in addition to those cited in the current NHS commissioning guidance. An explanation for use of treatment in these groups, who are regularly documented to be at high risk of more severe outcomes if covid infected, might be offered. For example, an overweight woman of 68 with no other risk factors has a 1:734 chance of dying from COVID according to the QCovid risk calculator, while an overweight male of 65 with chronic respiratory disease has a 1:475 chance of dying, c) The calculator does not list the risk of hospitalisation: if this could be added perhaps use of the risk calculator and a defined risk of hospitalisation/death is proposed then this would enable doctors to advise patients.	The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) 1b. **Comment noted.** **McInnes definition:** The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19. Another benefit of using this definition is that outcomes data (OpenSAFELY and DISCOVERNOW database see comment #1c) has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected. (Please see section 3.4 to 3.7 of FDG)

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			1c. **Hospitalisation rates:** The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort from OpenSAFELY which captures the identical McInnes defined high-risk population and 4% for people contraindicated to nirmatrelvir plus ritonavir (using OpenSAFELY and DISCOVERNOW database both sources capture the McInnes defined high-risk population). Please see section 3.22 in FDG.
49	Faculty of Pharmaceutical Medicine (Comment 2)	It is observed that NICE guidance is applicable only to access in the NHS. At what point will members of the public able to pay for therapy be able to access these treatments?	2.Comment noted. This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. Recommendations outside of the context of NHS setting is not within NICE's remit.

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50	Faculty of Pharmaceutical Medicine (Comment 3)	The expert panel that provided an independent view of patient groups eligible for treatment was restricted to the identification of patient groups *deemed to be at the very highest risk of an adverse COVID-19 outcome, namely hospitalisation and death.* The committee then restricted use primarily to immunocompromised patients as these individuals cannot respond adequately to vaccination. However, such groups include a high proportion of patients with poor T cell immunity and an inability to adequately clear virus, which has been reported in the past to contribute to the emergence of resistant viral variants in patients with influenza (van der Vries E et al), prolonged influenza virus shedding and emergence of antiviral resistance in immunocompromised patients and ferrets (PLoS Pathog. 2013;9(5):e1003343. pmid:23717200). Resistance to nirmatrelvir readily emerges in non-clinical experiments (Moghadasi SA et al). Transmissible SARS-CoV-2 variants with resistance to clinical protease inhibitors have emerged (bioRxiv [Preprint]. 2022 Aug 8:2022.08.07.503099. doi: 10.1101/2022.08.07.503099. PMID: 35982678; PMCID: PMC9387136.) suggesting that the current monotherapy strategy is inadvisable and may, if used widely among an immune compromised population, eventually result in the emergence of a transmissible, protease inhibitor resistant variant which would then threaten the general community. In immunocompromised patients, combination antiviral chemotherapy is preferable to monotherapy. This should be a subject for further research and also for additional cost benefit analysis.	3.Comment noted. Please see response to your comment #1a (Sotrovimab recommendation)
51	Faculty of Pharmaceutical Medicine (Comment 4)	While many monoclonal antibodies that were highly effective in the initial covid waves have now lost efficacy against omicron variants, researchers continue to explore new antibody treatments which may enable reconsideration of the use of these agents, not only for treatment but also for primary prevention of covid in patients unable to respond to vaccination.	**4.** Comment noted. NICE will take these suggestions on board as next steps. NICE has announced it is developing a new rapid update process to maintain these recommendations. Please also note 'This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for

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		Progress in this field should be kept under review and consideration given to reinstituting use, should newer antibodies become available.	people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as: • the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or • local or national circumstances of high rates of hospitalisation for COVID-19.'
52	Faculty of Pharmaceutical Medicine (Comment 5)	Given the significant shift in pattern of disease accompanying emergence of the Omicron variants and the considerable strain on the economy of workforce shortages to which covid may have contributed and continues to contribute, the decision not to model the cost impact of expanded use of antiviral treatments seems inappropriate. It is appreciated that the model was not designed to explore this but a model can nonetheless be derived from the outcomes of PANORAMIC and prior work with influenza treatments with which to explore the value to industry and the NHS of preserving workforce effectiveness by earlier alleviation of illness and return to work. In addition, nirmaltrelvir-ritonavir has been suggested to reduce the frequency of sequelae post covid (Yan Xie, Taeyoung Choi, Ziyad Al-Aly Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19 medRxiv 2022.11.03.22281783; doi: https://doi.org/10.1101/2022.11.03.22281783). Although data are not yet available for molnupiravir, the results of the PANORAMIC study are compatible with similar outcomes being likely to be observed in longer term follow up of that population.	5.Comment noted. To explore cost-effectiveness of nirmatrelvir plus ritonavir in a wider population. The committee also considered a hospitalisation rate of 0.77% from PANORAMIC which more closely approximated the marketing authorisation population for nirmatrelvir plus ritonavir. The ICERs were above £20,000 per QALY gained and nirmatrelvir plus ritonavir was likely not a cost-effective use of NHS resources in this broader lower risk population. (Please see section 3.22 and 3.28 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
			Please also see response to your comment #4.
53	Faculty of Pharmaceutical Medicine (Comment 6)	It appears that the cost of Long Covid may have been considerably underestimated. For patients with residual lung injury, post infection new onset diabetes, cardiovascular events or kidney disease, which are observed in patients following both community based and hospitalised disease, the costs are likely to be substantively higher than the costs of care for patients with Chronic Fatigue Syndrome. Several long covid clinics have been established and it would be appropriate to ask these centres for their own estimates of costs of care (https://www.england.nhs.uk/2020/12/long-covid-patients-to-get-help-at-more-than-60-clinics/) in their centre. Recent work investigating long term outcomes of patients with covid has documented a considerable increase in cardiovascular disease and stroke which is highest immediately following a disease episode in patients managed in the community and in hospital, and then persists, particularly in older persons for up to 12 months after infection (Knight R, Walker V, Ip S et al. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales. Circulation. 2022 Sep 20;146(12):892-906. doi: 10.1161/CIRCULATIONAHA.122.060785. Epub 2022 Sep 19. PMID: 36121907; PMCID: PMC9484653). The authors recommend consideration of post covid anticoagulation for vulnerable high risk adults and this should be further considered in treatment guidance, while investigating whether antiviral treatment might reduce the incidence of these complications, which has been observed in the past with influenza antivirals (Dutkowski R, Thakrar B, Froehlich E, Suter P, Oo C, Ward P. Safety and pharmacology of oseltamivir in clinical use. Drug Saf. 2003;26(11):787-801. doi: 10.2165/00002018-200326110-00004. PMID: 12908848.) and may also be an appropriate topic for further research.	6.Comment noted. Based on stakeholder consultation comments the AG increased the cost of long COVID in the model. (Please see section 3.25 in the FDG)

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54	Faculty of Pharmaceutical Medicine (Comment 7)	No explanation is given for the continued recommendation of nirmatrelvir-ritonavir but the omission of molnupiravir for community use. The Panoramic study has yet to report the outcomes of the nirmatrelvir -ritonavir arm, but it is possible that the very low incidence of severe outcomes may also preclude convincing evidence of reduction of severe outcomes with this agent, as it did for molnupiravir, given the very low risk of hospitalisation/death in general, even in higher risk patients, during the Omicron era. Nirmatrelvir-ritonavir has not been shown to specifically reduce the overall duration of illness in affected patients – indeed in a study investigating this outcome in low risk patients (EPIC-SR) no difference in duration of illness, calculated as time to alleviation of all symptoms for at least 4 days, was observed (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-reports-additional-data-paxlovidtm-supporting). In addition, the required use of ritonavir in this agent is a problem, as mentioned at the meeting, for patients post-transplant taking anti-rejection therapy for which concomitant administration with ritonavir is contraindicated. It is recommended the panel consider whether molnupiravir might be offered as an alternative in this group, or indeed for other patients for whom use of ritonavir could cause serious adverse drug-drug interactions, as is recommended by the WHO.	7. Comment noted. **Nirmatrelvir plus ritonavir clinical effectiveness:** For nirmatrelvir plus ritonavir, along with EPIC HR, OpenSAFELY evidence, the committee noted the subgroup analysis from the recent EPIC-SR trial that included people who were vaccinated with at least one risk factor for severe COVID-19. Committee still considered there to be substantial uncertainty with the EPIC-HR trial data because of generalisability concerns with the mean-efficacy estimate. Therefore, the committee considered the range between the mean- and lower-efficacy estimates for nirmatrelvir plus ritonavir from the trial to be more suited to the current endemic setting, despite the limitations with this approach. (Please see section 3.11, 3.12 and 3.19 of FDG) The committee noted that PANORAMIC was also recruiting a nirmatrelvir plus ritonavir treatment arm that could answer questions about its

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			effectiveness for people with high risk factors for severe COVID-19 but are not defined in the McInnes high-risk group. (Please see section 3.19 of FDG) **Molnupiravir clinical effectiveness:** The committee noted that PANORAMIC may have excluded some of the highest risk groups that could have powered the study to see benefits in hospitalisation or mortality. The mean-efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were uncertain because of the population differences. The committee noted the results of the UK based OpenSAFELY data, which included a McInnes-defined high-risk population for molnupiravir, support the limited hospitalisation and mortality benefits observed in PANORAMIC and from the overall NMA. The committee noted that any benefit for hospitalisation or mortality is likely to be minimal when the HRs are close to 1, and stronger

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			clinical evidence is needed to justify a difference in relative clinical effects. (Please see section 3.12, 3.16 and 3.19 of FDG) Please also see response to your comment #1a (Sotrovimab recommendation)
55	Faculty of Pharmaceutical Medicine (Comment 8)	Examination of the AG model used to assess cost effectiveness is unclear as to the incidence of hospitalisations and deaths assumed to follow covid infections in the UK. Page 1 provides data from the ONS dated May 2022 suggesting a hospitalisation rate of >4% in the population overall, although the risk increases very steeply reaching very high levels in older individuals (aged >65). This observation makes the decision not to evaluate cost effectiveness according to age inexplicable, particularly as it is the older, frailer population that may be disproportionately admitted to hospital from which it may be difficult, due the present difficulties with the social care sector, to move recovered patients back to community based care. This is not discussed at all in the guideline other than to comment on potential for discrimination if recommendations were to be made based on age. It is suggested that it is discriminatory NOT to permit appropriate use of antiviral treatment in the community for a broader population of older patients with other conditions increasing risk of more severe disease following COVID infection. In the decision-tree page the presumed hospitalisation/death rate in SOCi (i.e. untreated) patients is 2.7%, which does not match the apparent community data based on the May UK analysis. In addition, neither of these percentages matches the incidence of hospitalisation/death reported in the PANORAMIC trial (0.8%) and these discrepancies should be discussed as to which are the appropriate presumptions to use in the analysis. FPM has commented previously that the publication of results from PANORAMIC suggest a potential reduction in the rate of	8.Comment noted. **Age as risk factor for severe COVID-19:** The committee acknowledged that age is a risk factor for progression to severe COVID 19. The committee considered that the relationship between age and comorbidities can be important in explaining risk of severe disease. The committee also noted that additional evidence is needed to model age over 70 years as an independent subgroup for the mild COVID-19 setting. The committee said the evidence for inclusion of age in the model should include: age-adjusted hospitalisation and mortality rates for the untreated population and relative treatment effects for the intervention. (Please see section 3.6 in FDG) The committee concluded that the McInnes report's definition of high risk included the most robust evidence of people who have a high risk

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		hospitalisation/deaths among molnupiravir treated subjects aged 65 and over but insufficient details are provided in the publication and should be sought from the trial centre. It is suggested that the discrepancies in the basic assumption for hospitalisation/death from covid is further discussed and if appropriate the model adjusted to accommodate more accurate and up to date information relevant to current practice.	for progressing to severe COVID-19, and this did not include age as an independent risk factor. Please see response to your comment #1c (hospitalisation rate)
56	Kidney Care UK (Comment 1)	We are very concerned that implementation of this draft guidance would result in the highest risk kidney patients in the community having no available treatment options to prevent them from developing severe Covid. As the guidance notes, Paxlovid (the only treatment option recommended in the draft guidance for non-hospitalised patients) is contraindicated in severe kidney disease and for most people taking widely used immunosuppressant medications. Kidney patients have been among those at highest risk from Covid (Williamson et al, 2020) and OpenSafely data confirms that they remain at much higher risk. Amongst those on dialysis compared to people not on dialysis, the risk of death increased from 8 times greater in wave 1 (March 2020 to May 2020) to 12 times greater in wave 3 (May 2021 to Dec 2021). In people with a kidney transplant, the relative risk increased from 7 times higher compared to people without a kidney transplant in wave 1, to 26 times in wave 3. (Nab et al, 2022). A decision to remove all community treatment options from such a high-risk group cannot be justified given the issues within the appraisal which we outline below.	1.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)

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57	Kidney Care UK (Comment 2)	A recommendation by NICE to remove all community treatment options for high-risk kidney patients would cause considerable anxiety and distress among this group of patients and their families, particularly immunosuppressed people who are less likely to be protected by the vaccine. Kidney Care UK hear from many patients that are struggling to take their first steps to come out of shielding and implementation of this guidance is likely to discourage people from ending their isolation. The mental health impact is considerable and it is hard to access support from overstretched mental health services. The heavy burden on shielders' mental health has been underscored by research from the University of Bath. Poor mental health increases the likelihood of poorer health outcomes among kidney patients (Tsai, Y., Chiu, Y., Hung, C., Hwang, S., Tsai, J., Wang, S., Lin, M., & Chen. H. (2012). Association of symptoms of depression with progression of CKD. American Journal of Kidney Diseases, 60(1), 54-61. https://doi.org/10.1053/j.ajkd.2012.02.325) The reports we received from kidney patients in response to this draft guidance highlight their concern: • *I have been a transplant patient for 26 years with my second one in 2010. I thought the idea of transplants was to give a person and their family a life. I have worked and lived a full life up until 3 years ago… However, if covid treatments are withdrawn then transplants are going to be pointless! What is the point in being alive but not being able to see family, socialise, go out, enjoy holidays etc.* • *I have basically shielded with my wife now for 3 years. I cannot continue to live like this and if the few treatments which are available in most other countries are withdrawn then please bring in voluntary euthanasia for the most*	2.Comment noted. The committee noted the 'value of treatment options available as insurance for people who are shielding' is a potential uncaptured benefit. The committee considered the advice in section 6.2.36 of NICE's manual on health technology evaluations. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained. Please see response to your comment #1 where sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)

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		vulnerable in society who just cannot continue to live in a country that will not protect or help them. • *Please add our voice in expressing concern over the NICE recommendations. The very idea that an immuno-suppressed/compromised group already at a higher risk of severe illness and death from Covid-19 should be forced into hospitalisation in order to get treatment when appropriate GP prescribed medication is denied to them is utterly abhorrent. Making an alternate drug available to those for whom Paxlovid is not an option is the only right, proper and morally defensible choice. Not only would this, by early intervention, have the potential to reduce the severity of any illness but it also reduces the burden on the NHS by not tying up a bed, always a good option where possible.*	
58	Kidney Care UK (Comment 3)	The draft guidance acknowledges that the studies were carried out in different stages of the pandemic with an ever-changing context. It is not clear how well the data accurately reflects the clinical and cost effectiveness of the drug treatments in the high-risk group (as defined by the McInnes report) which informs current commissioning policy for the community treatments. The appraisal has used different scenarios to reflect uncertainty. However, we do not think NICE have achieved fairness. The Panoramic data is used for the lower estimate of hospitalisation rates despite the Panoramic population being different to those at highest risk. People at highest risk would have had access to the treatments via CMDUs and would not therefore have entered Panoramic and indeed would be unlikely to choose to do so, given there would be a 50/50 chance of receiving a placebo. Hospitalisation rates within the McInnes group are likely to be higher found in the Panoramic study. And Shields et al. 2022 highlights that hospitalisation rates for people who are immunosuppressed are	3.Comment noted. Please see response to your comment #1 where sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) **Hospitalisation rates:** The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41%

Comment number	Organisation name	Stakeholder comment	NICE Response
		particularly high (18.4% for people with primary or secondary immunodeficiency). It is unfair to use lower estimates from Panoramic, particularly as hospitalisation rates are a key driver of cost effectiveness. The clinical efficacy data is unlikely to reflect the clinical efficacy for kidney patients in the McInnes group. For example, the COMET-ICE trial (included within the COVID-NMA review) included people with CKD 3 and 4 (inclusion criteria was at least one risk factor for Covid, which included CKD defined as eGFR less than 60). This group of people would not be eligible for treatment under current commissioning policy. We recognise that it may not have been possible to use only data that reflects clinical and cost effectiveness for high-risk kidney patients, but given that: • limitations are likely to lead to underestimating the cost effectiveness of the treatments (particularly due to hospitalisation rates) • the current recommendations remove all treatment options for kidney patients who remain at highest risk from Covid • the cost per QALY for sotrivomab is close to £30k when using high hospitalisation and mean efficacy We believe it is unreasonable for NICE not to have used its flexibility in accepting an ICER slightly higher than usual, for those in the highest risk group who are currently left with no treatment options in the community.	for the high-risk cohort from OpenSAFELY which captures the identical McInnes defined high-risk population and 4% for people contraindicated to nirmatrelvir plus ritonavir (using OpenSAFELY and DISCOVERNOW database outcomes for advance renal disease both sources capture the McInnes defined high-risk population). Please see section 3.22 in FDG. **Nirmatrelvir plus ritonavir clinical effectiveness:** For nirmatrelvir plus ritonavir, along with EPIC HR, OpenSAFELY evidence, the committee noted the subgroup analysis from the recent EPIC-SR trial that included people who were vaccinated with at least one risk factor for severe COVID-19. Committee still considered there to be substantial uncertainty with the EPIC-HR trial data because of generalisability concerns with the mean-efficacy estimate. Therefore, the committee considered the range between the mean- and lower-efficacy estimates for nirmatrelvir plus ritonavir from the trial to be more

Comment number	Organisation name	Stakeholder comment	NICE Response
			suited to the current endemic setting, despite the limitations with this approach. (Please see section 3.11, 3.12 and 3.19 of FDG)
59	Kidney Care UK (Comment 4)	We consider it unfair not to take into consideration the reduced protection provided to immunosuppressed people by the Covid vaccine (discussed in para 3.4). A single definition of high risk is used, because of model limitations. However, the much higher hospitalisation rates identified in the Shields study highlights the impact of immunosuppression on risk from Covid. The treatments can therefore provide an important lifeline for people who are immunosuppressed. The higher estimate of hospitalisation rate (2.79%) is very likely to be an underestimation for the immunosuppressed group. We believe it would be unreasonable not to do a subgroup analysis for the immunosuppressed group or adopt greater flexibility in ICER accepted for this vulnerable group.	Comments noted. Please see responses to your comment #1(sotrovimab recommendation) and #3 (hospitalisation rates)
60	Kidney Care UK (Comment 5)	The Committee acknowledged the contraindications of nirmatrelvir plus ritonavir and tocilizumab means the draft guidance could affect some people with protected characteristics disproportionately which would contribute to health inequality. We believe it would be appropriate to assess the cost and clinical effectiveness of the Covid treatments in the subgroup of people who	Comment noted. Please see response to your comment #1 where sotrovimab is recommended

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		will be left without a treatment option. If this could not be done, we believe it would be unreasonable for the Committee not to apply flexibility in the ICER it would accept in order to address such health inequalities, particularly given the level of uncertainty on the clinical and cost effectiveness of the drug treatments in this specific group.	as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) In the severe COVID-19 setting: In the severe COVID-19 and supplemental oxygen setting the committee was only able to recommend tocilizumab. For remdesivir the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG)

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61	Kidney Care UK (Comment 6)	Implementing the draft guidance would also risk increasing inequality based on race. As noted in the draft guidance, CKD is more common in BAME groups, who also experienced a substantially higher risk of COVID-19-related death than white people. Removing treatment options from this group would exacerbate this inequality and it is unfair not to be flexible in the level ICER accepted, particularly given the level of uncertainty on the clinical and cost effectiveness of the drug treatments in this specific group.	Comment noted. Please see response to your comment #1 where sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address this race inequality issue. (Please see section 3.32 for all the equality issues considered by committee)
62	Kidney Care UK (Comment 7)	We believe NICE was unreasonable to have accepted the WHO's recommendations against Sotrovimab when there is ongoing debate in the academic literature. In particular, NICE have not properly explained how they took into consideration the observational evidence from OpenSafely which found continued efficacy of Sotrovimab against the Omicron BA.2 subvariant. New OpenSafely data (currently in pre-print) supports the ongoing efficacy of Sotrovimab in patients on kidney replacement therapy (dialysis and kidney transplantation). Given that implementation of the draft guidance would remove all treatment options from this group we believe NICE have a duty to consider all available data and err on the side of supporting access to treatment for highest risk kidney patients while uncertainty continues.	7.Comment noted. **Sotrovimab clinical evidence:** The committee acknowledged that observational OpenSAFELY evidence supported the clinical efficacy seen in COMET-ICE but was mindful not to make conclusions about relative treatment effect solely based on non-randomised evidence.

Comment number	Organisation name	Stakeholder comment	NICE Response
			The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.12,3.16,3.18-3.19 of FDG) To explore cost effectiveness for people contraindicated to nirmatrelvir plus ritonavir the committee looked at a scenario in which the hospitalisation rate was set to 4.00%. For sotrovimab assuming the efficacy was between mean and low efficacy and with a lower administration cost (£410, equivalent to the cost used for providing an oral antiviral), the ICER was within the range normally considered an acceptable use of NHS resources. (Please see section 3.28 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
63	Kidney Care UK (Comment 8)	We note the 1st December alert to state that Sotrovimab should only be used by exception only and that Paxlovid is the first line treatment from now on. We very much regret this statement, which pre-empts a NICE decision. It creates a barrier to kidney patients receiving prompt treatment while approval is sought. It also means that specialists will have to spend valuable time justifying the use of a therapy which kidney doctors believe is efficacious to kidney patients. It is important that kidney patients can still access Sotrovimab, but if this is something that NICE might consider, we would urge them to recommend a process that avoided the additional hurdle of seeking approval for exceptional use.	Please see response to your comment #1 and #7
64	Kidney Research UK (Comment 1)	The draft guidance would leave many kidney patients with no effective treatment outside of hospital, despite being in a high-risk group for COVID-19. This does not present a sound and suitable case for guidance to the NHS. Kidney patients are less likely to have adequate responses to vaccinations and are more vulnerable to infection. To remove all potential treatments from this group of patients is grossly unfair. Paxlovid is not appropriate for this patient population, as it cannot be used alongside anti-rejection drugs or in patients with reduced kidney function. The committee agreed in their summary that the risk of hospitalisation and death, and other longer-term impacts of COVID-19, can result in severe physical and mental health burden. This is without a greater consideration of the impact of long COVID, which can have significant impacts on other comorbidities, such as cardiovascular health, and wider societal economic impacts. NICE should allow additional flexibility to QALY thresholds given the severity of risk for this patient population through the newly implemented severity modifier. This is particularly pertinent for consideration of sotrovimab. Sotrovimab has no significant interactions reported with other medicines. Extensive laboratory data,	1.Comment noted. Sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) **Sotrovimab clinical evidence:** The committee acknowledged that observational OpenSAFELY evidence supported the clinical efficacy seen in COMET-ICE but was mindful not to make conclusions about relative treatment effect solely based on non-randomised evidence. The committee said considerable uncertainty remained in the clinical efficacy estimates

Comment number	Organisation name	Stakeholder comment	NICE Response
		including the OPENSAFELY study, and recent analysis by the Francis Crick Institute, has demonstrated continued efficacy of sotrovimab against newer COVID-19 variants.	because of the in vitro evidence showing reduced neutralisation against the prevailing subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.12,3.16,3.18-3.19 of FDG) To explore cost effectiveness for people contraindicated to nirmatrelvir plus ritonavir the committee looked at a scenario in which the hospitalisation rate was set to 4.00%. For sotrovimab assuming the efficacy was between mean and low efficacy and with a lower administration cost (£410, equivalent to the cost used for providing an oral antiviral), the ICER was within the range normally considered an acceptable use of NHS resources. (Please see section 3.28 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
65	Kidney Research UK (Comment 2)	We do not believe that relevant evidence has been appropriately considered with regards to the risk of hospitalisation for high-risk kidney patients. Evidence used to analyse hospitalisation risk focused primarily on the PANORAMIC study. This study did not include higher risk patients, who would have been treated via CMDU, which makes it less relevant for consideration of these treatments for this group of patients. Other studies, such as OPENSAFELY and the DISCOVER NOW study of the cohort in the McInnes report have indicated higher hospitalisation risks than the data used in this analysis. The OPENSAFELY study found COVID-19-related hospital admissions for those with kidney transplants, dialysis, and chronic kidney disease: 76.08 (95% CI 71.03–81.49), 70.73 (95% CI 63.34–78.99), and 49.49 (95% CI 45.33–54.02), respectively. We believe that it would be fair and reasonable to conduct sub-group analyses of high-risk patient populations. A recent analysis of data from the Scottish Renal Registry looked at hospitalisation rates for patients on kidney replacement therapy (dialysis and transplant) from 17 Dec 2021 to 27 March 2022 (during the Omicron wave). Hospitalisation rates in triple-vaccinated individuals were 22%. Clearly this is significantly higher than the generic 2.79% used in the committee's calculations. Without this sub-analysis, we do not reasonably believe that the potential impact for high-risk renal patients, including either loss of transplantation or progression to dialysis, has been fully costed and considered.	2. Comment noted. Please see response to your comment #1 where sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) **Hospitalisation rates:** The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort from OpenSAFELY which captures the identical McInnes defined high-risk population and 4% for people contraindicated to nirmatrelvir plus ritonavir (using OpenSAFELY and DISCOVERNOW database outcomes for advance renal disease both sources capture the McInnes defined high-risk population). Please see section 3.22 in FDG.

Comment number	Organisation name	Stakeholder comment	NICE Response
66	Kidney Research UK (Comment 3)	We do not believe that this process has been approached in a way that will enable the timely consideration of evidence in relation to a rapidly evolving virus. We appreciate that COVID is an on-going challenge for the health-system, and this is no different for those responsible for reimbursement and regulatory decisions. However, new variants and mutations demand the need for greater flexibility and the acceptance of greater uncertainty. Most of the clinical evidence presented for this assessment is analysed from studies completed before the Omicron variant was dominant, for example. We believe that it would be reasonable therefore to allow greater acceptance of present data uncertainty. This is particularly important when considering a potential recommendation which will leave kidney patients unprotected without the only treatment currently available to them, sotrovimab. It is reasonable to accept that there will be continued uncertainty and rolling updates to evidence on the efficacy of these treatments against new variants and mutations, but it is unjust to remove access based on narrow cost-effectiveness assessments on already out-of-date data. As noted by the committee, 'observational evidence (OPENSAFELY) suggests continued efficacy of sotrovimab against the Omicron BA.2 subvariant' and the Francis Crick Institute's COVID surveillance unit suggests that 'neutralising monoclonal antibodies have only a reduced effect (against the BA.2 subvariant) that may be mitigated by an increased dose'. This evidence further emphasises the need to maintain this treatment options for high-risk patients.	3. Comment noted. NICE will take these suggestions on board as next steps. NICE has announced it is developing a new rapid update process to maintain these recommendations. Please also note 'This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as: • the widespread incidence of variants of COVID 19 to which the general

			population has no natural or vaccine immunity, or • local or national circumstances of high rates of hospitalisation for COVID-19.' Please also see response to your comment #1 (Sotrovimab clinical evidence) The committee could not comment on whether increasing dosages outside of marketing authorisations impacts clinical effectiveness of neutralising monoclonal antibodies. This is because the risk–benefit profiles of increased doses have not been assessed by the Medicines and Healthcare Regulatory products Agency (MHRA) and NICE must appraise treatments within their licensed doses. (Please see section 3.18 of FDG) **In vitro evidence** The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. The advisory group

Comment number	Organisation name	Stakeholder comment	NICE Response
			included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. (Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG)
67	Kidney Research UK (Comment 4)	The summary makes clear that the committee did not consider that family background can have a significant impact upon access to a treatment, while at the same time agreeing that the prevalence of kidney disease is higher in people from ethnic minority backgrounds. Merely noting that nirmatrelvir plus ritonavir was contraindicated in people with renal impairment, is not an acceptable consideration of health inequalities for a body which has reducing health inequalities as one of its core principles. As such, we do not believe that the recommendation is a sound and suitable basis for recommendation to the NHS.	4.Comment noted. Please see response to your comment #1 where sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address this race inequality issue. (Please see section 3.32 for all the equality issues considered by committee)

Comment number	Organisation name	Stakeholder comment	NICE Response
68	Long Covid Kids (Comment 1)	The definition of 'high risk' is flawed and does not include Long Covid as an outcome, it only considers those at the "highest risk of an adverse COVID-19 outcome, namely hospitalisation and death". Yet there are currently over 1.6million people in the UK whose symptoms adversely affect their day to day lives. Children and adults of all ages are disabled by Long COVID. With it occurring for a period of months and years for significant numbers. It should therefore be classified as disability. Ignoring a population with a disability could be seen as discrimination against those with Long COVID as the impact of an acute Covid-19 infection on this group is not considered or detailed in the published document. There is increasing evidence that there's an increased risk of Blood clots, Pulmonary emboli, strokes, heart attacks etc in the 12 months after a confirmed Covid-19 infection. This is not mentioned or considered in the guidance. Long COVID should be considered as both an outcome to prevent, and as a high-risk group because repeated infections can increase symptoms, and those with Long Covid are already proved beyond any doubt to have come to lasting and potentially lifelong as well as life changing harm. The WHO says, ""we need all countries in the WHO European Region to recognize that Long COVID is a serious problem with serious consequences and that it requires a serious response to stop the lives of those affected from getting any worse – and not just on a physical health level," said Dr Kluge. "We are hearing stories of so many individual tragedies, of people in financial crisis, facing relationship problems, losing their jobs, and falling into depression. Many health workers who risked their lives on the front lines of the pandemic now have this chronic and debilitating condition as a result of an infection acquired in the workplace. They, and millions of others, need our support. The consequences of long COVID are clearly severe and multifaceted." " In Children this is affecting their ability to attend school, socially interact with other children and to live and have a "normal" childhood, affecting their future life opportunities and experiences significantly.	**1.Comment noted.** **McInnes definition:** The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected. (Please see section 3.4 to 3.7 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
69	Long Covid Kids (Comment 2)	Children with Long COVID and those who have Long COVID and other conditions which also increase their risk should be considered. Using a definition of “high risk” which omits children under 12, is discriminating on their age, as is excluding PIMS as a cause of death and morbidity caused by SARS-CoV-2. From the draft guidance, which references the Department of Health and Social cares advisory group guidance on “high risk” definition. The “DHSC asked the independent advisory group to identify a set of patient conditions based on who is at the highest risk of an adverse COVID-19 outcome, particularly hospitalisation and death” according to the guidance this group did not include the main ways SARS-CoV-2 affects children, they defined COVID-19 as “Disease caused by SARS-CoV-2 infection, disambiguated from long COVID, paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) and multisystem inflammatory syndrome in children (MIS-C)”. To create a definition of high risk from Covid-19, but exclude Paediatric multisystem inflammatory syndrome, which is a cause of death in children and significant morbidity is excluding them from any potential assessment of benefit. This should be corrected, and “high risk” should consider other SARS-CoV-2 driven diseases, and all ages.	2.Comment noted. Based on stakeholder consultation comments, at ACM2 a paediatric clinical expert was present and the committee heard from the expert about the impact of COVID-19 on younger people (aged 18 years or less). The FDG has included the clinical expert and paediatric patient organisation perspectives where possible (section 3.1,3.5,3.32 and 3.33 of FDG). The initial failure to include paediatric organisations from the stakeholder list was an oversight. However, during the scoping phase we do ask respondents to let us know if we have missed any important organisations from the stakeholder list, and did not receive any comments relating to paediatric organisations. (section 3.1,3.5,3.32 and 3.33 of FDG).

Comment number	Organisation name	Stakeholder comment	NICE Response
70	Long Covid Kids (Comment 3)	The severity and impact of Long COVID needs to be appreciated or at least acknowledged in the guidance. The paragraph Impact of COVID-19 3.1 defines Long COVID as “These are health problems that can last several months ”. That is incorrect. The ONS data shows that at least “half (55%) reported experiencing long COVID symptoms for at least one year. Around a quarter (27%) reported experiencing symptoms for at least two years.” It should read instead Post COVID-19 symptoms (Long COVID) can last months, years and potentially life long, there significant numbers infected in the first wave in 2020 who are yet to recover. The condition fluctuates and is complex as new issues can present with repeated infection and over time. It can cause over 200 different symptoms. (the NHS website lists 20 main ones https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-effects-of-coronavirus-long-covid/) The evidence is that Long COVID lasts at least 2.5 years, and counting, by the time this is published some with have had it for 3 years.	3.Comment noted. Following stakeholder comments the description of long COVID has been partially updated. (Please see section 3.1 of FDG)
71	Long Covid Kids (Comment 4)	There is increasing evidence that viral infections and long term consequences, the long term consequences of a COVID-19 infection are currently unknown. Human papilloma virus (HPV) has been identified as the cause of most cervical cancers as an example. The risk of infections with viruses must not be downplayed. It is important that research happens into preventing both long and short term sequala. Long COVID should therefore be assessed as both an outcome to determine effectiveness and as a condition to be treated, especially as we do not know if there is viral persistence in Long COVID.	4. Comment noted. Where possible the AG has included the most recent and relevant data on long COVID. (Please see section 3.21,3.24 and 3.25 of FDG). The model captures the impact of long COVID in terms of cost and utility consequences. All key clinical trials were considered by committee in the second meeting. Please see

Comment number	Organisation name	Stakeholder comment	NICE Response
			section 3.10 of FDG. For the mild COVID-19 setting the key trials included these clinical endpoints: • relative risk of hospitalisation or death • relative risk of all-cause mortality at 28 days. The severe COVID-19 setting included these clinical endpoints: • hazard ratio of time to death • hazard ratio of time to discharge • relative risk of clinical improvement at 28 days. The committee agreed with inclusion of these endpoints and the committee considered the model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19. (Please see section 3.10 and 3.21 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
72	Long Covid Kids (Comment 5)	The Impact of COVID-19 3.1 paragraph states; Long Covid can ", potentially affect their ability to work or do their usual activities." This should be corrected to read "affects their ability to work and for over 75% of people their usual activities are adversely affected , the fluctuating nature of Long Covid, with relapses, along with the wide variety of body systems affected make it difficult to manage and predict and causes significant impact on people ability to continue to or return to work or carry out their activities of daily living. (from ONS data "Symptoms adversely affected the day-to-day activities of 1.6 million people, or 75% of those with self-reported long COVID."). In Children this is affecting their ability to attend school, socially interact with other children and to live and have a "normal" childhood, affecting their future life opportunities and experiences significantly.	5.Comment noted. Please see response to your comment #2 and #3
73	Long Covid Kids (Comment 6)	Re the statement "PUBLISHED Draft guidance consultation – Therapeutics for people with COVID-19 Page 23 of 37 Issue date: November 2022 © NICE [2022]. All rights reserved. Subject to Notice of rights. distributions to long COVID data from the Office of National Statistics (ONS) and estimated the mean duration of long COVID to be 108.6 weeks. The AG assumed that 100% of people in the hospital setting and 10% in the non-hospital setting would have long COVID." Our question is where did the average 108.6 weeks come from? To fully understand the modelling, need to know how many we are predicting to be lifelong/last years. The recent Long Covid Kids study https://www.futuremedicine.com/doi/10.2217/fmb-2021-0285#F1 showed a mean length of 249 days with significant numbers, having it for over 12 months. The data also showed at their initial COVID-19 infection, only 4.3% children were hospitalized; 62 were asymptomatic, 74% were managed at home and 9.4% went to hospital but were not admitted. 80.6% children had no pre-COVID mental health concern or diagnosis, which means they were left with significant life changing symptoms after their infection.	6.Comment noted. Following stakeholder comments the duration of long COVID has been updated in line with updated UK specific sources. See AG report for further details. the AG updated the model which estimates that 30% of people will still have symptoms at 2 years, 10% at 5 years and 3% at 10 years. (Please see section 3.21 of FDG)
74	Long Covid Kids (Comment 7)	The cost calculated for Long COVID are using incorrect modelling "Costs Long COVID costs 3.17 The AG assumed the annual per person management costs of long COVID to be comparable with	7.Comment noted. Based on stakeholder comments during DG consultation the AG

Comment number	Organisation name	Stakeholder comment	NICE Response
		chronic fatigue syndrome (£1,013).” Long COVID- cannot be equated to chronic fatigue syndrome. The NICE definition of long covid is Post-COVID-19 syndrome is“Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.” Therefore, when modelling it is clear by NICE’s own definition that Chronic fatigue syndrome is not an ideal option for modelling costs, and morbidity. Because; 1) as stated alternative underlying disease needs to be assessed and ruled out, 2) the fatigue element is only one of many symptoms, which as stated can affect any system in the body, from cardiovascular, to immune system, to respiratory to haematological and many more, only a small amount of the costs and impact on life and function are considered if fatigue is taken as the only symptom. Over 200 symptoms have been identified. 3)Each individual should be investigated thoroughly, initial diagnostic costs should be included. The long-term prognosis is unknown and with repeated infections causing worsening symptoms it is likely symptoms for many will worsening and require review/input. If paediatric multisystem inflammatory syndrome is not considered then the costs of the virus on children have not been included in the modelling.	updated the long COVID cost and duration. The best source of evidence for long COVID available at the time of evaluation was used. (Please see section 3.21, 3.24 and 3.25 of the FDG)
75	Long Covid SOS Registered Charity no 1199120 (Comment 1)	We believe that whilst it is unknown what causes the development of Long Covid, anyone with current or history of Long Covid should be treated as a high-risk population. Emerging evidence suggests that repeat infections with Sars-Cov-2 can lead to increased risk of hospitalisation as well as development of Long Covid.	1.Comment noted. **McInnes definition:** The committee considered that the McInnes report’s definition of high risk was based on the

Comment number	Organisation name	Stakeholder comment	NICE Response
		[redacted]	most robust evidence of people who have a high risk for progression to severe COVID-19. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected. (Please see section 3.4 to 3.7 of FDG) The model captures the impact of long COVID in terms of cost and utility consequences.
76	Long Covid SOS Registered Charity no 1199120 (Comment 2)	We agree with the recommendation of nirmatrelvir plus ritonavir (an oral dose antiviral combination) to be used in the community setting. As stated above, we request that this is available to those with (a history of) Long Covid on a subsequent Sars-Cov-2 infection.	2. Please see response to your comment #1.
77	Long Covid SOS Registered Charity no 1199120 (Comment 3)	With the emerging evidence of common infections potentially leading to future disease burden (Human Papilloma Virus (HPV), cervical cancer and Epstein Barr Virus (EBV), Multiple Sclerosis), we would encourage caution with rushing to an endemic setting with Covid-19 in the absence of long-term surveillance studies and investigation of factors within the acute phase of Covid that lead to the causation of Long Covid within the community. Scientifically we don't believe it is demonstrated that the interface between acute and Long Covid meets the current definitions used. What is it about the acute phase that leads a proportion to develop	3. Comment noted. This final draft guidance provides recommendations to the NHS on the future routine commissioning of therapeutics for

Comment number	Organisation name	Stakeholder comment	NICE Response
		Long Covid? At what stage can potential biomarkers be seen, can potential risk be identified in the acute period? Do protocols defining test dates adequately capture the causation of any relapses as it is not a steady state or worsening condition? It may be a new methodology of research and evidence gathering is required for the emerging evidence of the chronic burden of infectious disease	people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as: • the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or • local or national circumstances of high rates of hospitalisation for COVID-19.
78	Long Covid SOS Registered Charity no 1199120 (Comment 4)	We feel that the concept that severity of COVID is denoted by acute hospitalisation or need for oxygen therapy is narrow, and has skewed research, clinical practice and practice. In reality, severe impact of COVID has occurred since March 2020 in non-hospitalised individuals who develop Long Covid, and this continues to have a major impact on individuals, populations, health systems and the economy. Treatment trials are urgently required.	4. Where possible the AG has included the most recent and relevant data on long COVID. (Please see section 3.21,3.24 and 3.25 of FDG). The model captures the impact of long COVID in terms of cost and utility consequences. All key clinical trials were considered by committee in the second meeting. Please see section 3.10 of FDG. For the mild COVID-19

Comment number	Organisation name	Stakeholder comment	NICE Response
			setting the key trials included these clinical endpoints: • relative risk of hospitalisation or death • relative risk of all-cause mortality at 28 days. The severe COVID-19 setting included these clinical endpoints: • hazard ratio of time to death • hazard ratio of time to discharge • relative risk of clinical improvement at 28 days. The committee agreed with inclusion of these endpoints and the committee considered the model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19. (Please see section 3.10 and 3.21 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
79	Long Covid SOS Registered Charity no 1199120 (Comment 5)	Any modelling of Long Covid effects or potential impact on people with Long Covid must properly account for impact on morbidity, loss of function and quality of life, as well as the impact of time off work and lost earnings. These aspects are currently neglected in the economic models.	5. Comment noted. Where possible the AG has included the most recent and relevant data on long COVID. (Please see section 3.21,3.24 and 3.25 of FDG). The model captures the impact of long COVID in terms of cost and utility consequences.
80	Long Covid SOS Registered Charity no 1199120 (Comment 6)	The language used in section 3.1 'COVID-19 may cause long-term symptoms that continue or develop after acute infection called 'long COVID'. These are health problems that can last several months which severely impact a person's physical or mental health, or both, and potentially affect their ability to work or do their usual activities.' minimises the impact of Long Covid for the significant proportion that still have chronic health impacts from 2020 Covid infections.	6. Comment noted. Long COVID does not impact everyone who has COVID. The definition is in line with what is being modelled. See AG report for further details. the AG updated the model which estimates that 30% of people will still have symptoms at 2 years, 10% at 5 years and 3% at 10 years. (Please see section 3.21 of FDG)
81	Long Covid Support (Comment 1)	**The utility impact of Long Covid (-0.13) used by the AG in the economic model is too low, leading to an underestimation of the cost-effectiveness of the various drugs.** The AG has underestimated the severity of Long Covid (section 3.3.5.3). The evidence for this estimation is problematic as it is from the PHOSP study (Evans 2021). This study is of hospitalised patients that show a different phenotype and prognosis to those with Long Covid, the majority who are not hospitalised.	7.Comment noted. **Disutility value:** The AG considered the alternative utility sources provided by stakeholders during consultation. None of the sources were deemed suitable for

Comment number	Organisation name	Stakeholder comment	NICE Response
		The evidence that has not been taken into account, that demonstrates that Long Covid has a greater impact on health-related quality of life, includes: **1. Evidence from Long Covid** i) Dec 22 ONS survey - 370,000 (17%) said their ability to undertake their day-to-day activities had been limited a lot. The Oct 22 ONS Survey 70% percent of people with Long Covid in England (1.4 million people) say that their ability to do things in their day to day live is adversely affected and a fifth say this has been limited “a lot” (398,000 or 20% of people). The EQ-5D takes into account the mobility, self-care and usual activities – these are significantly affected in Long Covid so the disutility scale should be higher. ii) [redacted] iii) ‘Characterising Long Covid in an international cohort – 7 months of symptoms and their impact’ (Davis et al 2021) - PEM (post exertional malaise) affects 89% of people with Long Covid; fatigue, pain, orthostatic intolerance, sleep disturbance, cognitive impairment other common Long Covid symptoms lead to low functionality and quality of life. iv) Long Covid Support Reinfection Study We asked respondents to rate their health now compared with before Covid on a scale of 0-100. The average score was 48. “I still have symptoms which are having a MAJOR impact on my life” 42.62% -” I am SEVERELY DISABLED by Long Covid” 11.58% **2. Evidence from MECFS** NICE are using the data from a CFS study for the cost effectiveness so we feel that data from ME/CFS should be considered for the utility decrement calculation. This is also supported by the evidence that 50% of people with Long Covid meet ME//CFS Criteria; 46 %(Mancini	the disutility value needed for the economic model. Where possible the AG has included the most recent and relevant data on long COVID. (Please see section 3.21,3.24 and 3.25 of FDG). **Duration of long COVID:** Following stakeholder comments (See AG report for further details) the AG updated the model which estimates that 30% of people will still have symptoms at 2 years, 10% at 5 years and 3% at 10 years. The committee agreed with these changes.

Comment number	Organisation name	Stakeholder comment	NICE Response
		et al., 2021); 50% (Kedor et al., 2021); 50% (Haffke et al., 2022) and 58.7% (Twomey et al. 2022). i) 'The Health-Related Quality of Life for Patients with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)' (Hvidberg et al 2015) - ME/CFS has an unadjusted disutility scale 0.47 - OLS regression estimated disultility scale 0.29 for ME/CFS, compared to 20 other conditions – ME/CFS had the lowest quality of life compared to all 20 conditions. ii) 'What is known about severe and very severe chronic fatigue syndrome? A scoping review' (Strassheim 2017) - - 25% of ME patients are severe Long Covid severity is being underestimated because 50% of people with Long Covid meet ME/CFS criteria which means a significant amount are severely incapacitated and disabled. iii) 'The functional status and **well-being** of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers' (Nacul et al 2011) - ME/CFS is as disabling and has a greater impact on functional status and well-being than other chronic diseases. People with ME/CFS experience on average greater disability than those with	

		type 2 diabetes, congestive heart failure, back pain/sciatica, lung disease, osteoarthritis, multiple sclerosis and even most cancers (Buchwald *et al* 1996) (Hvidberg *et al* 2015) (Komaroff *et al* 1996) (Schweitzer *et al* 1995) (Winger *et al* 2015) – also confirm that the scale of impairment across a range of physical and mental activities can be just as great or greater than in many other chronic medical conditions. iv) ME Association review 2017 **-** ME/CFS has been compared to MS in a range of studies – people with ME/CFS are significantly more disabled in functional ability compared to MS. Yet MS disultility score 0.66 - 0.63 'A Scoring Algorithm for Deriving Utility Values from the Neuro-QoL for Patients with Multiple Sclerosis' (Matza et al 2020) If 50% of people with Long Covid have ME/**C**FS and ME/**C**FS is functionally worse than MS with a disultility score of 0.66- 0.63 surely the 0.13 figure is far too low? **3. Other Evidence** i) For context other disutility scales for other conditions are: moderate migraine- 0.186; Flu like symptoms - 0.2;, Mild rash - 0.13; Severe migraine - 0.493; Depression - 0.47; Mild anaemia - 0.12. Noting the vast array of symptoms (up to 200) that can affect people with Long Covid a rating of 0.13 the same as a mild rash is not sufficient. The EQ-5D measure includes 5 dimensions: mobility, self-care, usual activities, pain or discomfort, anxiety, or depression the NICE evidence does not sufficiently take into account these for Long Covid.	

Comment number	Organisation name	Stakeholder comment	NICE Response
82	Long Covid Support (Comment 2)	**The use in the model of £1013 for the annual cost of Long Covid is too low, leading to an underestimation of the cost-effectiveness of the various drugs. The reasons for this include:** • Underestimation of the Severity of Long Covid • Underestimation of consultant specialisms ie Cardiology, Respiratory, GI, ENT (BMJ Long Covid - an update in primary care) • Underestimation of tests needed • Underestimation of the type and continuous extent of care needed for Long Covid • Underestimation of Occupational Health needed • Underestimation of the NHS financial support needed for severe patients especially in Social Care Many Long Covid services are not fit for purpose and patients are dissatisfied and feel they are not receiving adequate care. Evidence not taken into account: **1. Evidence from Long Covid** i) Even with the investment made into clinics, patient satisfaction with services is poor. A survey undertaken by Healthwatch (n=858) 'What people told us about Long Covid (Healthwatch, 2022) ii) The initial plan, The NHSE Long Term Plan for Long Covid was an underestimate and a misjudgement on the nature on the need for the clinics. The plan in 2020 set out plans for £10m for services. This assumed that 68k people would need services. This was based on the false assumption that services would predominantly be needed by those who had been hospitalised. Therefore, the extent of the investment needed and the numbers needing long term care has been historically underestimated. iii) [redacted]	2. Comment noted. Based on stakeholder comments during DG consultation the AG updated the long COVID cost. The best source of evidence for long COVID available at the time of evaluation was used. (Please see section 3.21, 3.24 and 3.25 of the FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
		[redacted] iv) 'Experiences of living with long COVID and of accessing healthcare services: a qualitative systematic review' (Macpherson et al 2022) - A qualitative systematic review which included three surveys from the UK in addition to two international surveys examined patient experience of healthcare and found a lack of information, knowledge and understanding of Long Covid amongst health professionals which contributed to patients sometimes receiving patchy, inconsistent information and support which could generate anxiety and confusion at the point where patients were specifically seeking clarity. **2. Evidence from ME/CFS** The evidence from other ME/CFS sources is not considered, we feel that because evidence for the duration of Long Covid is derived from ME/CFS evidence it should be considered for other clinical and cost-effective calculations. The evidence from ME/CFS states that the nature and the costs for the NHS services for ME/CFS are underestimated especially when considering nonspecialised treatment which is significantly higher. So, there is the possibility the NHS is running a false economy on Long Covid and ME/CFS. i) ME Association Counting the Cost Report 2017 2016 -" Based on financial data obtained from 35 specialised CFS/ME services in the UK, service running costs average at just under £1,000 per referral, with 75% of those referred receiving a CFSME diagnosis. A number of services reported an average of 8–10 clinical contacts (quoted range of 1 – 24 contacts) during the course of a year. Eight services reported running costs at less than £100,000 per annum" "Health boards, CCGs and trusts that have not invested in CFS/ME expertise may be running false economies. Our economic analysis revealed NHS spending on people with CFS/ME to be in the region of	

Comment number	Organisation name	Stakeholder comment	NICE Response
		£542 million. Drawing on matched sample findings by Lin et al. (2011), this amounts to well over £300 million more than a 'non-fatigued' population. Just 3% of the £542 million applies to the running of joined up, specialised services. Clinicians with CFS/ME specialism are not of course exclusive to such services, but it is highly probable that the NHS is spending substantial amounts of money on the non-specialised treatment of CFS/ME."	
83	Long Covid Support (Comment 3)	**The estimated mean duration of Long COVID of 108.6 weeks is too low, leading to an underestimation of the cost-effectiveness of the various drugs.** The research that has not been taken into account to lengthen the prognosis of Long Covid is: **1. Evidence from Long Covid** i)ONS December 2022 27% duration of LC over 2 yrs. ii) Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort (Tran et al 2022)- At 12 months, the probability of symptom persistence (including patients in remission who relapsed) was 84.9%. iii) Outcomes among confirmed cases and a matched comparison group in the Long-COVID in Scotland study (Hastie et al 2022) Up to 18 month follow up, 6% don't recover, 42% partially recover. **2. Other SARS Post-Acute Viral Illness** i) **Is 'Long Covid' similar to 'Long SARS'?(** Patcai 2022) -A report of a 7 year follow up on 50 healthcare workers who had severe	3. Comment noted. Based on stakeholder comments during DG consultation the AG updated the long COVID duration. The best source of evidence for long COVID available at the time of evaluation was used. (Please see section 3.21, 3.24 and 3.25 of the FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
		SARS1 from the 2022/3 Toronto outbreak showed that **none of them** regained their former state of health. **3. Evidence from ME/CFS** **i**)' A systematic review describing the prognosis of chronic fatigue syndrome' (Cairns et al 2005) – a systematic review of 14 studies of ME/CFS found a median full recovery rate during the follow-up periods of 5%, and the median proportion of patients who improved during follow-up was 39.5%. ii) Report to the CMO ME/CFS Independent Working Group – "Prognosis is extremely variable. Although many patients have a fluctuating course with some setbacks, most will improve to some degree. However, health and functioning rarely return completely to the individual's previous healthy levels; most of those who feel recovered stabilise at a lower level of functioning than before the illness…." "Overall, there is wide variation in the duration of illness with some people recovering in less than two years while others remain ill after several decades. Those who have been affected for several years seem less likely to recover; full recovery after symptoms persist for more than five years is rare." **iii)** 'Factor analysis of symptoms among subjects with unexplained chronic fatigue: What can we learn about chronic fatigue syndrome?' (Nisenbaum et al) estimated a duration of 6yrs.	

Comment number	Organisation name	Stakeholder comment	NICE Response
84	Long Covid Support (Comment 4)	**We are concerned that the evidence that people with Long Covid are immunocompromised, have a maladaptive immune response and T cell exhaustion is not being taken into account.** This evidence that hasn't been taken into account demonstrating the need that people with Long Covid should be considered at risk and eligible for antivirals: i)'Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms' (Peluso et al 2021) ii)'Neuro-COVID long-haulers exhibit broad dysfunction in T cell memory generation and responses to vaccination' (Visvabharathy et al 2021) iii)'Long-term perturbation of the peripheral immune system months after SARS-CoV-2 infection' Ryan et al 2022 iv)'SARS-CoV-2-specific T cells associate with inflammation and reduced lung function in pulmonary post-acute sequalae of SARS-CoV-2' Palmer et al 2022 v)'Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection' Patterson et al 2022 vi)'Distinguishing features of Long COVID identified through immune profiling' Klein et al 2022 vii) 'Immune signatures underlying post-acute COVID-19 lung sequelae' Cheon et al 2021	4.Comment noted. **McInnes definition:** The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected. (Please see section 3.4 to 3.7 of FDG) The model captures the impact of long COVID in terms of cost and utility consequences.

Comment number	Organisation name	Stakeholder comment	NICE Response
			Sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address this race inequality issue. (Please see section 3.32 for all the equality issues considered by committee)
85	Long Covid Support (Comment 5)	**The clinical and cost effectiveness summaries fail to take adequate account of the considerable evidence of excess mortality and morbidity following acute Covid infection, that is not classified as Long Covid. This evidence includes cardiovascular events (eg heart attacks and strokes), endocrine disorders (diabetes) as well as neurological consequences.**	5. Comment noted. Where possible the AG has included the most recent and relevant data on long COVID. (Please see section 3.21,3.24 and 3.25 of FDG). The model captures the impact of long COVID in terms of cost and utility consequences. All key clinical trials were considered by committee in the second meeting. Please see section 3.10 of FDG. For the mild COVID-19

		Taking account of these will further improve the ICERs associated with the various drugs. **1 Evidence for Excess Mortality** i) Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality' (Lancet 2022) ii) "Coronavirus Pandemic (COVID-19)". (Mathieu et al 2020-22) iii) '. Excess deaths associated with covid-19 pandemic in 2020: age and sex disaggregated time series analysis in 29 high income countries' (Shkolnikov et al 2021) iv) WHO Global excess deaths associated with COVID-19, January 2020 - December 2021 **2. Evidence for Negative Cardiovascular Outcomes** i) 'Long-term cardiovascular outcomes of COVID-19.'(Al-Aly et al 2020) ii) https://www.science.org/doi/10.1126/science.abe2813#body-ref-R7 Covid can damage the heart iii) 'Risk of Cardiovascular Events after Covid-19: a double-cohort study' (Tereshchenko et al 2021) iv) 'Cardiovascular disease and mortality sequelae of COVID-19 in the UK Biobank' (Raisi-Estabragh et al 2022)	setting the key trials included these clinical endpoints: • relative risk of hospitalisation or death • relative risk of all-cause mortality at 28 days. The severe COVID-19 setting included these clinical endpoints: • hazard ratio of time to death • hazard ratio of time to discharge • relative risk of clinical improvement at 28 days. The committee agreed with inclusion of these endpoints and the committee considered the model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19. (Please see section 3.10 and 3.21 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
		3. Evidence for the increase of Diabetes risk: i) 'The Incidence of Diabetes Among 2,777,768 Veterans With and Without Recent SARS-CoV-2 Infection.' (Wander et al 2022) **4. Evidence for the increase of Neurological complications:** i) 'Long-term neurologic outcomes of COVID-19' (Al-Aly et al 2022)	
86	Long Covid Support (Comment 6)	**We are concerned that the evidence for deterioration in people with Long Covid on reinfection is not being taken into account:** 1 Long Covid Support Reinfection Survey 80% worsened with reinfection. Of those who had recovered or were in remission from Long Covid, reinfection caused a recurrence in 60%. 2. 'Acute and postacute sequelae associated with SARS-CoV-2 reinfection. (Al-Aly et al 2022) – "evidence shows that reinfection further increases risks of death, hospitalization and sequelae in multiple organ systems in the acute and post-acute phase".	6.Comment noted. Please see response to your comment #5. The committee discussed the uncaptured benefits in section 3.31 of the FDG. The committee considered that some of these benefits fall outside of the NICE reference case or there is limited evidence to support them. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained.

Comment number	Organisation name	Stakeholder comment	NICE Response
87	Long Covid Support (Comment 7)	**The AG report and the draft guidance fail to take account of the considerable psychological and social costs associated with fear of infection or of reinfection. A key benefit associated with treatments for acute covid is the reduction in fear and social isolation for immunocompromised people and people with Long Covid. Taking account of this benefit would greatly improve the cost-effectiveness of the various drugs.** The evidence of personal testimony on the potential harmful impact of reinfection is not being taken into account. Many are self-imposing restrictions, limitations and/or shielding, to reduce their risk of reinfection which would mean the risk of their Long Covid and/or pre-existing health condition worsening. This is having an unnecessary adverse effect on those with a pre-existing disability. In the work place this contradicts making reasonable adjustments under the Equality Act (2010) and health and safety law as people or their families are not able to safely access work without significant risk of reinfection and with no precautionary antiviral or MAB treatment. The availability of treatments for acute covid will reduce those fears and increase health related quality of life (HRQoL). This means that the model will greatly underestimate the HRQoL benefits of treatment.	7. Comment noted. Please see response to your comment #5 and #6 (uncaptured benefits). The model captures the impact of long COVID in terms of cost and utility (HRQoL) consequences. Sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)
88	Long Covid Support (Comment 8)	**We are concerned that the evidence for reducing the risk of Long Covid through the treatment of acute Covid with Paxlovid is not being taken into account:** 'Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19' (Al-Aly et al 2022) – which shows that people given Paxlovid in the first five days of their infection were 26% less likely to come down	8. Please see response to your comment #5. The committee agreed with inclusion of the clinical endpoints in the model and the committee considered the model appropriate to capture the

Comment number	Organisation name	Stakeholder comment	NICE Response
		with Long Covid. Paxlovid significantly reduced 10 of the 12 sequelae assessed, including cardiovascular disease, coagulation disorders, kidney problems, etc. as well as fatigue, musculoskeletal pain, and cognitive problems.	most important outcomes and appropriate for decision making given the available evidence base for COVID-19. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained. (Please see section 3.10 and 3.21 of FDG) At the time of evaluation the impact of treatment on long COVID was not being consistently collected across all the trials captured by the COVID-NMA systematic reviews. The individual impact of treatment on long COVID has been indirectly taken into consideration in the economic model.
89	Long Covid Support (Comment 9)	**We are concerned that not all the evidence has been taken into account to justify the removal of many of the acute Covid treatments:** i) Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe COVID-19 outcomes in non-hospitalised patients: an	9. Comment noted. i) OpenSAFELY data has been considered by committee (Please see section 3.11)

		observational cohort study using the OpenSAFELY platform (Zeng et al 2022) – shows that the Cilgavimab component still displays neutralising activity against BA 5 needs to be considered to reinstate Evushield Crick News. "Our data strongly suggest that we should be more aggressive in getting monoclonal antibodies into the clinic to treat COVID-19." David LV Bauer, Group Leader of the Crick's RNA Virus Replication Laboratory and member of the G2P-UK National Virology Consortium. ii) WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed -Sotrovimab also shows that it still retains active ability against current variants. iii) 'Early Remdesivir to prevent progression to severe Covid 19 in outpatients' (Gottlieb et al 2022)- shows remdesivir still works when given at early stage to reduce hospitalisation so should be reinstated. Especially as it can be used in paediatrics. iv) PANORAMIC – was the lower performing ability of Molnupiravir considered in the light that the recent patient cohort was recently vaccinated?	ii) **In vitro evidence** The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. The advisory group included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. (Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG) iii) PINETREE trial has been considered for remdesivir as part of the COVID-NMA. Please see section 3.19 of FDG (Discussion on remdesivir) iv) PANORAMIC trial has been considered by committee. (Please see committee discussion in section 3.22,3.4,3.6,3.7,3.13,3.28 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
90	Long Covid Support (Comment 10)	We are concerned that the provisional guidelines as a provisional basis for the NHS lack the flexibility and the adaptability needed for mutations and waves of Covid. The possibility of the dangers of resistance are not being taken into account.	10.Comment noted. NICE will take these suggestions on board as next steps. NICE has announced it is developing a new rapid update process to maintain these recommendations.
91	Long Covid Support (Comment 11)	We are concerned that provisional recommendations are not a suitable basis for guidance to the NHS because without mitigations in place and then the removal of another layer of defence through a wide arsenal of therapeutics it's seriously questionable if the most vulnerable are being considered as worthy to be given a chance of a normal life.	**11.** Sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) NICE expects its advisory bodies to use their scientific and clinical judgement in deciding whether the available evidence is sufficient to provide a basis for recommending or rejecting particular clinical or public health measures (Social Value Judgements; 'Principles for the development of NICE guidance', principle 1). Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 4 and 5).
92	Long Covid Support (Comment 12)	We are concerned that provisional recommendations are not a suitable basis for guidance to the NHS because the 5 treatments no longer recommended will have an unacceptable impact on patients at highest risk i.e. immunocompromised, elderly, those with co-	12. Comment noted. Please see response to your comment #11. Please also refer to the FDG

Comment number	Organisation name	Stakeholder comment	NICE Response
		morbidities.	for committee discussion on the recommended and non-recommended treatments.
93	Long Covid Support (Comment 13)	We are concerned that provisional recommendations are not a suitable basis for guidance to the NHS because by taking away a wide spectrum of medicine this takes away the safety net and leaves more people at risk from Covid – from death & disability from long covid & long-term cardiovascular complications.	13. Comment noted. Please see response to your comment #11 and #12
94	Long Covid Support (Comment 14)	We are concerned that the removal of Evushield has a significant negative psychological and physical effect on the immunocompromised. Leading to more people shielding, being left behind, being forced to work in unsafe conditions at risk to their morbidity and mortality.	14. Comment noted. Sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) Based on committee conclusions, tixagevimab plus cilgavimab is not recommended because it is unlikely to be effective at treating COVID-19 and it is not possible to reliably estimate their cost effectiveness. (Please see section 1 in FDG). Taking account of the trial evidence generalisability concerns the committee concluded the clinical effectiveness of tixagevimab plus cilgavimab is highly uncertain in terms of reducing hospitalisation or mortality rates. (Please see section 3.12 to 3.17 in FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
95	Long Covid Support (Comment 15)	We are concerned that provisional recommendations are not a suitable basis for guidance to the NHS because by not considering combinations of direct antivirals/monoclonals which improve activity and longevity against Covid.	15. Comment noted. Please see response to your comments #11 to #14 above.
96	LUPUS UK (Comment 1)	We are concerned that the lack of treatment options in the community setting within the preliminary recommendation will disproportionately impact people with medical conditions or existing treatment(s) that are contraindicated for nirmatrelvir plus ritonavir (Paxlovid). Without other treatment options in the community setting, these people will be unable to access therapeutics to reduce the risk of COVID-19 progressing to severe disease. Paxlovid is the only recommended treatment for the community setting but it has wide-ranging contraindications (**HERE**). In their systematic review, Dessie & Zewotir (**HERE**) found that diabetes, CVDs, COPD, hypertension, and acute kidney injury were the most significant risk for COVID-19 mortality. For most of these patient cohorts Paxlovid will be contraindicated due to their disease and/or medications. Without other treatments to prevent the progression of COVID-19 to severe disease in the community setting, many people will be exposed to increased risk; they will either need to recover from COVID-19 by themselves or become sufficiently severe as to require hospitalisation and access to therapies. *"The availability of sotrovimab made it possible to enjoy some ordinary close contact with my school and university-aged children after 18+ miserable, damaging months. When I got covid from my son last June, prompt treatment with sotrovimab was both reassuring and successful despite lupus-related lung and heart disease, immunosuppression, and weak antibody/vaccine protection. Paxlovid is totally contraindicated if you take colchicine- so I will be back to square one without the sotrovimab option. It feels like a hard choice between increased social disability/inequality, even in my own home,*	1.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) The committee noted the 'value of treatment options available as insurance for people who are shielding' is a potential uncaptured benefit. The committee considered the advice in section 6.2.36 of NICE's manual on health technology evaluations. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been

Comment number	Organisation name	Stakeholder comment	NICE Response
		or increased medical disability since I'm tempted to stop the colchicine if this goes ahead; so that Paxlovid would be an option (although with active lupus pericarditis that's not a good idea)." The withdrawal of viable COVID-19 treatments in the community setting will incentivise some people to maintain or return to shielding in order to minimise exposure to Cov-SARS-2 and reduce risk of contracting COVID-19. This can have a significant detrimental impact on an individual and their household. *"Shielding has had a negative impact on all aspects of my life - apart from the fact that I've succeeded so far in avoiding catching Covid"* Sloan et al. (Jan 2021) found shielding has a negative influence on mental health. The changes included: ○ **Increased isolation** - feeling isolated and depressed from reduced social interaction; especially severe among those fully following shielding guidance and living alone. • *"I was so, so lonely. I haven't been shielding for months now but I still haven't mentally recovered from the isolation. I felt like the people shielding were often an afterthought for the government and it made me feel like I wasn't valuable compared to others. I am so scared of needing to shield again in the future."* ○ **Fear** – many estimated their mortality risk from COVID-19 as very high and expressed great anxiety. Additional risk factors, such as being from a Black, Asian and minority ethnic group, also increase anxiety. • *"As time has gone on it is much more stressful. I am still being very cautious, no planes, holidays, restaurants, cinemas etc. only meeting others outside. I feel isolated in winter. I have missed funerals, weddings, and milestone birthdays. It has caused friction with some*	inadequately captured and may therefore misrepresent the health utility gained. (Please see section 3.31 in FDG)

		family members and friends who act like covid is over and no longer a risk (as per government spin). I now have issues with my employer who thinks as some 'clinically vulnerable' people have returned, we all should." ○ **Identity** - for many, the shielding classification provided medical and societal acknowledgement, and validation of the severity of their disease. However, the term 'clinically extremely vulnerable' was sometimes reported to have negative impacts on social and self-identity, with some perceiving their disease to have greater control over their lives than before the pandemic. • *"I was lucky enough to have a husband to support me in shielding, but I was unable to work as a nurse. This was very distressing, watching the circumstances that my colleagues and friends were working in. Because I was unable to work for about 2 years my registration has lapsed, and I am now not able to work as a nurse after almost 40 years. I am still grieving this loss."* The availability of viable COVID-19 treatments in the community setting provides important reassurance to people from our community. Knowing that treatments are available to help reduce the risk of severe illness from COVID-19 has enabled some people to live a better quality of life and be less isolated than that otherwise might have been. • *"I am grateful for the treatment I received. I had remained shielding and concerned for 28 months until I caught COVID-19 from my son, but knowing I can access treatment and recover if I get it again has made me a bit less concerned and I am shielding less (but still not socialising in crowded indoor settings/other's homes)."* • *"As clinically vulnerable and immunosuppressed, knowing that I will be given priority for treatments should I get COVID has allowed me to stop shielding and return to the office but I still do avoid busy places."* • *"The availability of treatments greatly puts my mind at ease. I feel less scared about contracting COVID knowing that*	

Comment number	Organisation name	Stakeholder comment	NICE Response
		treatments are now available. This means I'm happier going out and about in my daily life." • *"Knowing that the antiviral medication would be available to me, should I contract COVID again, means that I have become more confident to leave the house and start living my life, carefully again."* Due to the widespread use of immunosuppressants, corticosteroids and biologic treatments in the management of lupus, many people in our community do not have as much reassurance of protection from the vaccines. As such, the availability of viable post-exposure treatments is essential.	
97	LUPUS UK (Comment 2)	We are concerned that the preliminary recommendations are based on an incomplete review of evidence. Within the Committee's report, they assert that, *"…it is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (all neutralising monoclonal antibodies) are effective against the Omicron variant"*. We recommend that the committee includes these published studies within their review: • Wu et al. (**HERE**) advises an urgent reassessment of WHOs recommendation against using sotrovimab or casirivimab–imdevimab. Their study indicated that sotrovimab, imdebvimab and cilgavimab neutralised Omicron BA.2, BA.2.12.1, BA.4 and BA.5. • Zheng et al. (**HERE**) examined clinical data from patients on kidney replacement therapy in England between 16th December 2021 and 1st August 2022. During the 28 days of follow-up after COVID-19 treatment initiation, 1.1% in the sotrovimab group had COVID-19 related hospitalisations/deaths compared to 3.3% in the molnupiravir group. Those who received sotrovimab had substantially	2. Comment noted. Please see section 3.12 to 3.19 for an overview of the clinical evidence considered by committee. Data from OpenSAFELY (Section 3.11 of FDG) and recent in vitro evidence (section 3.14 of FDG) for currently circulating variants were considered by committee. **Sotrovimab's clinical effectiveness**: The committee considered the COMET-ICE trial evidence, alongside the in vitro and OpenSAFELY observational evidence for sotrovimab. The committee said considerable

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		lower risk of severe COVID-19 outcomes than those receiving molnupiravir. • Zheng et al. (**HERE**) examined the comparative effectiveness of sotrovimab and molnupiravir between 16th February and 1st May 2022 when the Omicron BA.2 was the predominant variant in England. They demonstrated a reduced risk of hospitalisation or death from all causes within 28 days in the sotrovimab group compared to the placebo group. They also found risk of hospitalisation or death within 28 days was lower in the molnupiravir group compared to the placebo group, although this was a weaker effect. This supports the persistent protective role of sotrovimab and, to a lesser degree, molnupiravir.	uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing BQ.1 and BQ.1.1 subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.19 in FDG) Clinical evidence suggests that: • sotrovimab is likely to be effective at treating mild COVID-19 compared with standard care but some of the evidence is uncertain • molnupiravir has limited effectiveness at treating mild COVID-19 compared with standard care because it does not reduce hospitalisation and mortality rates.

Comment number	Organisation name	Stakeholder comment	NICE Response
			Other evidence suggests that it is highly uncertain that casirivimab plus imdevimab and tixagevimab plus cilgavimab are effective against Omicron variants of COVID 19.
98	LUPUS UK (Comment 3)	We are concerned that the preliminary recommendations are over-reliant on in-vitro evidence of the neutralising effect of mAbs such as casirivimab plus imdevimab, sotrovimab, and tixagevimab plus cilgavimab. This approach makes significant assumptions regarding tissue penetration and mechanism of action of mAbs. Research has indicated that in-vitro studies analysing the neutralising effect of mAbs on different variants of SARS-Cov-2 do not accurately demonstrate the real-world, clinical efficacy of the treatment. In some cases a mAb developed for a historic variant could regain activity against the spike protein of a future variant. As such, the recommendations should not be reliant on in-vitro analyses. Uraki et al. (**HERE**) demonstrated that molnupiravir and sotrovimab can restrict viral replication in the lungs of hamsters infected with Omicron BA.2 in an in-vivo experiment, despite in-vitro experiments suggesting that Omicron BA.2 had resistance to sotrovimab. It is also important to assess the trial population of the evidence for COVID-19 treatments. Some trials only recruited non-vaccinated populations which may not capture some mechanisms of action that could provide additional protection for vaccinated populations. The threshold of evidence to enter a COVID-19 treatment into clinical practice is unrealistically high, especially due to the rapid changes in circulating variants and lower hospitalisation rate impacting recruitment of trial participants. On the other hand, the threshold to withhold or withdraw the same treatment is much lower when based on in-vitro neutralising evidence alone. This	3. Comment noted. Please see response to your comment #2. **In vitro evidence** The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. The advisory group included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. (Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG)

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		disproportionately affects people at higher risk of COVID-19 whose medications or comorbidities exclude COVID-19 therapeutics other than a neutralising mAb (i.e. Paxlovid).	**Molnupiravir clinical effectiveness:** The committee noted that PANORAMIC may have excluded some of the highest risk groups that could have powered the study to see benefits in hospitalisation or mortality. The mean-efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were uncertain because of the population differences. The committee noted the results of the UK based OpenSAFELY data, which included a McInnes-defined high-risk population for molnupiravir, support the limited hospitalisation and mortality benefits observed in PANORAMIC and from the overall NMA. The committee noted that any benefit for hospitalisation or mortality is likely to be minimal when the HRs are close to 1, and stronger clinical evidence is needed to justify a difference in relative clinical effects. (Please see section 3.12, 3.16 and 3.19 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
99	Royal College of Physicians (Comment 1)	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with the British Thoracic Society (BTS), The UK Kidney Association (UKKA), the Faculty of Pharmaceutical Medicine (FPM), the British Geriatric Society, and the British Society for Rheumatology (BSR) to inform our response. We have also created an RCP working group of clinical experts and would like to comment as follows.	1. We thank you for your comments on the DG.
100	Royal College of Physicians (Comment 2)	Our experts are concerned that this recommendation restricts access to treatment for COVID to a small group of non-hospitalised patients with a single antiviral agent. This group of patients are defined according to the criteria identified by an independent advisory group formed early in 2022 and targets those at increased risk of progression to severe COVID-19. This restriction will particularly impact vulnerable individuals, who have been identified by the JCVI for receipt of vaccination boosters by virtue of their disease susceptibility, and risk of more severe outcomes, but who have not been included by the independent advisory group criteria to be included for anti-viral treatments. In addition, this guidance stands in contrast to similar recommendations for the use of antiviral treatment for influenza, which provide access to treatment for the identical same group of patients that are recommended for free influenza vaccination (https://www.nice.org.uk/guidance/ta168).	2. Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)
101	Royal College of Physicians (Comment 3)	Our experts are concerned that although it is noted that vaccinated patients may be less likely to have severe pneumonitis and a reduced need for ventilation, the assumption that the finding of longer hospital stays for those with COVID-19 is due to infection control restrictions is simplistic. Clinical feedback suggests that older hospitalised COVID patients are more likely to have non-specific symptoms such as delirium which lengthens their hospitalisation. Wider NHS benefits from reducing viral load and shortening illness for patients should be considered in health economic analysis. Reducing hospital stay will	3. Comment noted. Following stakeholder comments the statement 'longer hospital stays for those with COVID-19 is due to infection control restrictions' has been removed. The committee also noted that clinical experts in both meetings explained that people hospitalised

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		be critical for managing recovery from the COVID pandemic in NHS hospitals.	with COVID-19 have very different symptoms at present (the time of this evaluation) compared with early stages of the pandemic. Also that the population is heterogeneous (Please see sections 3.2 and 3.3). The committee was not presented with additional evidence on time to discharge or clinical improvement and was uncertain about the treatment benefit in the endemic setting. The committee concluded it was reasonable to remove these treatment effects. (Please see section 3.23 in FDG) Please also see the 3.20 of FDG for the committee discussion on remdesivir's clinical evidence. The committee discussed the uncaptured benefits in section 3.31 of the FDG. The committee considered that some of these benefits fall outside of the NICE reference case or there is limited evidence to support them. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been

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			inadequately captured and may therefore misrepresent the health utility gained.
102	Royal College of Physicians (Comment 4)	Our experts want to highlight the group of patients who are very immunosuppressed e.g., those receiving antiCD20 treatment with rituximab and those with primary immune deficiencies who have no/reduced antibody production. These patients are less likely to mount a good response to COVID-19 vaccines and remain extremely vulnerable to serious consequences from COVID-19 infection. Those who are not eligible for nirmatrelvir/ritonavir (Paxlovid) require an effective alternative. We support the continuing use of sotrovimab for these patients.	4.Comment noted. Please see response to your comment #1.
103	Royal College of Physicians (Comment 5)	Our experts are concerned that there is no analysis of the % of immunocompromised patients who would be ineligible for treatment with Paxlovid because of this drug combination's contraindications including renal and liver disease. It was also noted that Paxolvid is associated with numerous drug interactions which may be difficult to stop or replace during any COVID-19 treatment period. Renal colleagues highlighted particularly the vulnerable post –transplant group and we would expect that this MTA would consider other options for such immunocompromised patients, ineligible for Paxlovid. Key to any decision about providing a single antiviral option is the alternative options if the drug is unsafe or not tolerated. Renal colleagues have specifically highlighted a lack of therapeutic options for patients with low GFR (< 30mls/min) with Paxlovid and Remdesivir requiring further urgent clarification of safety in these patients. Recently published new evidence for consideration: Preprint online in MedRxiv (www.medrxiv.org), posted on 04.12.2022. Comparative effectiveness of sotrovimab and molnupiravir for preventing severe COVID-19 outcomes in non-hospitalised patients	5. Comment noted. Please see response to your comment #1.

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		on kidney replacement therapy: observational cohort study using OpenSAFELY-UKRR linked platform and SRR database. The OpenSAFELY Collaborative; Zheng B, Campbell J, Carr EJ et al https://medrxiv.org/cgi/content/short/2022.12.02.22283049v1 This paper concludes that in the routine care of non-hospitalised patients with COVID-19 on kidney replacement therapy, those who received sotrovimab had a substantially lower risk of severe COVID-19 outcomes than those receiving molnupiravir raising concerns that molnupiravir may not be optimal treatment for this group. Whilst acknowledging recent concerns about the efficacy of sotrovimab against newer COVID-19 variants, our experts remain concerned that specific consideration needs to be given to patients with renal disease who currently remain exceptionally vulnerable with limited therapeutic options.	
104	Royal College of Physicians (Comment 6)	We are concerned that this guideline will provide anti-inflammatory therapy only, with tocilizumab or baricitinib, for hospitalised patients requiring oxygen, with no antiviral or neutralising mAb provision. • Thresholds for admission vary, and we are increasingly seeing patients with early disease but a high comorbidity burden (particularly the elderly) being admitted to hospital +/- oxygen requirements. One would hypothesise a role for antivirals in this patient group • There is likely a transition period, even in those with more severe disease, who have both ongoing viral replication and a growing inflammatory response. There is likely a role for	6. Comment noted. **In the severe COVID-19 and supplemental oxygen setting**: the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about

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		both antiviral and anti-inflammatory treatment in this patient group. • This approach makes no provision for immunocompromised patients / those with persistent viral PCR positivity who are admitted to hospital unwell, with failure to clear the virus – this is a growing proportion of our (extended) hospital admissions in whom antiviral treatment is essential.	whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG)
105	Royal College of Physicians (Comment 7)	No explanation is given for the continued recommendation of nirmatrelvir-ritonavir but the omission of molnupiravir for community use. It is recommended the panel consider whether molnupiravir might be offered as an alternative in this group and for other patients for whom use of ritonavir could cause serious adverse drug-drug interactions, as is recommended by the WHO.	7. Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG). The committee concluded that molnupiravir has limited effectiveness at treating mild COVID-19 compared with standard care because it does not reduce hospitalisation and mortality rates.

Comment number	Organisation name	Stakeholder comment	NICE Response
			Molnupiravir clinical evidence: The committee noted that PANORAMIC may have excluded some of the highest risk groups that could have powered the study to see benefits in hospitalisation or mortality. The mean-efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were uncertain because of the population differences. The committee noted the results of the UK based OpenSAFELY data, which included a McInnes-defined high-risk population for molnupiravir, support the limited hospitalisation and mortality benefits observed in PANORAMIC and from the overall NMA. The committee noted that any benefit for hospitalisation or mortality is likely to be minimal when the HRs are close to 1, and stronger clinical evidence is needed to justify a difference in relative clinical effects. (Please see section 3.12, 3.16 and 3.19 of FDG)

Comment number	Organisation name	Stakeholder comment	NICE Response
106	Royal College of Physicians (Comment 8)	Our experts are concerned about the modelling of long Covid. We have some questions about the assumptions made within the model re. long Covid: • The analysis seems to conflate complications of an ITU admission amongst hospitalised patients, with the experience of long-Covid. These are two distinct sequelae of Covid disease, with different types of care required, different duration of illness, and affecting different Covid patient groups. We have concerns that one set of utility values may not be appropriate across these conditions. • Similarly, the assumptions made on p23 re. the proportion of hospitalised/non-hospitalised patients experiencing long-covid seem inaccurate. Our experts question whether there is data to support this. Clinical experience suggests that there is a poor correlation between disease severity and the incidence / severity of long-Covid with a high burden of disease seen amongst non-hospitalised individuals who had relatively 'mild' initial disease.	8. Comment noted. Based on stakeholder comments during DG consultation the AG updated the long COVID cost and duration. The best source of evidence for long COVID available at the time of evaluation was used. (Please see section 3.21, 3.24 and 3.25 of the FDG)
107	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA) (Comment 1)	Extremely concerned that the recommendation for use of Paxlovid only in non-hospitalised, higher risk patients will exclude solid organ transplant recipients or patients on immunosuppression for renal autoimmune diseases due to complex, high clinical risk drug interactions with Paxlovid involving tacrolimus, ciclosporin or sirolimus. The latter drugs have a narrow therapeutic index whereby high levels can lead to nephrotoxicity which in extreme cases can lead to a patient requiring dialysis support due to acute kidney injury. Ritonavir (pharmacokinetic enhancer for nirmatrelvir in Paxlovid) is a potent liver enzyme inhibitor so co-administration will increase tacrolimus drug levels (up to ten-fold higher). But on stopping	1.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is

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		ritonavir there is then a time period of usually 7 days (but can be much longer in some) before liver enzyme activity normalises. Patients during this period are then at risk of under exposure of tacrolimus which can lead to graft organ rejection which if severe can lead to transplant graft loss. This draft guidance is inequitable - it excludes from pre hospital treatment, the group of patients consistently shown to be at the highest risk of developing severe COVID-19 infections (OPENSAFELY study). A key reason for this is the high proportion of transplant patients who are vaccine non responders or poor responders as evidenced by the OCTAVE study amongst others.	contraindicated or unsuitable. (Please see section 1 of FDG) The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address some of the inequality issues raised by stakeholders at consultation. (Please see section 3.32 for all the equality issues considered by committee)
108	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA) (Comment 2)	There is some real-world experience in Canada of using Paxlovid in solid organ transplant recipients (personal communication). However, managing this interaction is extremely labour intensive (estimated 4-6 hours extra senior MDT staff time per patient to follow up individual patients and ensure safe dosing) and there are high risk stakes if drug levels are not forthcoming, timely or patient misunderstands dosing advice especially as this advice will be given verbally over the phone. Patients would need to be advised to stop tacrolimus based immunosuppression for 7 days on starting Paxlovid and then tacrolimus would be reintroduced at reduced dose with blood levels every 2-4 days to guide tacrolimus dose up titration. Levels would need to be taken in hospital (but patients likely still covid positive) so logistics here would be extremely challenging. Tacrolimus levels need to be measured by the same laboratory to ensure consistency, as there is some intra-laboratory variation. The degree and duration of ritonavir liver enzyme inhibition is patient specific and variable. For some patients' enzyme inhibition can be extremely prolonged, with tacrolimus drug levels not normalising for some weeks and therefore extended intensive monitoring would be	2. Comment noted. Please see response to your comment #1 where sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)

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		required, which adds further logistical challenges and significant clinical risk. Co-administration of these medicines would carry a high risk of toxicity (nephrotoxicity which in extreme may require dialysis support for acute kidney injury or graft organ rejection). This interaction would similarly apply to ciclosporin or sirolimus based immunosuppression. Furthermore, transplant patients are on many different medications including blood pressure medication. For example, Paxlovid can elevate the drug levels of calcium channel blockers commonly used for hypertension, rendering patients hypotensive, which may lead to acute kidney injury, and necessitate further medication changes and further confusion for the patient.	
109	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA) (Comment 3)	Similarly, extremely concerned that there is no UK licensed dose or proven safe dose for use of Paxlovid in patients with severe renal impairment, eGFR <30ml/min (Chronic Kidney Disease: CKD stage 4-5) or patients on renal replacement therapy (haemodialysis/peritoneal dialysis), therefore excluding these patients, known to be at high risk of developing severe COVID-19 infections (OPENSAFELY study) from pre hospital treatment with Paxlovid. A trial protocol was accepted by the company to address this safe dosing question, but they chose to follow this up in Canada and to link it to trialling a paediatric, non-solid dose formulation. A published Canadian case series of 15 haemodialysis patients reported safe use of a reduced dose regimen – published 17/08/2022 CJASN Aug 2022, 17 (8): 1247–1250. Hiremath S, McGuinty M, Argyropoulos K et al. Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD Any use of Paxlovid in this cohort is outside of UK product license as an appropriate dose has not been determined. This exclusion of patients with advanced kidney disease therefore makes the draft	3. Comment noted. Please see response to your comment #1 where sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) NICE must appraise treatments within their licensed doses. This is because the risk–benefit profiles of increased doses have not been assessed by the Medicines and Healthcare Regulatory products Agency (MHRA).

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		guidance inequitable as this group are at higher risk of developing severe covid disease.	The economic model is modelling a high-risk cohort and not individual subgroups. The committee however looked at cost-effectiveness analysis for people with contraindications to nirmatrelvir plus ritonavir. A higher hospitalisation rate of 4% was considered by committee for people contraindicated to nirmatrelvir plus ritonavir (using OpenSAFELY and DISCOVERNOW database outcomes for advance renal disease both sources capture the McInnes defined high-risk population). Please see section 3.22 in FDG.
110	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA) (Comment 4)	There is a significant medicine safety risk of incorrect dosing/medication error when any dose other than 300mg nirmatrelvir /100mg ritonavir is used in the UK due to how the drug is packaged.	4. Comment noted. Please see response to your comment #1 where sotrovimab is recommended as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)

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111	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA) (Comment 5)	New evidence for consideration: A recently published paper in British Medical Journal on 16/11/2022 (*BMJ* 2022;379:e071932) – reported real world observational data on use of sotrovimab and molnupiravir in community according to NHSE national policy. This paper demonstrated that patients who received sotrovimab were at lower risk of severe outcomes of covid-19 than those treated with molnupiravir.	5.Comment noted. **Sotrovimab clinical evidence:** The committee acknowledged that observational OpenSAFELY evidence supported the clinical efficacy seen in COMET-ICE but was mindful not to make conclusions about relative treatment effect solely based on non-randomised evidence. The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and a scenario between mean and low efficacy for sotrovimab. (Please see section 3.12,3.16,3.18-3.19 of FDG) **Molnupiravir clinical effectiveness:**

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			The committee noted that PANORAMIC may have excluded some of the highest risk groups that could have powered the study to see benefits in hospitalisation or mortality. The mean-efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were uncertain because of the population differences. The committee noted the results of the UK based OpenSAFELY data, which included a McInnes-defined high-risk population for molnupiravir, support the limited hospitalisation and mortality benefits observed in PANORAMIC and from the overall NMA. The committee noted that any benefit for hospitalisation or mortality is likely to be minimal when the HRs are close to 1, and stronger clinical evidence is needed to justify a difference in relative clinical effects. (Please see section 3.12, 3.16 and 3.19 of FDG)
112	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney	Further evidence for consideration: published on line 6/10/2022 in The Lancet, the Crick group reported that sotrovimab neutralised	6.Comment noted.

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	Association (UKKA) (Comment 6)	Omicron variants BA.2, BA.4 and BA.5 in vitro to similar extents and suggesting that sotrovimab would remain effective against BA.5.	Please see response to your earlier comment #5 (Sotrovimab clinical evidence) **In vitro evidence** The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. The advisory group included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. (Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG)
113	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA)	Recently published new evidence for consideration - preprint online in MedRxiv (www.medrxiv.org), posted on 04.12.2022. Comparative effectiveness of sotrovimab and molnupiravir for preventing severe COVID-19 outcomes in non-hospitalised patients on kidney replacement therapy: observational cohort study using OpenSAFELY-UKRR linked platform and SRR database. The OpenSAFELY Collaborative; Zheng B, Campbell J, Carr EJ et al	7. Comment noted. Please see responses to your earlier comments #1, #5 and #6

Comment number	Organisation name	Stakeholder comment	NICE Response
	(Comment 7)	[redacted] In summary this paper concluded in the routine care of non-hospitalised patients with COVID-19 on kidney replacement therapy, those who received sotrovimab had substantially lower risk of severe COVID-19 outcomes than those receiving molnupiravir.	
114	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA) (Comment 8)	Considering all above points, we believe it is imperative to retain the use of sotrovimab in these patient groups, where Paxlovid cannot be used safely or effectively. This is especially so for patients on concomitant tacrolimus, ciclosporin or sirolimus as detailed in points 1 and 2.	8. Comment noted. Please see response to your earlier comments #1,
115	UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA) (Comment 9)	If Paxlovid is recommended in the final guidance, then allowing the off-license use of Paxlovid in patients with CKD stage 4-5 and on dialysis should be included with unlicensed dose recommendation specified and corresponding revision of the blueteq form. The medication safety risks identified in point 4 require further consideration. Reduced dosing has been trialled in a small number of patients with advanced CKD as discussed in point 3. Liverpool COVID-19 drug interactions group/website has produced a Paxlovid in Renal disease dosing guide, accessed 2.12.22 www.covid19-druginteractions.org/prescribing_resources/paxlovid-renal-dosing This same reduced dosing regimen is also referenced in the Renal Drug Database, accessed 2.12.22 https://renaldrugdatabase.com	9. Comment noted. Please see response to your earlier comment #3.

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116	UKCPA Pharmacy Infection Network (Comment 1)	The revised guideline provides no viable treatment option for patients in which Paxlovid is contra-indicated. This is a significant proportion of high-risk patients treated currently through the CMDUs and acute hospitals at present. Based on local performance, we may expect one in three patients to be excluded from future CMDU treatments based on Paxlovid contra-indications including organ dysfunction and or concurrent interacting medications. This will result in a) patients being deprived any treatment options due to their concurrent medications or renal / hepatic dysfunction or b) clinicians using this Paxlovid therapy outside of the product license for patients with known interacting drugs or renal / hepatic impairment. The latter is expected based on patient pressure for treatment and the lack of viable alternative options. If this does occur, we may see some significant drug related toxicities due to unexpected interactions and / or Paxlovid toxicities in renal/hepatic dysfunction. Thus the current treatment recommendations with lack of alternative will make for non-equitable delivery of treatment for patients and increase pressures on prescribers.	1.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address some of the inequality issues raised by stakeholders at consultation. (Please see section 3.32 for all the equality issues considered by committee)
117	UKCPA Pharmacy Infection Network (Comment 2)	The loss of remdesivir as a treatment option for CMDU patients appears inconsistent with other recommendations made within the guidelines. The primary study findings of EPIC-HR (Paxlovid) and PINETREE (Remdesivir) are similar in the study design and timing (pre-vaccination population predominantly) and their results and conclusions also overlap with similar relative risk reductions seen in the primary outcomes. Whilst accepting a lower mortality burden within the Remdesivir study (both control and treatment) compared to the EPIC-HR study, we cannot draw firm conclusions on mortality differences between the two therapies yet the recommendations	2. Comment noted. The committee explored both the clinical and cost-effectiveness outcomes for remdesivir in the mild and severe COVID-19 setting.

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		appear to differ based on this finding. Independent of costing of the therapies, there is little published data to demonstrate any differences in efficacy between these two therapies. We would welcome further clarification therefore on the contrasting recommendations made for these two therapies in the setting of CMDU.	Please see section 3.19 and 3.20 of FDG for the committee discussion on the treatment effects of remdesivir and nirmatrelvir plus ritonavir treatment. Please see section 3.28 and 3.30 for the committee discussion on the cost-effectiveness of remdesivir and nirmatrelvir plus ritonavir **Remdesivir recommendations:** **In the mild COVID-19 setting:** the committee concluded that remdesivir is not a cost-effective use of NHS resources. (Please see section 3.28 of FDG) NICE expects its advisory bodies to use their scientific and clinical judgement in deciding whether the available evidence is sufficient to provide a basis for recommending or rejecting particular clinical or public health measures (Social Value Judgements; 'Principles for the development of NICE guidance', principle 1). Deciding which treatments to recommend involves balancing the needs and wishes of

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			individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 4 and 5). **In the severe COVID-19 and supplemental oxygen setting**: the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG)

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118	UKCPA Pharmacy Infection Network (Comment 3)	The guidelines for management of acutely unwell patients with COVID-19 requiring O2 supplementation recommend against the use of remdesivir based on the assumption that antiviral therapy will be too late to benefit the patients. There is little published evidence to support this assumption and the ACTT-1 NIHR study showed some modest clinical benefits in this studied population. This assumption about lack of antiviral activity in this group of patients may not reflect patients with immunodeficiencies where viral clearance can be significantly impaired. Delaying or avoiding antivirals may have infection prevention and control implications (increased onward spread of disease) and result in delayed time to clearance of active infection. This assumption of lack of remdesivir in moderate – severe COVID-19 needs further scrutiny and transparency as well as some options for high-risk patient groups. We may suggest that routine use is recommended against but treatment may be considered in patients were viral clearance may be impaired due to host immune deficiencies. This would enable the most vulnerable patients to have some available antiviral options.	3. Comment noted. Following stakeholder consultation comments. The statement on antiviral activity mechanism of action has been removed. Please see response to your comment #2 (remdesivir recommendations) Please also note for the mild COVID-19 setting the committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)
119	UKCPA Pharmacy Infection Network (Comment 4)	The removal of all neutralising monoclonal antibody therapies (nMAB) therapies poses a major change in clinical practice. Will the OpenSafely database and scrutiny of the CMDU patient clinical outcomes for treated patients over the summer 2022 (predominantly exposed to the Omicron variants) be used to inform this recommendation? Comparison to first-line (Paxlovid) should be possible and provide a more objective analysis in the absence of timely prospective studies in Omicron infected patients.	4. Comment noted. Please also note for the mild COVID-19 setting the committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for

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			whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) Taking account of in vitro study differences, clinical expert conclusions and the in vitro expert advisory group framework (Please see sections 3.14 to 3.16) the committee concluded that casirivimab plus imdevimab and tixagevimab plus cilgavimab were unlikely to retain sufficient neutralisation activity against most variants circulating at the time of this evaluation. Also, this was the most useful estimate of effect against future variants. The committee concluded the clinical effectiveness of both casirivimab plus imdevimab and tixagevimab plus cilgavimab is highly uncertain in terms of reducing hospitalisation or mortality rates. The committee concluded the in vitro evidence for sotrovimab was ambiguous and the clinical effectiveness was uncertain. (Please see section 3.17 and 3.18)

Comment number	Organisation name	Stakeholder comment	NICE Response
120	UKCPA Pharmacy Infection Network (Comment 5)	Will the Panoramic study data be available for Paxlovid outcomes prior to the publication of these guidelines?	5.The results for nirmatrelvir plus ritonavir from PANORAMIC were not published at the time of ACM2. The committee noted that PANORAMIC was also recruiting a nirmatrelvir plus ritonavir treatment arm that could answer questions about its effectiveness for people with high risk factors for severe COVID-19 but are not defined in the McInnes high-risk group. (Please see section 3.19 of FDG)
121	UKCPA Pharmacy Infection Network (Comment 6)	The committee welcomes the recommendations for tocilizumab and baricitinib for deteriorating patients with COVID19 infection. The current advice and recommendations do not provide explicit data on when these therapies need to be introduced and the when combination therapy can be considered. This has resulted in some variation in implementation across the country with these agents used at same time as dexamethasone introduction for some practices or reserved for patients who are not responding to dexamethasone treatment after 1-3 days. The study design of RECOVERY had early steroid introduction before randomisation (on to the study). Some clarification on when to introduce these therapies relative to dexamethasone in patients not on high-flow O2 / intensive care would be useful. Furthermore, advice on when to combine the JAKi and IL-6i would be useful for standardised implementation nationally.	6.Comment noted. NICE have made recommendations for tocilizumab within its current marketing authorisation in Great Britain. Tocilizumab is indicated ‘for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation’.

Comment number	Organisation name	Stakeholder comment	NICE Response
122	NHS England (Comment 1)	We broadly agree that the relevant evidence has been taken into account. It is not clear if this [OpenSAFELY latest data] has yet been made available to NICE as part of the appraisal process	1. Comment noted. **Real world evidence:** The committee considered real world evidence in particular OpenSAFELY alongside the clinical trial evidence. The committee however cautioned against solely relying on non-randomised evidence when making conclusions on treatment effect. The views of the companies, clinical experts, patient/carer representatives, the public and NHS England surrounding this issue were considered by committee at the second meeting when formulating its recommendations (Please see section 3.11, 3.18, 3.19 and 3.22).
123	NHS England (Comment 2)	We note that the draft refers to the SOLIDARITY trial for remdesivir, and that not all results from this study were included in the AG's evidence synthesis, which the AG commented 'would likely have likely impacted the final conclusions for remdesivir'. We understand that company may be making further data available to NICE as part of its consultation response.	2. Comment noted. **Missing clinical trials:** The committee considered the missed clinical trials highlighted by the companies (SOLIDARITY and ACTT-1) when formulating its

Comment number	Organisation name	Stakeholder comment	NICE Response
			recommendations (Please see section 3.10, 3.20, 3.23) All key clinical trials were considered by committee in the second meeting.
124	NHS England (Comment 3)	The draft includes a comment on the use of remdesivir in people hospitalised due to COVID-19, that '…antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation'. This appears to be the view of the committee based on the therapy's potential mechanism of action; we feel that it is important to consider the evidence for effectiveness of remdesivir in people hospitalised with COVID-19 rather than base recommendations on a mechanistic hypothesis	3. Comments noted. The statement regarding antiviral mechanism of action has been removed from the FDG following stakeholder comments. Please also see an overview of the remdesivir recommendations. **Remdesivir recommendations:** In the mild COVID-19 setting the committee concluded that remdesivir is not a cost-effective use of NHS resources. (Please see section 3.28 of FDG) NICE expects its advisory bodies to use their scientific and clinical judgement in deciding whether the available evidence is sufficient to provide a basis for recommending or rejecting particular clinical or public health measures (Social Value Judgements; 'Principles for the

Comment number	Organisation name	Stakeholder comment	NICE Response
			development of NICE guidance', principle 1). Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 4 and 5). In the severe COVID-19 and supplemental oxygen setting the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably

Comment number	Organisation name	Stakeholder comment	NICE Response
			estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG).
125	NHS England (Comment 4)	Based on the two points above, we would encourage NICE to assure itself that all of the relevant SOLIDARITY results have been considered	4. Comment noted. Please see responses to your comments #2 and #3.

Comment number	Organisation name	Stakeholder comment	NICE Response
126	NHS England (Comment 5)	We would be grateful to receive confirmation that evidence of improvements in time to recovery have been considered alongside evidence of reductions in the risk of hospitalisation or death	5.Comment noted. For mild COVID-19 setting these clinical endpoints were considered in the AG model: • relative risk of hospitalisation or death • relative risk of all-cause mortality at 28 days. The severe COVID-19 setting included these clinical endpoints in the AG model: • hazard ratio of time to death • hazard ratio of time to discharge • relative risk of clinical improvement at 28 days. (Please see section 3.10 of FDG and 3.12 to 3.20 of FDG for the clinical evidence considerations for all technologies evaluated) The committee agreed with inclusion of these endpoints and the committee considered the

Comment number	Organisation name	Stakeholder comment	NICE Response
			model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19. (Please see section 3.10 and 3.21 of FDG)
127	NHS England (Comment 6)	We know there is significant clinical interest in the potential to use therapies in combination (and the World Health Organization (WHO) specifically recommends the consideration of combination use of dexamethasone, baricitinib and an IL-6 inhibitor in patients admitted due to COVID). Is NICE intending to comment on combination use of licensed COVID-19 therapies?	6. Comment noted. NICE cannot make recommendations outside of marketing authorisation in Great Britain.
128	NHS England (Comment 7)	Testing of patients will be an integral part of the patient treatment pathway and an additional deployment cost to the NHS specific to the treatment of eligible non-hospitalised cohorts. It is not clear if the additional cost of testing (which will involve the provision of multiple tests to be available to eligible patients should they experience COVID-type symptoms) has been included in the cost-effectiveness analysis	7.Comment noted. The decision problem evaluated in the MTA was following diagnosis of COVID-19. Testing costs were not included.
129	NHS England (Comment 8)	We note that an estimated average CMDU deployment cost for the administration of oral antivirals has been used (£410) in the analysis; please note that future delivery models are likely to change, for example, access through GPs and community pharmacies; so the associated cost of delivery/administration may change	8. Comment noted. The FDG includes a statement in section 3.26.
130	NHS England (Comment 9)	It is noted that the AG assumed the annual per person management costs of long COVID to be comparable with chronic fatigue syndrome; we agree with the need to consider evidence on long COVID costs as they become available	9. Comment noted. Comment noted. Based on stakeholder comments during DG consultation the AG updated the long COVID cost and duration. The best source of evidence for long

Comment number	Organisation name	Stakeholder comment	NICE Response
			COVID available at the time of evaluation was used. (Please see section 3.21, 3.24 and 3.25 of the FDG)
131	NHS England (Comment 10)	We note that the draft states 'Baricitinib is recommended as an option for treating COVID-19 in adults, subject to it receiving a marketing authorisation in Great Britain for this indication'. There is a concern that a clinically- and cost-effective therapy may be available, but not recommended if the marketing authorisation for GB is not granted in time for the final MTA recommendations. This risks continuity of provision of a clinically and cost-effective medicine and does not seem to be a suitable basis for guidance to the NHS	10. Comment noted. NICE cannot make recommendations outside of marketing authorisation in Great Britain.
132	NHS England (Comment 11)	The recommendation for nirmatrelvir plus ritonavir suggests use only in people who have an increased risk for progression to severe COVID-19 as defined by the Independent Advisory Group report. It would be helpful to understand how the cost-effectiveness analysis in the highest-risk cohort was considered (given different definitions of 'high-risk' group/s utilised in individual therapy trials)	**11.** Comment noted. The economic model is modelling a McInnes defined high-risk group cohort and not individual subgroups within the cohort. **Highest-risk and high-risk group:** At ACM2, the committee noted the draft guidance consultation comments highlighted the need for separate 'high risk' and 'highest risk' groups, or a separate high-risk group contraindicated to nirmatrelvir plus ritonavir. The committee saw examples on how the risk group could be split based on Patel et al. 2022. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. The committee did not see additional evidence to justify splitting the high-risk group. (Please see section 3.4 to 3.7 of FDG) For inclusion of additional subgroups the committee noted additional functionality, clinical or cost inputs and treatment-effectiveness

Comment number	Organisation name	Stakeholder comment	NICE Response
			assumptions would be required to make differential subgroup recommendations and this would not be practical or aligned with the decision problem. (Please see section 3.7 in FDG) The committee however explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)
133	NHS England (Comment 12)	It might be helpful if the final guidance could signal that the guidance will apply whilst COVID is an endemic disease and may need to be reviewed in other circumstances	12. Comment noted. The FDG now includes this statement in Section 1.
134	NHS England (Comment 13)	It might be helpful if the final guidance could consider whether the use of any remaining stocks of medicines procured by DHSC, which would effectively be available to the NHS at zero additional cost, and therefore only incur the costs associated with their distribution and administration, would represent a clinically and cost-effective use case	13. Comment noted. For the purposes of this guidance, NICE cannot take into account stock already purchased by the Department of Health and Social Care.

Comment number	Organisation name	Stakeholder comment	NICE Response
135	NHS England (Comment 14)	The draft recommendation of nirmatrelvir plus ritonavir being the only therapy recommended for people in the highest risk group who do not need supplemental oxygen for COVID-19, could mean there is no treatment available for individuals who: o Are pregnant (marketing authorisation: not recommended during pregnancy) o Are children and adolescents (safety and efficacy in paediatric patients younger than 18 years of age have not yet been established) o Have disabilities linked to the medicine's specific cautions and contraindications	14. Comment noted. The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address some of the inequality issues raised by stakeholders at consultation. (Please see section 3.32 for all the equality issues considered by committee)
136	NHS England (Comment 15)	Section 1: Refers to '*These treatments are recommended through the NHS interim clinical commissioning policy on antivirals or neutralising monoclonal antibodies for people with COVID-19 who are not in hospital*.' – To note treatments are also commissioned through NHS interim clinical commissioning policy 'Treatments for hospital-onset COVID-19'	Comment noted. The guidance has been updated following DG consultation (Please see section 3.8-3.9)
137	NHS England (Comment 16)	Section 3: Refers to '*The McInnes report was used by the NHS interim commissioning policy on antivirals or neutralising monoclonal antibodies for people with COVID-19 who are not in hospital to define high risk and is a narrower definition than that in PANORAMIC*.' – To note treatments are also commissioned through the NHS interim clinical commissioning policy 'Treatments for hospital-onset COVID-19'	Comment noted. The guidance has been updated following DG consultation (Please see section 3.8-3.9)
138	NHS England (Comment 17)	Section 3.3: Refers to '*These interim policies and McInnes report's high-risk definition would have influenced the risk level of people who enrolled in PANORAMIC*.' To note that the McInnes report refers to those at 'highest-risk'	Comment noted. Please see response to your comment #11

Comment number	Organisation name	Stakeholder comment	NICE Response
139	NHS England (Comment 18)	Section 3.7: Refers to '*Antivirals aim to reduce viral load and viral replication which may reduce risk of severe disease. They are administered orally*.' To note that remdesivir is administered intravenously rather than orally	Comment noted. The guidance has been updated following DG consultation (Please see section 3.8-3.9)

Abbreviations: ACM2, Second appraisal committee meeting; DG, Draft guidance; FDG, Final draft guidance

Comments received from patient experts

Comment number	Expert	Comment [sic]	Response
1	Sophie Wheldon (Comment 1)	Whilst I am pleased that antiviral access is not planned to be completely revoked, I still have some concerns about the reduction in the amount of treatments available in a community setting. During my two most recent infections with COVID-19 this year, I have required an infusion of sotrovimab in my local COVID Medicines Delivery Unit. Knowing that this treatment was an option felt like a lifeline, which positively contributed to me being able to live as I am. Having a range of different options for community treatments has been very reassuring to me in the past, so it does make me feel anxious as a patient to think that there will now only be one potential community treatment available – one which I have not got any experience with receiving.	1.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)
2	Sophie Wheldon (Comment 2)	I am concerned that there could be some access issues if only one community drug is planned to be available for the 500,000 clinically extremely vulnerable people in the UK. If there is a supply issue in the future, how will patients be able to access the treatment that they need? I worry that this could lead to an increase in patients becoming very unwell with COVID, leading to higher hospital admissions and ultimately, increased rates of death, which is terrifying. I would certainly feel extremely anxious if I was to contract COVID-19 again in these circumstances.	2.Comment noted. Please see response to your comment #1. Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. (Please see section 4)

Comment number	Expert	Comment [sic]	Response
3	Sophie Wheldon (Comment 3)	Being in hospital with COVID-19 when you are immunocompromised is extremely scary and can have a significant physical, psychological and financial impact on patients. If patients aren't able to access community treatments for whatever reason (e.g. not suitable due to contraindications; no community treatments available etc), then this may lead to more patients progressing to a more serious condition with COVID, leading them to require treatment in hospital which would end up costing more money. The hospital admission rates used by NICE in their analysis were based on the Omicron variant, which has typically been reported as a more mild variant of COVID-19. The numbers used in the analysis underestimate the potential impact of future, more severe variants which may result in higher hospital admissions and inevitably increase costs. Patients who end up in hospital will need more options.	3. Comments noted. **Lack of alternative hospital treatments:** The guidance has been updated to clarify that the mild COVID-19 setting also includes people with hospital onset COVID-19. COVID-19 (Please see section 3.8 and Table 1 Overview of recommendations). Please also see the response to comment #1 above. **Hospitalisation rates and endemic setting:** The remit of the guidance is to provide recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as: • the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or • local or national circumstances of high rates of hospitalisation for COVID-19. The committee considered the different hospitalisation rates available from literature. The views of the companies, clinical experts, patient/carer representatives and the public surrounding this issue were considered by committee when formulating its recommendations (Please see section 3.27).

Comment number	Expert	Comment [sic]	Response
			MTA next steps: Comment noted. NICE has announced it is developing a new rapid update process to maintain these recommendations.
4	Sophie Wheldon (Comment 4)	Further to my points about the reduction in community treatments, I was disappointed to see that the number of hospital treatments has also been reduced. This further increases my anxiety about potential access issues and delays in getting the appropriate treatment for those at high risk of severe infection, including myself. As mentioned above, being hospitalised with COVID-19 as someone who is immunocompromised is very scary. In August 2021, I required a double dose of Remdesivir to help me to fight the infection. I think that this emphasises the point that more options are needed, as the variable response in patients may mean that their treatment will need to be altered or changed in order to get them the best possible outcome. Reducing the number of treatment options will make this much more difficult.	4.Comment noted. **Remdesivir recommendations:** In the mild COVID-19 setting the committee concluded that remdesivir is not a cost-effective use of NHS resources. (Please see section 3.28 of FDG) NICE expects its advisory bodies to use their scientific and clinical judgement in deciding whether the available evidence is sufficient to provide a basis for recommending or rejecting particular clinical or public health measures (Social Value Judgements; 'Principles for the development of NICE guidance', principle 1). Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 4 and 5). In the severe COVID-19 and supplemental oxygen setting the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit of remdesivir compared with standard care (Please see section 3.20 of

Comment number	Expert	Comment [sic]	Response
			FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG)
5	Sophie Wheldon (Comment 5)	I feel that patient preference has been overlooked in this appraisal. I would personally prefer to go to the local COVID Medicines Delivery Unit for an infusion of medication rather than having to wait around for a delivery of tablets. I know of other people who much prefer to receive tablets, because they live far away from a delivery unit. There are many reasons why a patient may prefer one treatment delivery option over another, and I feel that reducing the community treatments down to just one option severely limits this. I understand that it is believed that Sotrovimab is not clinically effective, but I personally had a lot of faith in the treatment as it had made me better on both occasions that I needed it. I feel anxious that Paxlovid is very different to an infusion.	5.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)
6	Sophie Wheldon (Comment 6)	Before COVID-19 treatments were made available, the thought of contracting a COVID-19 infection was utterly petrifying, especially as I knew I would not mount a vaccine response as a result of my treatment. To go from that feeling, to being able to access treatments, was like being handed a lifeline. As a young leukaemia patient, I had already spent much of my early 20s in isolation. Just as I was getting back to 'living' again, COVID-19 struck and I was back in an isolated state. Knowing that I could access a range of	6.Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)

Comment number	Expert	Comment [sic]	Response
		treatments if I was to contract the virus was a huge relief and has allowed me to continue with my education and employment, allowing me to meet many amazing people and fellow patients, too. However, reality feels quite bleak when I think about the potential decision to axe most of the treatments that I know so well. I feel like this is a big setback and it induces a high level of anxiety for me and uncertainty about the future. I worry that Paxlovid will not be as effective for me, and that I could end up back in hospital if I'm not careful. My point is quite simple. I don't want to go back into isolation – I want to live my life, just as everyone else who is not clinically vulnerable is now able to. Being fully vaccinated against COVID-19 is simply not enough for people like me - we need more support, and more treatment options. Our lives depend on it.	The committee noted the 'value of treatment options available as insurance for people who are shielding' is a potential uncaptured benefit. The committee considered the advice in section 6.2.36 of NICE's manual on health technology evaluations. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained.
7	Miranda Scanlon (Comment 1)	I thank the Committee for their work in developing this Draft Guidance. I'm aware that it has been a difficult task in the face of the uncertainty about much of the evidence in a continually evolving situation.	1.Comment noted. No action required.
8	Miranda Scanlon (Comment 2)	Whilst I am commenting from the point of view of kidney patients, I acknowledge that there may be patients with other conditions for whom my comments may be relevant, especially those with other solid organ transplants.	2.Comment noted. No action required.
9	Miranda Scanlon (Comment 3)	I would like to register my deep concern as a kidney patient myself that the only drug recommended for use in the community setting is nirmatrelvir-ritonavir. This is not suitable for individuals with severe renal impairment and has a significant number of drug interactions including with tacrolimus, widely used for immunosuppression in kidney transplant recipients. Unlike other users of immunosuppressants, organ transplant recipients are not able to suspend use of their immunosuppression due to risk of organ rejection. This recommendation therefore	3. Comments noted. **Sotrovimab recommendation:** The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an

Comment number	Expert	Comment [sic]	Response
		leaves the majority of kidney patients in Chronic Kidney Disease (CKD) Stages 4 and 5, on dialysis or with a transplant with no suitable treatment if they contract Covid. I note that the Committee are aware of these facts (3.11, page 19) and considered them in coming to their recommendations. We know that these patients are some of the most vulnerable in terms of hospitalisation and mortality (see later comments) and that many do not respond adequately to vaccines (also noted by the Committee 3.4, p12). The guidance as drafted appears to leave a large population of kidney patients unprotected from Covid which is not only surprising but unfair and unreasonable. This is not a sound and suitable basis for guidance in this group of patients.	alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) **Hospitalisation rates:** The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort from OpenSAFELY which captures the identical McInnes defined high-risk population and 4% for people contraindicated to nirmatrelvir plus ritonavir (using OpenSAFELY and DISCOVERNOW database outcomes for advance renal disease both sources capture the McInnes defined high-risk population). Please see section 3.22 in FDG.
10	Miranda Scanlon (Comment 4)	The Committee did not consider that a sub-group analysis was necessary (3.3 page 11; 3.6 pages 13-14). However, given that the only recommended treatment nirmatrelvir-ritonavir is not suitable for many kidney patients, it could be considered as fair and reasonable for this group of patients to be considered separately to establish the effectiveness and cost-effectiveness of the treatments which are actually available to them. The current models of cost-effectiveness for the other treatments (sotrovimab, molnupirivir and remdesivir) include assumptions pooled across a wide range of high-risk individuals, many of whom are less at risk of serious consequences than kidney patients and for whom treatments may be less effective than in kidney patients. This creates bias in the	4. Comment noted. Please see responses to your comment #3 The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address some of the inequality issues raised by stakeholders at consultation. (Please see section 3.32 for all the equality issues considered by committee)

Comment number	Expert	Comment [sic]	Response
		models which has not been addressed and discriminates against kidney patients. In order to justify a sub-group analysis, I understand that it would need to be shown that kidney patients have differing risks to other high-risk groups considered in the economic model. The following comments address these points.	
11	Miranda Scanlon (Comment 5)	I am concerned that an appropriate hospitalisation rate has not been used to calculate the cost-effectiveness of available treatments for kidney patients which has disadvantaged this group when considering Covid treatments for them. This comment includes evidence about hospitalisation rates which has not already been taken into account by the Committee and highlights that rates of hospitalisation and mortality are higher in kidney patients than in other high-risk groups as mentioned in my previous comment. The Committee note that the hospitalisation rate is a key driver for the cost-effectiveness models and that for sotrovimab a £37,143 QALY gain was calculated with mean efficacy and a 2.79% hospitalisation rate (this rate derived from a report from GSK from a McInnes group in the DISCOVER-NOW dataset) making it more cost-effective than remdesivir. [For kidney patients, the more cost-effective treatment of nirmatrelvir-ritonavir has to be disregarded; other treatments are not shown in the Draft Guidance due to confidentiality]. Several studies have shown that kidney patients have a much higher rate of hospitalisation and mortality than other high-risk groups. For example, OpenSAFELY (https://doi.org/10.1186/s12916-022-02422-0 showed hospitalisation rates (in 1000 person-years) for Stage 5 CKD, dialysis and transplant of 49.49, 70.73 and 76.08 respectively, compared to 16.45 for those more generally immunocompromised and 4.77 nationally. Kidney patients had rates of hospitalisation 10-16 fold greater than the	5. Comment noted. Please see response to your comment #3 (hospitalisation rates)

Comment number	Expert	Comment [sic]	Response
		general population and 3-6 greater than other immunosuppressed individuals. Mortality rates (in 1000 person-years) for Stage 5 CKD, dialysis and transplant were 17.81, 25.71 and 18.9 respectively, compared to 5.08 for those more generally immunocompromised and 1.07 nationally. Although these were rates during the Delta period, these differential risks have remained through successive waves, as shown in a subsequent paper by OpenSAFELY (http://dx.doi.org/10.1101/2022.07.30.22278161). In fact relative hazard risks increased as groups more likely to experience impaired vaccine effectiveness, including kidney patients, did not see the same benefit in COVID-19 mortality reduction as other individuals. **Evidence not previously taken into account by the Committee**, published by Bell et al https://doi.org/10.1093/ckj/sfac173, using Scottish Renal Registry data collected during the Omicron wave (17 December 2021 until 27 March 2022) in triple-vaccinated patients on kidney replacement therapy showed hospitalisation rates of 22% and a mortality rate of 4%. This hospitalisation rate of 22% in kidney dialysis and transplant patients during the Omicron wave contrasts sharply with the rate of 2.79% used in the calculation of cost effectiveness, and well exceeds the bounds of the sensitivity analyses conducted. Using hospitalisation rates applicable to a more widely defined high risk group is unfair to kidney patients who are at greater relative and absolute risk. Using this evidence to include a rate of this magnitude in the calculation would increase the cost-effectiveness of treatments available to kidney patients.	
12	Miranda Scanlon (Comment 6)	I am concerned that the Draft Guidance says "it is highly uncertain whether sotrovimab is effective against the Omicron variant" and concluded that the WHO'S recommendations against the use of sotrovimab were reasonable. The Committee state that they considered	6.Comments noted **In vitro evidence:**

Comment number	Expert	Comment [sic]	Response
		evidence from the Francis Crick Institute but that they were unable to comment on the validity of in vitro data. Leading independent UK virologists are clear that the work resulting in the WHO's recommendation to withdraw Sotrovimab are flawed, resulting from a misinterpretation of the data and is an artefact of a poorly constructed neutralisation assay. The Committee may wish to consult with experts on this point. Data published on 5 December 2022 by OpenSAFELY https://doi.org/10.1101/2022.12.02.22283049 was not available to Committee at the time they published their Draft Guidance. This looks at the real world effectiveness of Sotrovimab compared to Molnupirivir in kidney replacement therapy patients testing positive for Covid and treated with those drugs during the Omicron wave from 16 December 2021 to 1 August 2022. It includes data from both England and Scotland, linked to the renal registries in those countries. Of 1852 kidney patients in England treated with sotrovimab, 1.1% were hospitalised (molnupirivir 515, 3.3%). In Scotland of 723 kidney patients treated with sotrovimab, 1.7% were hospitalised (molnupirivir 270, 2.6%) . Although this study does not include comparative data for those who did not receive treatment, it does include Scottish data from the same source as and for an overlapping time period with the Bell et al analysis https://doi.org/10.1093/ckj/sfac173 where an overall hospitalisation rate was calculated for a similar group of patients (dialysis and transplant, identified by the Scottish Renal Registry) during the early part of the Omicron wave. Whilst not directly comparable, this analysis had a hospitalisation rate of 22% in the first three months of the Omicron wave which suggests a high level of effectiveness for both treatments in this population of kidney replacement therapy patients.	The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the 'in vitro expert advisory group' commissioned by NICE. The advisory group included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. (Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG) **Sotrovimab clinical evidence:** The committee acknowledged that observational OpenSAFELY evidence supported the clinical efficacy seen in COMET-ICE but was mindful not to make conclusions about relative treatment effect solely based on non-randomised evidence. The committee said considerable uncertainty remained in the clinical efficacy estimates because of the in vitro evidence showing reduced neutralisation against the prevailing subvariants. The committee considered there was not enough evidence from COMET-ICE to consider a mean-efficacy scenario and instead preferred to consider the low-efficacy scenario and

Comment number	Expert	Comment [sic]	Response
		This strengthens the evidence that in the real world, sotrovimab is effective in significantly reducing hospitalisation rates for kidney patients and that a high efficacy, high hospitalisation rate model for cost effectiveness would be appropriate. Reworking this calculation of ICER for the sub-group of kidney patients (and excluding nirmatrelvir-ritonavir) would be fair and reasonable and produce a sounder basis to form recommendations.	a scenario between mean and low efficacy for sotrovimab. (Please see section 3.12,3.16,3.18-3.19 of FDG) **Hospitalisation rates:** Please also see response to comment #3
13	Miranda Scanlon (Comment 7)	I am concerned that additional costs of Covid in kidney patients have not been adequately recognised. It is known that infections in kidney patients can lead to loss of kidney function and Covid is no exception. For patients with CKD Stage 5, this could reduce their kidney function to a level where they need dialysis which costs in the region of £30-35,000 annually. For transplant patients there is the potential for a serious Covid infection to cause a loss of graft, again necessitating dialysis treatment. As well as the financial cost of dialysis treatment, the mental health impact of starting dialysis, particularly after losing a kidney is devastating, and perhaps particularly if that kidney has been donated by a loved one.	7.Comment noted. The economic model is modelling a McInnes defined high-risk group cohort and not individual subgroups within the cohort. Highest-risk and high-risk group: At ACM2, the committee noted the draft guidance consultation comments highlighted the need for separate 'high risk' and 'highest risk' groups, or a separate high-risk group contraindicated to nirmatrelvir plus ritonavir. The committee saw examples on how the risk group could be split based on Patel et al. 2022. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. The committee did not see additional evidence to justify splitting the high-risk group. (Please see section 3.4 to 3.7 of FDG)

Comment number	Expert	Comment [sic]	Response
			For inclusion of additional subgroups the committee noted additional functionality, clinical or cost inputs and treatment-effectiveness assumptions would be required to make differential subgroup recommendations and this would not be practical or aligned with the decision problem. (Please see section 3.7 in FDG) The committee however explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)
14	Miranda Scanlon (Comment 8)	I am concerned that the decision not to provide Covid treatments for the majority of kidney patients could affect some people with protected characteristics disproportionately. The 2019 Kidney Research UK report *Kidney Health Inequalities in the UK* stated that in the UK, people from Black and South Asian backgrounds are more likely to suffer from conditions that are risk factors for developing chronic kidney disease and are 3-5 times more likely to start dialysis than those from Caucasian backgrounds. In 2020, the *24th UK Renal Registry Report* shows that of those starting renal replacement therapy 13.9% were Asian (compared to around 7.5% in the general population) and 7.9% were Black (compared to around 3.3% in the population). We also know that Covid affects those from Black and Asian disproportionately. Removing a treatment which has been available up till now will impact on those populations unfairly.	8. Comment noted. The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address some of the inequality issues raised by stakeholders at consultation. (Please see section 3.32 for all the equality issues considered by committee)
15	Miranda Scanlon (Comment 9)	Whilst perhaps not directly in the remit of the MTA Committee, I am very concerned about the effect of these recommendations on the mental health of kidney patients. The Committee acknowledged that the risk of	**Uncaptured benefits and additional flexibility:** Comment noted. The committee understood that in future higher QALY gains or cost savings could be captured if the

Comment number	Expert	Comment [sic]	Response
		hospitalisation, death and other longer-term impacts of Covid can result in a severe physical and mental burden and I am grateful for that acknowledgement. However, since the publication of the Draft Guidance I have witnessed what is probably best described as a sense of bewilderment and disbelief that NICE could have issued guidance that so disregards kidney patients. This is a group of people who have been disproportionately affected by the Covid pandemic, who have had to radically alter their lives in ways that few others in the country have experienced. It is almost impossible to explain how it feels to literally not step outside your front door for three months, to fear that any human contact will kill you, to not experience any human touch for a year until vaccinations began. Some people with no antibodies to Covid vaccines are still living these lives. For those of us who have relaxed a little, we have known that the safety net of Covid treatments has been available to us. Many people are left unprotected and fearful. None of us know how effective our vaccinations have been, nor how sick we will get with Covid. Treatments have offered us a vital lifeline which has allowed some of us to leave our homes, to meet with friends and family, to begin to get some vague semblance of normality back in our lives. I hope that the Committee will give due regard to the circumstances and understand the loss of hope that the withdrawal of Covid treatments means for kidney patients.	model includes the additional uncaptured benefit of treatments. One of these benefits was the insurance value of COVID-19 treatments being available to people who are shielding. The committee considered that some of these benefits fall outside of the NICE reference case or there is limited evidence to support them. The views of clinical and experts and patient/carer representatives were considered by the committee when formulating its recommendations (Please see section 3.31). The committee noted the equalities issues outlined in section 3.32, and considered flexibility as part of the principles that guide the development of NICE guidance and standards. (Please see section 3.33)
16	Miranda Scanlon (Comment 10)	I have a further concern that NICE technology appraisals are usually conducted for long term use and are unlikely to have a helpful role in the circumstances of a rapidly changing virus, where drugs are expensive and it can be hard to evaluate their ongoing effectiveness. We have already seen that the majority of the effectiveness evidence comes from trials carried out in waves of variants which are no longer relevant. Waiting for evidence of the current variants in circulation will likely be out of date by the time it is produced. Quite possibly this	**10.MTA next steps:** Comment noted. NICE has announced it is developing a new rapid update process to maintain these recommendations.

Comment number	Expert	Comment [sic]	Response
		guidance will be out of date by the time it is published - new variants may arrive on the scene which are susceptible to treatments which are no longer recommended or which are resistance to ones which are. In my personal view, this appraisal seems premature in the current changing climate, and the prescribing landscape needs to be far more agile.	
17	Miranda Scanlon (Comment 11)	I am also concerned that the remit of the MTA was too large, covering treatment of Covid in both community settings and in hospital. My reflection is that, as a result, the Committee were put in a position where they did not have enough time to consider the complex evidence in detail. The two settings could have been appraised separately, with separate Committee meetings which would have given them the necessary time to consider the recommendations.	**11.MTA process:** Comment noted. The community and hospital setting outcomes are linked within the economic model framework. From a process point of view it was more appropriate to evaluate all technologies at the same time by the same committee members to avoid inconsistencies in recommendations.

Note: Comments were not received from clinical specialists
Abbreviations: ACM2, Second appraisal committee meeting; DG, Draft guidance; FDG, Final draft guidance

Summary of themes comments received from members of the public

Note: 60 separate submissions were received as part of the web comments. The individual comments have been themed in the table.

Core theme	Sub theme	Response

Limited treatment options for the highest risk group who are contraindicated to nirm/rit (1/2)
(Comment 1)
	• High unmet need for nirm/rit contraindicated population
	• Impact of removing treatment from people not considered
	  ○ People needing to stop their current medication and risking progression of underlying condition (for example Lupus)
	  ○ High burden on shielders and its impact on mental well being / quality of life / economic consequences not considered
	• Opportunity cost of NHS money already spent on people with an immunocompromised state / people with transplants not considered
	• Inequalities are potentially worsened
		1.Comments noted.
		Sotrovimab recommendation:
		The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG)
		The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address some of the inequality issues raised by stakeholders at consultation. (Please see section 3.32 for all the equality issues considered by committee)
		Uncaptured benefits:
		The committee noted the 'value of treatment options available as insurance for people who are shielding' is a potential uncaptured benefit. The committee considered the advice in section 6.2.36 of NICE's manual on health technology evaluations. The committee concluded that it

Core theme	Sub theme	Response
		had not been presented with strong evidence that the health benefits of the technologies have been inadequately **Hospitalisation rates:** The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort from OpenSAFELY which captures the identical McInnes defined high-risk population and 4% for people contraindicated to nirmatrelvir plus ritonavir (using OpenSAFELY and DISCOVERNOW database outcomes for advance renal disease both sources capture the McInnes defined high-risk population). Please see section 3.22 in FDG.
Limited treatment options for the highest risk group who are contraindicated to nirm/rit (2/2) (Comment 2)	• Despite declining clinical efficacy having some treatment options for vulnerable people is still useful • Need for alternative treatments prophylactic treatment already approved in 32 countries	2. Comment noted. Please see response to comment 1 (sotrovimab recommendations) Comment noted. The remit of the MTA was treating people with COVID-19 and not for prophylactic treatment. A separate STA (ID6136) is assessing prophylactic treatment for COVID-19. No action required.
Modelling assumptions (1/2) (Comment 3)	• Hospitalisation rates are low and not representative of high-risk population. The hospitalisation rate of 0.77% lacks face validity and is more representative of background rates. • Admin costs: CMDU costs were prior to paxlovid: Paxlovid, on average takes 45 mins to safely prescribe, unlike molnupiravir which was 5-10 mins	3.Comments noted. **Hospitalisation rates:** The committee considered a wide range of hospitalisation rates. The economic model is modelling a high-risk cohort and therefore committee's preferred assumptions was 2.41% for the high-risk cohort from OpenSAFELY which captures the identical McInnes defined high-risk population and 4% for people contraindicated to nirmatrelvir plus

Core theme	Sub theme	Response
	• CMDUs should be consulted to understand the hospital admission rates	ritonavir (using OpenSAFELY and DISCOVERNOW database outcomes for advance renal disease both sources capture the McInnes defined high-risk population). Please see section 3.22 in FDG. The draft guidance was open for consultation to the public including the CMDUs who were given the opportunity to indicate any key clinical trials or model cost inputs missed by the AG. **Administration costs:** The committee acknowledged the different administration costs provided during draft guidance consultation. The committee considered the differences in administration costs in relation to the net monetary benefit outcomes, noting the uncertainty about future delivery models. The views of the companies, clinical experts, patient/carer representatives and the public surrounding this issue were considered by committee when formulating its recommendations (Please see section 3.26).
Modelling assumptions (2/2) (Comment 4)	• CMDUs should be consulted to understand the clinical efficacy of treatments. • The value of Direct Acting Antivirals (DAAs) for severely immunocompromised patients has been significantly under-estimated.	4.Comment noted. The draft guidance was open for consultation to the public including the CMDUs who were given the opportunity to indicate any key clinical trials or model cost inputs missed by the AG. The committee considered the missed clinical trials highlighted by the companies (SOLIDARITY and ACTT-1). **Remdesivir recommendations:** In the severe COVID-19 and supplemental oxygen setting the committee concluded there was insufficient evidence to show meaningful difference in mortality benefit of remdesivir compared with standard care (Please see section 3.20 of FDG). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for

Core theme	Sub theme	Response
		patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir's cost effectiveness. (Please see section 3.30 of FDG)
Limitations of the indirect comparison (Comment 5)	• The whole analysis depends on very crude outcomes, with considerable limitations	5.Comment noted. The committee understood the limitations of the indirect comparison but also noted that best practice guidelines for using 'living systematic reviews' was used by the AG. The committee looked at the entire evidence base which included clinical trials, observational evidence and laboratory data. The views of the companies and clinical experts alongside the individual clinical evidence for each treatment was considered when formulating its recommendations (Please see section 3.10 to 3.20)
Long Covid assumptions (Comment 6)	In the hospital setting - mortality is no longer really relevant in the changing covid landscape and more important is to model the consequences of untreated covid on the patient's long term health which can be costly. The long covid cost is concerning and misleading. ME/CFS has been underfunded and may not reflect the true cost. Model does not consider the treatment benefits of Paxlovid and Remdesivir (PINETREE) in terms of long-covid	6. Comment noted. The committee understood that overall, hospitalisation and mortality from COVID-19 has reduced. The committee acknowledged that based on draft guidance consultation comments the AG had increased the cost and duration of long COVID. The best source of evidence for long COVID available at the time of evaluation was used. (Please see section 3.21, 3.24 and 3.25 of the FDG) The committee agreed with inclusion of the clinical endpoints in the model and the committee considered the model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately

Core theme	Sub theme	Response
		captured and may therefore misrepresent the health utility gained. (Please see section 3.10 and 3.21 of FDG) The model captures the impact of long COVID in terms of cost and utility (HRQoL) consequences. At the time of evaluation the impact of treatment on long COVID was not being consistently collected across all the trials captured by the COVID-NMA systematic reviews. The individual impact of treatment on long COVID has been indirectly taken into consideration in the economic model.
High-risk population definition to be revisited (Comment 7)	• Need for separate high-risk subgroups to account for population difference Age not considered as risk factor • Vaccine roll out used arbitrary age cut offs • It is not clear why that is acceptable but allowing Paxlovid in the community for those over 65 is not • Age should be considered similar to the wording for HIV patients in McIness report Many high risk patients are in their 20s-50s	7. Comments noted. a) Highest-risk and high-risk group: At ACM2, the committee noted the draft guidance consultation comments highlighted the need for separate 'high risk' and 'highest risk' groups, or a separate high-risk group contraindicated to nirmatrelvir plus ritonavir. The committee saw examples on how the risk group could be split based on Patel et al. 2022. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. The committee did not see additional evidence to justify splitting the high-risk group. McInnes definition: The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be

Core theme	Sub theme	Response
		reviewed if a difference in clinical or cost effectiveness is expected. (Please see section 3.4 to 3.7 of FDG) b) Age: Comment noted. The committee acknowledged that age is a risk factor for progression to severe COVID 19. The committee considered that the relationship between age and comorbidities can be important in explaining risk of severe disease. The committee also noted that additional evidence is needed to model age over 70 years as an independent subgroup for the mild COVID-19 setting. The committee concluded that the McInnes report's definition of high risk included the most robust evidence of people who have a high risk for progressing to severe COVID-19, and this did not include age as an independent risk factor. Additional evidence for subgroupd: For inclusion of additional subgroups the committee noted additional functionality, clinical or cost inputs and treatment-effectiveness assumptions would be required to make differential subgroup recommendations and this would not be practical or aligned with the decision problem. (Please see section 3.7 in FDG) The committee said the evidence for inclusion of age in the model should include: age-adjusted hospitalisation and mortality rates for the untreated population and relative treatment effects for the intervention. (Please see section 3.6 in FDG)

Core theme	Sub theme	Response
Role of antivirals in the hospital setting (Comment 8)	Clinical effectiveness of antivirals not adequately considered in hospital setting	8. Comment noted. Please see earlier responses to your comment #4
Treatment gaps in hospital setting (Comment 9)	If patients are high risk and would get Paxlovid in the community they should be allowed it in hospital. Instead of saying "Covid-19 positive....and oxygen requirement (in the case of dexamethasone and tocilizimab)", the terminology be changed to "clinico-radiological evidence of Covid-19 pneumonitis....and oxygen requirement". This is a different disease with a different incidence and too many patients that are swab Covid-19 positive are being misdiagnosed with Covid-19-pneumonitis and being given potentially harmful drugs. We are also missing opportunities to make alternative diagnoses as by proxy covid-19 +ve and hypoxic is still being regarded as most likely covid-19 pneumonitis. O2 requirement is no longer a specific surrogate for early identification of moderate to severe covid-19 pneumonitis in the covid positive patient	**9.Comments noted.** **Hospital onset COVID-19:** Comment noted. The guidance has been updated to clarify that the mild COVID-19 setting also includes people with hospital onset COVID-19. (Please see section 3.8 and Table 1 Overview of recommendations) **Treatment pathway for severe COVID-19:** Comment noted. The committee understood that the incidence of COVID-19 pneumonitis in hospital has lowered, as has the need for supplemental oxygen or mechanical ventilation. However NICE can only evaluate and recommend technologies within their current marketing authorisations in Great Britain. (Please see section 2)
Generalising neutralising monoclonal antibody in vitro evidence (Comment 10)	All nMABS clinical efficacy are ‘swept into the same basket’	10. Comment noted. In vitro evidence: The committee considered the in vitro evidence per technology versus the currently circulating Omicron variants. The committee noted the in vitro evidence assessment framework developed by the ‘in vitro expert advisory group’ commissioned by NICE. The advisory group included members who are consulting on the WHO living guideline and also part of the Francis Crick Institute and therefore a wide range of views have been considered by the committee when making its recommendations. (Please see detailed discussion on in vitro evidence in section 3.14 to 3.18 of FDG)

Core theme	Sub theme	Response
		The committee looked at the entire evidence base which included clinical trials, observational evidence and laboratory data. The views of the companies and clinical experts alongside the individual clinical evidence for each treatment was considered when formulating its recommendations (Please see section 3.10 to 3.20)
Inconsistencies (Comment 11)	Loss of income not considered in cost-effectiveness evaluation Different standard applied for vaccine rollout compared with antivirals (for example vaccine did not originally target omicron)	11. Comment noted. The committee considered that some of the uncaptured benefits fall outside of the NICE reference case or there is limited evidence to support them. (Please see section 3.31) The remit of the guidance is to provide recommendations to the NHS on the future routine commissioning of therapeutics for people with COVID-19 while COVID-19 is an endemic disease. The committee therefore assessed the clinical and cost-effectiveness evidence in line with NICE's reference case using the latest information available on the clinical efficacy of the technologies.
Evidence that should have been considered (Comment 12)	RWE not given enough weight given in the recommendations Sotrovimab retains clinical effectiveness according to RWE. If it is not used anymore it will be challenging to collect further data its future clinical effectiveness • Both the Francis Crick institute and the OPENSAFELY data provide strong theoretical and real world data that sotrovimab works. RECOVERY research group data not considered CMDUs should have been included as stakeholders and contacted for their input	**12.Comments noted.** **Observational evidence:** Regarding observational evidence (Please see section 3.11 of FDG). The committee acknowledged that the analysis of OpenSAFELY was done well and made efforts to account for confounding bias when possible. The analysis was done in a dynamic environment with changing treatment practices and linkages with various data sources which can increase risk of confounding bias. The committee was willing to accept the OpenSAFELY data on relative treatment effectiveness as supplementary evidence to the

Core theme	Sub theme	Response
		trial evidence and for modelling estimates for hospitalisation rates. The committee cautioned against solely relying on non-randomised evidence when making conclusions on treatment effect. **In vitro evidence:** Please see response to your comment #10 **Other evidence sources:** Comment noted. RECOVERY data was considered as part of the clinical trial evidence. The draft guidance was open for consultation to the public including the CMDUs who were given the opportunity to provide their input. No action required.
Additional evidence to consider (Comment 13)	Expert opinion should be sought where published empiric evidence is not available: • Efficacy scenarios • Hospitalisation rates	13.Comment noted. NICE sought expert opinion as part of their consultation process (during AG report and draft guidance consultation). Experts also attended both the committee meetings. The views of the experts were considered by committee when formulating its recommendations. (Please see section 3.1 to 3.7, 3.9 to 3.10, 3.12, 3.14 to 3.23, 3.25)
Areas where guidance needs to be clearer (Comment 14)	Guidance needs to be explicit about the indications for dexamethasone, baricitinib and tocilizimab treatment.	14. Comment noted. Following DG consultation, the FDG has been updated to reflect the treatment pathway in the severe COVID-19 setting (Please see section 3.9) NICE evaluates technologies within their marketing authorisation in Great Britain. (Please see section 2). Baricitinib is no longer being evaluated because the company has withdrawn its marketing authorisation application for the treatment for severe COVID-19.
Equalities issues (Comment 15)	In breach of human rights for disabled people. • Not all high risk groups being given equal treatment	15. Comment noted. **Sotrovimab recommendation:**

Core theme	Sub theme	Response
		The committee explored cost effectiveness of technologies for people with contraindications to nirmatrelvir plus ritonavir and was therefore able to recommend sotrovimab as an alternative treatment option for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. (Please see section 1 of FDG) The committee noted that the recommendation of sotrovimab for people contraindicated to nirmatrelvir plus ritonavir may partially address some of the inequality issues raised by stakeholders at consultation. (Please see section 3.32 for all the equality issues considered by committee)

Abbreviations: ACM2, Second appraisal committee meeting; DG, Draft guidance; FDG, Final draft guidance

NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

Draft Guidance comments form

Consultation on the Draft Guidance document – deadline for comments 5pm on Wednesday 7 December 2022. Please submit via NICE Docs.

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

The Appraisal Committee is interested in receiving comments on the following:

- has all of the relevant evidence been taken into account?
- are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- are the provisional recommendations sound and a suitable basis for guidance to the NHS?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

Draft Guidance comments form

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1	**AstraZeneca consider that Evusheld should be positioned in a subgroup of its licensed indication where the highest unmet need exists** In response to consultation, AstraZeneca are seeking a recommendation for a specific target population within Evusheld's marketing authorisation. The target population would be for: The treatment of COVID-19 within five days from symptom onset in adults who: 1. Do not require supplemental oxygen, and 2. Are at increased risk of progressing to severe COVID-19, as defined by the McInnes report(1), and 3. Are unsuitable for receiving nirmatrelvir plus ritonavir The rationale for seeking reimbursement within this target population is provided below. ***There remains a considerable unmet need in patients at high-risk of severe COVID-19 outcomes for whom nirmatrelvir plus ritonavir is unsuitable*** It is important that the Committee thoroughly consider the inequity that currently exists. COVID-19 disproportionately affects high-risk populations, with substantial morbidity, mortality and societal burden.(2,3) Despite a shift in the COVID-19 landscape, patients who are immunocompromised in particular remain at substantial risk of severe COVID-19 resulting in hospitalisation and death. Reports from different countries show that immunocompromised individuals make up ≥40% of patients who are hospitalised with COVID-19.(2,4,5) Immunocompromised individuals are more likely to be hospitalised or die because of COVID-19, even when fully vaccinated;(6,7) up to 28% of intensive care admissions(8) and 18% of COVID-19–related deaths(5,9) in the UK are in this population. For context, immunocompromised individuals comprise <1% of the UK population. This substantial unmet need is not addressed by the current draft recommendations in the ACD. This is because, despite NICE recommending nirmatrelvir plus ritonavir for routine commissioning(10), a considerable unmet need remains, which could be met by Evusheld. A large proportion of the high-risk patients defined in the McInnes report(1) are unsuitable for treatment with nirmatrelvir plus ritonavir treatment, as it is contraindicated against numerous treatments, including anticancer drugs, antibiotics, and other drugs relied upon by populations defined in the McInnes report(11,12). In addition, contraindication to nirmatrelvir plus ritonavir is well documented in the literature.(13–16) This was acknowledged by patients and clinicians during consultation and in the ACD:

Therapeutics for people with COVID-19 [ID4038]

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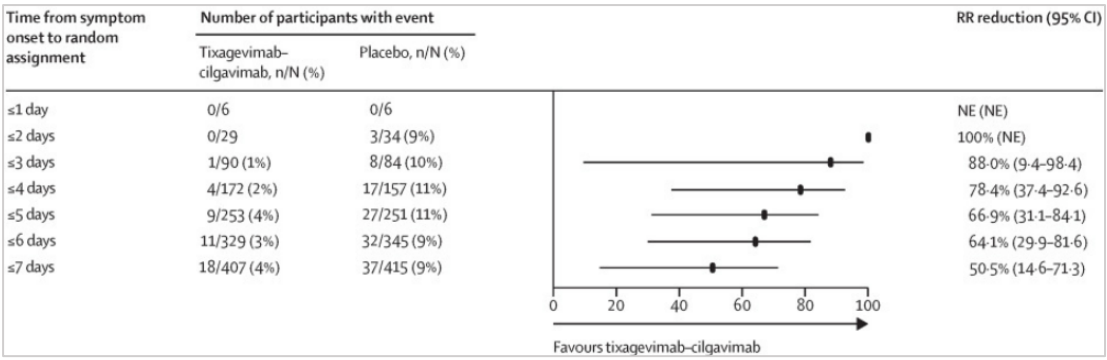
	"There are many contraindications for nirmatrelvir plus ritonavir, severe renal and hepatic impairment and interactions with many common treatments" (page 19, ACD). *Absence of monoclonal antibodies could give rise to an unmet need because some antivirals (for example nirmatrelvir / ritonavir, molnupiravir and remdesivir) are contraindicated. Some people who are at high-risk may not be offered antivirals because of these contraindications (page 70, committee slides).* Specifically, special warnings and precautions to use nirmatrelvir plus ritonavir refer to people with liver diseases and human immunodeficiency virus(11,12), two of the vulnerable subgroups defined in the McInnes report(1). Therefore, Evusheld would provide a valuable treatment option for patients who are unsuitable for nirmatrelvir plus ritonavir in a high-risk population. ***The potential for rebound infection with nirmatrelvir plus ritonavir suggests Evusheld would provide clinicians and patients with an important treatment option*** The Centers for Disease Control and Prevention issued a Health Alert Network Health Advisory to inform the public that patients treated with nirmatrelvir plus ritonavir have the potential for recurrence of COVID-19 (or COVID-19 rebound), which can occur 2 to 8 days after initial recovery.(17) Whilst information is still being collected, a recent retrospective cohort study comprising 13,644 adults in the US who contracted COVID-19 found that COVID-19 rebound was most common in people with underlying medical conditions who had been treated with nirmatrelvir plus ritonavir and molnupiravir.(18) Evusheld would provide an important option to people experiencing COVID-19 rebound, and for whom further treatment with nirmatrelvir plus ritonavir may not be suitable. ***Evusheld is more clinically effective and cost-effective when used within 5 days from symptom onset*** Though the license for Evusheld states that treatment should be given within 7 days of the onset of symptoms of COVID-19, the clinical effectiveness of Evusheld in protecting people from severe COVID-19 or death is greater when treatment is given within a shorter duration of time from symptom onset, as evidenced in Figure 1. In relation to the 5-day results, it is worth noting that the clinical effectiveness of Evusheld is well understood. TACKLE was powered to detect significant differences in response to exposure to Evusheld vs placebo at 5 days. The 5-day analysis indicated that 62% of all patients that received Evusheld within the 7-day indicated treatment period, did in fact receive Evusheld within 5 days. The importance of rapidly providing treatment to patients is also well known, as reflected in the interim clinical commissioning policy for antivirals or

	neutralising monoclonal antibodies for non-hospitalised patients with COVID-19(10), where treatment within 5 days is an eligibility criteria for all included antivirals and monoclonal antibodies Therefore, selecting 5 days as a treatment cut-off for Evusheld aligns with how clinicians would seek to use Evusheld in clinical practice, would align with the cut-off used for all other oral anti-virals and monoclonal antibodies currently used in clinical practice, and given its improved clinical effectiveness, would represent a more cost-effective use of treatment for the NHS. **Figure 1Figure 1: Severe COVID-19 or death from any cause up to day 29 after receiving Evusheld: modified full analysis set** (19)  **Abbreviations:** RR – Relative risk. **Source:** Montgomery et al. 2022 (10,19) To conclude, Evusheld should be positioned as a treatment option given within 5 days of treatment onset for patients who are unsuitable for nirmatrelvir plus ritonavir. This would provide an important treatment for a vulnerable and severely underserved patient population, who according to the NICE ACD will have no treatment options available to protect them.
2	**It is not appropriate to assume and apply a class effect to Evusheld based on other neutralising monoclonal antibodies. In addition, treatment options outside of antivirals are essential now and for the future.** The ACD notes the clinical effectiveness of Evusheld in three specific places: *"It is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (all neutralising monoclonal antibodies) are effective against the Omicron variant." (page 5)* *"The committee noted the WHO's and FDA's strong recommendations against using casirivimab plus imdevimab and sotrovimab for the Omicron variant. It also noted in vitro*

	evidence suggesting that tixagevimab plus cilgavimab lacks clinical effectiveness against the dominant circulating Omicron BA.5 subvariant (Focosi et al. 2022).” (page 18) *“The WHO’s recommendations against the use of casirivimab plus imdevimab and sotrovimab were reasonable. Based on similar evidence suggesting reduced neutralisation effect against new variants, the committee considered it reasonable to extend the likelihood of reduced efficacy to tixagevimab plus cilgavimab.” (page 19)* All three statements appear to evaluate the clinical effectiveness of Evusheld, alongside two other neutralizing antibodies (casirivimab plus imdevimab and sotrovimab). Specifically, the third statement suggests that recommendations made by the WHO for casirivimab plus imdevimab and sotrovimab can be reasonably extended to Evusheld to suggest reduced efficacy against the Omicron variant, based on a similar evidence base. However, the presumption that such an extension can be made is without merit and in complete contrast to decisions made by regulators and competent authorities across the globe, including the MHRA. It is also in contrast with the mechanistic properties of Evusheld, while its well documented neutralizing activity contradicts the conclusions made by Focosi et al 2022. In fact, these statements demonstrate the need for alternative treatments outside antivirals**.** **Regulatory bodies support the continued use of Evusheld against Omicron** Whilst AstraZeneca acknowledge that the WHO and FDA recommends against the use of casirivimab plus imdevimab and sotrovimab, these recommendations were not extended to Evusheld. Specifically: • The FDA recommends the continued use of Evusheld at 600mg (20), and in October 2022 during which time Omicron BA.4 and BA.5 are predominant, affirmed that whilst there is evidence to suggest that Evusheld does not neutralise some specific variants “*Evusheld still offers protection against many of the currently circulating variants and may offer protection against future variants.*”(21). • The MHRA and EMA recommend the use of Evusheld treatment at 600mg, and state that "*Due to the observed decrease in in-vitro neutralisation activity against the Omicron subvariants BA.1, BA.1.1, BA.4 and BA.5 the duration of protection of Evusheld for these subvariants is currently not known*.”(22,23) • The WHO does not provide a recommendation with respect to Evusheld, positive or negative.(24) Given that regulatory bodies, who have considered the entire evidence base for Evusheld in their decision, continue to recommend the use of Evusheld in an environment where Omicron variants are predominantly circulating, we are unclear why NICE could decide it

	is therefore reasonable to "extend" the likelihood of reduced efficacy with Evusheld based on a single study by Focussi et al 2022, which has significant methodological limitations (see Issue 4). ***The unique combination and synergistic effect of Evusheld has not been considered*** The committee refers to one study (Focosi et al. 2022(25)) which suggests that Evusheld has less than desirable clinical efficacy against currently predominating subvariants Omicron BA.4/5. However, this study has significant methodological limitations (see Issue 4) and does not seem to consider the combination effect that is attainable in using two neutralising monoclonal antibodies in combination. AstraZeneca originally developed Evusheld as a combination of two antibodies capable of acting synergistically *in-vitro* to 3-fold higher potency than individual monoclonal potencies; with a combined dose of 79 ng/mL [16 ng/mL of cilgavimab and 63 ng/mL of tixagevimab] having the same activity as 250 ng/mL of each individual antibody alone.(26) Each antibody is highly potent on its own, but in a situation where the activity of one is significantly reduced, the potential exists for the other antibody to provide the required cover to neutralize the virus. In the case of BA.2, BA.4, and BA.5, where one of the antibodies appears to have lost neutralizing activity, the other antibody remains able to potently neutralize the virus. This is because the activity of each antibody is not dependent on the other. This also enables prevention against potential viral evolution in the case where one antibody is less active against a certain variant. Therefore, the potential exists for the Evusheld antibody combination to be better than either of the two alone. (27) A recent publication has shown that where tixagevimab has reported reduced efficacy against BA.4/5 and cilgavimab has shown reduced efficacy against BA1.1, the combination of tixagecimab and cilgavimab has continued to demonstrate neutralization activity, and has consistently shown neutralizing activity against variants of concern. (27) Should both combination antibodies demonstrate neutralizing ability, then the potential for significant synergy exist. Support for the concept of the synergy between tixagevimab and cilgavimab can be drawn from the BA.1 and BA.2 variants. Against these variants the IC_{50} for each antibody is substantially higher than the combination of both, even though the overall activity was reduced compared to the original SARS-CoV-2 strain.(28)(29) Despite the reduction in *in-vitro* neutralizing activity, Evusheld has been shown to be effective in preventing symptomatic and severe COVID-19 throughout the BA.1 and BA.2 waves (See Comment 2). These traits along with the long-acting benefit are unique characteristics of Evusheld compared with other monoclonal antibodies. Furthermore, the synergistic effects observed

	in real-world evidence contradict the conclusions made by Focosi et al. 2022, and AstraZeneca would reaffirm that Evusheld's mechanism of action, regulatory recommendations, and clinical evidence base should be evaluated on its own merits. ***Evusheld as a monoclonal antibody would provide those who need it the most with an important additional layer of protection during an evolving landscape*** The wording used in the ACD implies that there is a single Omicron variant, which is not the case. Monoclonal antibodies with reduced effectiveness against one subvariant have "recovered" their effectiveness against other, later subvariants, demonstrating that loss of clinical effectiveness is not linear. For example, for tixagevimab plus cilgavimab, a recent review of live virus in vitro neutralisation studies demonstrated that although this combination had reduced effectiveness against the original Omicron B.1.1.529 variant (range of half maximal inhibitory concentration [IC50] values: 147–6400 ng/mL), BA.1 subvariant (167–773 ng/mL) and BA.1.1 subvariant (1297–8090 ng/mL) compared with wild-type viruses (2.1–35 ng/mL), effectiveness was regained against the BA.2 (8.2–113 ng/mL), BA.3 (19–95 ng/mL), and BA.4 and BA.5 (38–224 ng/mL) subvariants.(30) Further to this, the example of casirivimab plus imdevimab is also of interest whereby this medicine was not effective against Omicron BA.1 variant but was subsequently able to neutralize Omicron BA.2, BA.2.12.2, BA.4, and BA.5 variants.(31) Again supporting the assertion that there is no single omicron variant and effectiveness between the variants is not linear. In the UK, there are currently several variants in circulation,(32) and in a scenario where one antibody treatment loses effectiveness against one variant, it is therefore likely that other antibody treatments will remain effective.(33) The more monoclonal antibodies that are approved and available for patient use, the better placed the UK is to respond to changes in what is a very dynamic clinical situation. Furthermore, as recently noted in a response to the UK government from several oncologists in Lee et al.(33), antibody treatments are not a "*magic wand*", but could provide considerable protection for the most vulnerable in our community. Evusheld would serve as an important additional layer of protection for the severely exposed high-risk patients who cannot confer protection from nirmatrelvir plus ritonavir. Considering the plethora of circulating variants, the effectiveness of antiviral and antibody treatment is likely to evolve and vary over time, which is an issue for all treatments recommended by NICE as part of this MTA. Emphasis on decision making to consider the predominant variant at that moment in time may confer numerous re-evaluations when other variants become predominant in the future.

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	Evusheld will provide an important extra layer of protection in a dynamic and unpredictable disease landscape, and clinicians are unlikely to use any treatment that they deem ineffective based on what may or may not be circulating in the future.(33) The response in Lee et al.,(33) published in November 2022, also states: *"Ultimately, the benefit of prophylactic antibody treatments must be based on published and peer reviewed evidence from human studies and not crystal ball gazing on what might come next."* This approach has been well adopted by regulators internationally, which continue to recommend the use of Evusheld today, given the significant clinical evidence that exists in human studies for Evusheld during Omicron (see Issue 3) and the limitations in relying solely on non-human in-vitro data for decision making. To conclude, it has been demonstrated that the clinical effectiveness of Evusheld cannot be generalised across the neutralising monoclonal antibody class, and the availability of additional treatment options outside of antivirals are essential now and for the future.
3	**Clinical evidence in human studies show that Evusheld is clinically effective against the Omicron variant (including BA.4/5)** The ACD concludes that the clinical effectiveness of Evusheld against the Omicron variant is highly uncertain: *"There is some clinical evidence suggesting that baricitinib, molnupiravir, nirmatrelvir plus ritonavir, remdesivir and tocilizumab are effective at treating COVID-19. But, it is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (all neutralising monoclonal antibodies) are effective against the Omicron variant." (page 5)* The Company appreciates that for most monoclonal antibodies, clinical efficacy demonstrated in phase 3 treatment trials predates Omicron. For casirivimab plus imdevimab, efficacy was demonstrated in a phase 3 clinical trial (NCT04425629), with a 71.3% relative risk reduction (RRR) of COVID-19–related hospitalisation or all-cause death.(34) The COMET-ICE study of sotrovimab demonstrated 85% RRR of COVID-19 progression leading to hospitalisation or death.(35) The TACKLE clinical study of tixagevimab plus cilgavimab showed a 66.9% RRR in the endpoint of severe COVID-19 or all-cause death in patients where time from symptom onset to randomization was ≤5 days.(19) However, there is a substantial body of clinical evidence in real-world settings which demonstrates that Evusheld is consistently, highly clinically effective against the Omicron

	variant. See Appendix A for full details of these studies, which appears to have been overlooked by NICE and the EAG in their evaluations of clinical effectiveness. Furthermore, of all human controlled studies that have been conducted for Evusheld across alpha, beta, delta, and Omicron variants and subvariants, the results have been consistent and conclusive: Evusheld has been shown to significantly reduce COVID-19 infections, hospitalisations and death. No human controlled studies have reported otherwise. On the other hand, molnupiravir, despite being deemed by NICE to have "some clinical efficacy for treating COVID-19", has been shown to have no effect on reducing the risk of hospitalisations or deaths among higher risk, vaccinated adults with COVID-19, during a time period with predominantly Omicron strains circulating.(36) In addition, a study which compared molnupiravir and sotrovimab during a period when Omicron was circulating found sotrovimab to be more efficacious than molnupravir.(36) We urge NICE to consider all available clinical evidence for Evusheld during Omicron waves, as summarised below, in their decision making. ***Summary of evidence demonstrating Evusheld effectiveness against severe and fatal COVID-19 outcomes during Omicron predominant waves*** A recently published retrospective study in France evaluated early treatment with tixagevimab plus cilgavimab 300 mg/300 mg following COVID-19 infection in adult kidney transplant recipients at high risk of COVID-19 during Omicron and demonstrated a reduction in hospitalisations due to COVID-19 (3.8% vs 34%, P=0.006) and oxygen need (3.8% vs 23%, P=0.04) compared to no treatment. Similar but non-significant trends were observed for intensive care unit (ICU) admissions (3.8% vs 14.3%, P=0.17) and mortality (0 vs 3, P=0.13).(37) Furthermore, there are five further real-world evidence studies which consistently demonstrate the continued efficacy of Evusheld as prophylaxis during Omicron. A recent systematic literature review(38) provided an updated summary of the real-world clinical evidence of Evusheld conducted during Omicron predominant waves. The review concluded that Evusheld is effective in reducing hospitalisation, ITU admission and mortality, during the Omicron wave. The review focused on Evusheld as prophylaxis, but since the mechanism of action is identical, results can be generalised to the treatment setting. Furthermore, the outcomes of hospitalisation, ITU admission and mortality are highly relevant to the treatment setting. Out of the 17 identified studies, six reported controlled effectiveness comparisons, of which the five outlined below took place during Omicron waves.

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	Young-Xu et al. 2022(39) • Retrospective observational study comparing Evusheld 600 mg and 300 mg (n=1,733) with a control group (n=251,756). • Population considered US veterans (aged ≥18 years), immunocompromised or otherwise at high risk for COVID-19. • Dominating variants were BA.1, BA.2, and BA.2.12.1. • COVID-19 vaccination was received in 95% of patients. • Propensity-score matched study undertaken, which matched Evusheld (n=1,733) to the control (n=6,354 post matching). ***Al Jurdi et al. 2022***(40) • Retrospective cohort study comparing Evusheld 300 mg, 600 mg, and 900 mg (n=222) in vaccinated solid organ transplant recipients to age-matched, vaccinated solid organ transplant recipients (n=222). • Population considered US kidney, liver, and lung transplant recipients. • Dominating strains were BA.1.1.529, BA.2 and BA.2.12.1. • The patient population was focused on vaccinated patients. ***Kertes et al. 2022***(41) • Large retrospective study in members of the of the Maccabi HealthCare Services in Israel which compared Evusheld 300mg (n=825) to unmatched controls (n=4,299). • Population considered severely immunocompromised patients aged 12 and over. • Dominating strains were BA.1 and BA.2. • The majority were vaccinated. In the Evusheld group, 98.8% had received at least 1 vaccine dose and 91.3% had received 3–4 doses. In the control group, 88.0% had received at least one vaccine dose, and 76.3% 3–4 doses. ***Kaminski et al. 2022***(42)

	• Retrospective study comparing Evusheld 300 mg (n=333) to controls (n=97). • The population reflected kidney transplant recipients from Bordeaux University Hospital in France with no or low response to COVID-19 vaccines. • Dominating strains were BA.1 and BA.2. ***Chen et al. 2022***(43) • Comparison before and after receiving Evusheld in n=1,295 patients. • Patients received treatment at the University of California San Diego's Health System in the US, a quaternary referral centre, serving many patients who require complex subspecialty care. • Dominating strains were BA.1, BA.1.1, BA.2.12 and BA.5. • The majority were vaccinated. Of the 121 patients who developed COVID-19 infection prior to receipt of Evusheld, 84.3% had received at least one dose, 57.0% had received 3–4 doses. The corresponding figures for those who had COVID-19 infection following receipt of Evusheld was 97% and 72.2% respectively. The clinical effectiveness results from the studies listed above, are presented in Figure 2. Evusheld significantly reduced the risk of: • COVID-19 hospitalisation by 69.23% • Intensive therapy unit admission by 87.89%, • All-cause mortality by 81.29%, and • COVID-19-specific mortality by 86.36%, compared to no treatment.(38) **Figure 2: Clinical effectiveness of Evusheld against breakthrough COVID-19 infection, hospitalisation, intensive care unit admission, mortality, and COVID-19 specific mortality**

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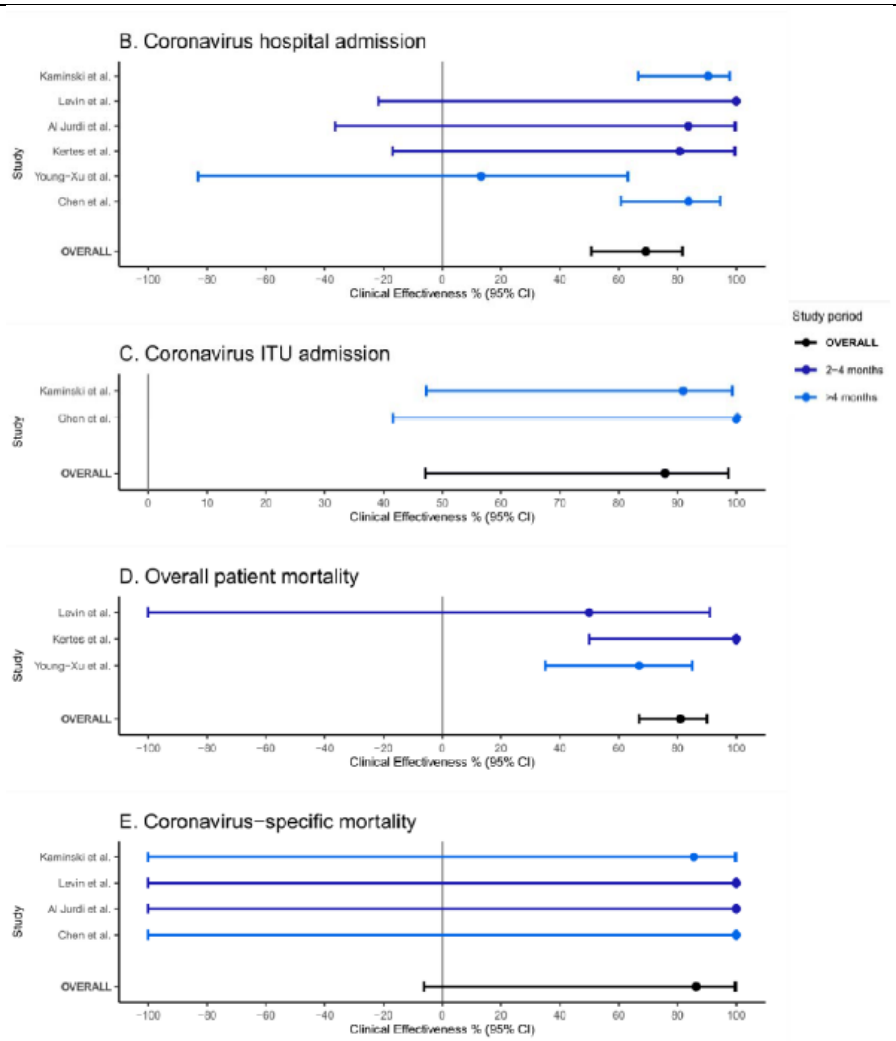

Abbreviations: CI – Confidence interval; ICU – Intensive care unit.
Source: Suribhatla et al. 2022 (38)

[redacted]

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	[redacted] In conclusion, all available clinical evidence for Evusheld conducted in humans during the Omicron waves (including BA.4/5) demonstrates that Evusheld is consistently, highly clinically effective as a treatment or prophylactic against the Omicron variant and its subvariants. There is no evidence in human clinical studies to suggest otherwise. This additional evidence, in combination with the primary evidence base for Evusheld as a treatment for COVID-19 (i.e the TACKLE study), demonstrates that Evusheld is an effective treatment for COVID-19 against the Omicron variant (including BA.4/5).
4	**There is clear evidence that *in-vitro* neutralisation data alone cannot be used to determine whether a treatment will be effective or ineffective in clinical practice** The ACD appears to conclude that *in*-vitro evidence is robust enough to conclude that Evusheld may lack clinical effectiveness against the Omicron variant: "In-vitro evidence suggest[s] that tixagevimab plus cilgavimab lacks clinical effectiveness against the dominant circulating Omicron BA.5 subvariant (Focosi et al. 2022)." However, there is a clear body of evidence for Evusheld, which indicates that *in-vitro* neutralisation data cannot predict whether a treatment will be effective in clinical practice. ***There is no defined threshold for determining treatment ineffectiveness based on in-vitro neutralising activity.*** Given the speed at which COVID-19 variants can appear and become dominant, robust *in-vitro* studies are an important contributor to any therapeutic decision-making process because they can be completed relatively quickly compared with clinical trials and real-world studies. As such, conclusions regarding the effectiveness of monoclonal antibodies have been made based on half maximal inhibitory (IC_{50}) or effective (EC_{50}) concentration results from *in-vitro* neutralisation assays. However, the Company warns against over-reliance on this type of data for several reasons as described in this response. Although higher IC_{50}/EC_{50} values make it more possible that real-world effectiveness of a monoclonal antibody will be reduced, there is yet no agreed threshold for determining when a treatment is deemed ineffective based on *in-vitro* neutralising activity alone. ***Real-world evidence demonstrates statistically significant Evusheld effectiveness in variants where in-vitro analyses have shown limited neutralisation activity***

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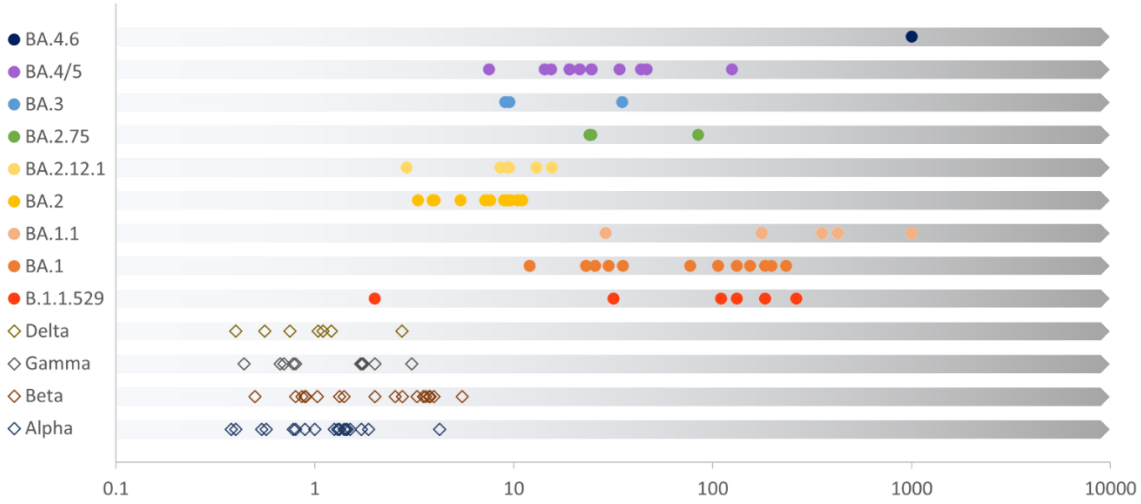
	While there is no agreed or known published correlate for determining when a treatment is deemed ineffective based on neutralising activity, it is known that the higher the IC_{50} values the more likely that efficacy may be reduced. Despite this, even in variants with the greatest IC_{50} values i.e., BA.1 and BA.1.1, real-world evidence has continued to demonstrate a statistically significant and clinically meaningful reduction in the risk of developing symptomatic COVID-19 and hospitalisation and/or death. Evusheld has demonstrated clinical effectiveness against BA. 1 and BA.1.1, since real-world evidence covering BA.1 and BA1.1 (see Issue 3) demonstrates that Evusheld is statistically significant, with large magnitudes of effect, in reducing infections, hospitalisations, ICU admissions, and death. *In-vitro* live virus neutralisation data for these subvariants, suggest high IC_{50} values of [redacted] ng/ml for [redacted] respectively.(44,45,27) Therefore, Evusheld is expected to be clinically effective against any variant (BA.1, BA.2, BA.4/5) with an IC_{50} below [redacted] ng/ml (44,45,27). This however does not suggest clinical ineffectiveness for any IC_{50} beyond [redacted] ng/ml but one can conservatively infer real-world efficacy against emerging variants of concern: those that are neutralised to the same extent as, or even better than, [redacted] (numerically, a lower IC_{50}) would be expected to remain effective.(31) ***Fucossi et al. 2022, used as the basis for NICE's decision making for Evusheld's clinical effectiveness against Omicron has significant methodological limitations; in-vitro neutralisation results and interpretation differ considerably across studies*** Summarising data on reduction in monoclonal antibody neutralising activity against different Omicron subvariants clearly shows highly disparate results from different analyses of the same monoclonal antibody (Figure 3).(46) • The assays used are not well standardised technically,(33,47) sometimes using cell lines which have been shown to be inappropriate for assaying certain classes of monoclonal antibodies.(31) • An important, but not often acknowledged, limitation of many *in-vitro* studies is the range of antibody concentrations tested, which are often lower than the average maximum serum concentrations.(48) • In addition, there is a lack of standardisation regarding interpretation of results; for example, two different studies of tixagevimab plus cilgavimab against BA.5 described similar reductions in effectiveness (30.7-fold reduction in inhibition against BA.5(49) versus 21-fold reduction against BA.4/5(25)), yet the conclusions

were different: the first study concluded that tixagevimab plus cilgavimab retained some neutralising activity, while the second stated that efficacy was lost.

Figure 3: Fold reduction in neutralising activity of tixagevimab plus cilgavimab against SARS-CoV-2 VoCs vs ancestral/reference strains



Abbreviations: SARS-CoV-2 – Severe acute respiratory syndrome; VoCs – Variants of concern
Source: National Center for Advancing Translational Services OpenData (50)
Note: values >1000 are not available in this online activity summary and are reported as = 1000.

When interpreting in-vitro neutralisation data of antibodies against COVID-19, it is vital to also critically appraise the technical methodologies used to draw any conclusions before inferring the likely impact on efficacy.

This comment is particularly evident in the case for the conclusions drawn in Focosi et al., 2022, which have significant methodological limitations, and so AstraZeneca assert that these analyses do not provide evidence that tixagevimab plus cilgavimab lacks clinical effectiveness against Omicron BA.5.

Focosi et al. 2022 make the following claim in their article that is not supported by the evidence they cite: *"…while the tixagevimab component has been ineffective against any Omicron sublineage so far (BA.1, BA.2, and BA.4/BA.5), the cilgavimab component is ineffective against BA.1 and BA.4/BA.5 but has preserved efficacy against BA.2."*

Only Aggarwal et al.(51) supports their claim that cilgavimab is ineffective against BA.1, specifically B.1.1.529. Articles by Cao et al.,(52) Planas et al.,(53) Liu et al.,(54) VanBlargan et al.,(55) and Touret et al.(56) all report reduced—but not complete loss of—

	neutralising activity against BA.1 by cilgavimab. Similarly, Yamasoba et al.(57) reports reduced but not complete loss of neutralising activity against BA.4 and BA.5. Kimura et al.(58) is incorrectly cited by Focosi and Tucori as it reports the results of Yamasoba et al.,(57) not the results of separate analyses. The loss of neutralizing activity against BA.4 and BA.5 is also contrary to results reported elsewhere by Cao et al.,(59) which show cilgavimab effectively neutralizes BA.4 and BA.5 in vitro. These conflicting results are likely due to most laboratories cited by Focosi et al. used techniques with ACE2-overexpressing cells, despite such methods previously showing a clear lack of neutralisation of SARS-CoV-2 by certain classes of monoclonal antibodies, yet clinical efficacy has been retained.(31) At a fundamental level, comparison of in-vitro data across laboratories is hampered by the use of different cell lines that may be infected by SARS-CoV-2 variants to different extents. A more robust in-vitro assay method utilised by the Francis Crick Institute's COVID surveillance unit (Wu et al. 2022 (31) has recently concluded that, counter to the conclusions of other reports, sotrovimab, imdevimab, and cilgavimab were able to neutralise BA.2, BA.2.12.1, BA.4 and BA.5, dominant variants of concern circulating in the UK at the time of the analysis. In addition to presenting EC_{50} values, the authors of this study also demonstrated that these neutralising values were well below the maximum antibody serum concentrations reported in the Summary of Product Characteristics.(31) The conclusions made by Wu et al are also supported by real-world evidence as discussed in Issue 3. In contrast to the techniques employed in the studies included by Focosi et al., the study by Wu et al. 2022 utilised an assay calibrated with the WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reporting of neutralisation titres in International Units – an assay useful for standardised comparisons of different monoclonal antibodies against various variants.(31,60) Using this assay, the authors calculated IC_{50} values by fitting a four-parameter dose–response curve to 288 independent data points, generated from three independent repeats of 12 independent titrations, each consisting of two technical replicates of a four-point dilution series against live virus variants. Some of the articles cited by Focosi et al, however, evaluated neutralisation using live viruses, others used lentivirus-based pseudoviruses or stomatitis-based lentiviruses. None performed assays to the strict standards of the assay method utilised by the Francis Crick Institute's COVID surveillance unit. In addition to the more rigorous and internationally recognised methodology utilised by Wu et al 2022, the authors also reported confidence intervals, rather than just point estimates. The reporting of confidence intervals is essential to evaluate the significance of any possible changes in neutralisation; particularly when considering IC_{90} values, which lie close to the plateau of the dose–response curve and are inherently noisy, both in cell-

	based assays and in fitting of a dose–response curve (the methodology utilised by the studies appraised by Focosi, et al. 2022). Furthermore, the study conducted by Wu et al. demonstrated that sotrovimab retained neutralisation activity against some variants in which other non-standardised methodologies reported a lack of neutralisation activity, such as was the case for BA.2. Focosi et al, have therefore not demonstrated that tixagevimab plus cilgavimab lacks clinical effectiveness. They make no attempt to discuss how apparent reduction of in vitro neutralising capacity in non-standardised assays relates to loss of efficacy in real-world clinical settings and present no data to show loss of clinical efficacy. Therefore, the studies reported and appraised by Focosi et al. should be reviewed critically and an appropriate quality control conducted to ensure the rigor and the scientific methodologies employed are appropriate to inform clinical and policy decision making. Moving forward, the use of *in-vitro* neutralising data should consider a more rigorous methodology, aligned with the MHRA's decision making. In conclusion, given the uncertainties, the conflicting nature of *in-vitro* neutralisation results and real-world evidence, it is clear that decision making based on neutralisation data alone is not a robust or sustainable methodology. Furthermore, NICE should consider the robustness of the methodology used and conduct a quality assessment to determine whether it complies with the standards set out by the WHO – in the case of Focosi et al, this does not meet the required standards.
5	**In the proposed positioning, the cost-effectiveness of Evusheld should be evaluated against standard of care using the modified full analysis set and considering data within 5 days of symptoms onset.** Since AstraZeneca has revised the positioning of Evusheld to be for patients unsuitable to receive nirmatrelvir plus ritonavir, the only treatment option recommended by NICE in this population is standard of care (i.e. no interventional treatment). As such, Evusheld should be compared to standard of care based on data from the modified full analysis set in the TACKLE study, which considered Evusheld versus placebo. It is unclear why NICE have concluded that it is acceptable to use two different datasets for evaluating the clinical effectiveness of Evusheld in the TACKLE study (randomised set for all cause death and the modified full analysis set for hospitalization or death) as part of the economic analysis. Note that the randomised set also included patients that did not receive treatment. AstraZeneca would hope that NICE recommend a consistent approach is used for the data considered as part of the economic analysis. This should align with that of the primary efficacy analysis for which regulatory approvals have been granted, and as such the modified full analysis set should be used for the purposes of economic modelling.

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	Furthermore, the modified full analysis set excluded 43 patients in the Evusheld and 33 in placebo group who were hospitalised at baseline for isolation purposes (in Japan and Russia), or were randomly assigned study drug after 7 days of symptom onset. Therefore, the modified full analysis set is representative of the population, and therefore the outcomes, of people who would be expected to receive treatment in the UK. Additionally, as already noted in AstraZeneca's response to the MTA Assessment Group report, and by the Assessment Group itself, the COVID-NMA utilised by NICE is flawed in several ways: • The trials included in the analyses were undertaken at different time-points, which given the dynamic nature of COVID-19 renders the disease landscape too dissimilar to allow meaningful comparison. • Similarly, the trials generally compared the intervention to the then-current standard of care, which have varied considerably throughout the pandemic. • The trial designs and reporting of efficacy outcomes also varied substantially – further exacerbating the limitations in any comparison between studies. • There are extensive imbalances between the trial populations, specifically with respect to age, disease severity, vaccination status, history of infection and available treatments in the standard of care arm. AstraZeneca reiterates that assuming none of these differences would be significant effect modifiers is naïve and we stand by our previous concern that these comparisons of treatment effects are substantially confounded and highly uncertain, and therefore inappropriate for decision making. Finally, as noted in Issue 1, our proposed positioning restricts Evusheld to treatment within 5 days from symptom onset. The current preferred economic modelling produced by the EAG utilises treatment data within 7 days of symptom onset for the hospitalisation or death outcome, and all-cause mortality outcome. Therefore, aligned with other interventions included in the MTA, all analyses which include Evusheld should be consistently undertaken using 5-day cut-off data in the economic model; in-line with the optimised positioning in which AstraZeneca is seeking reimbursement. In conclusion, the appropriate comparator for Evusheld in the economic evaluation is standard of care using the modified full analysis set considering data within 5 days of symptoms onset.
6	**The risk of hospitalisation for the highest-risk population is inconsistent with the most up to date evidence.**

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	The ACD states that: "*The committee acknowledged significant uncertainty in estimating the hospitalisation rate for the population who have high risk of progressing to severe COVID-19. Based on the strength of the evidence it concluded that it was likely to fall between the underestimate of PANORAMIC at 0.77% and the estimate of 2.79% from the interim database analysis."* (page 24) AstraZeneca can demonstrate that this range severely underestimates the real-world risk of the patients who would benefit from Evusheld. As already noted in AstraZeneca's response to the MTA Assessment Group report, acknowledged by NICE and the EAG, and confirmed by experts at the ACM, the value of 0.77% sourced from PANORAMIC is an underestimate. "*The clinical experts agreed given the committee's preferred definition of high risk (see section 3.6) that 0.77% could be an underestimation because the highest risk group may have been underrepresented in PANORAMIC*". *(page 24)* The PANORAMIC study is not reflective of the relevant population since it enrolled patients above the age of 50 regardless of comorbidities or lack thereof. Additionally, access to antivirals and neutralising monoclonal antibodies were available at the time of enrolment, meaning McInnes high-risk patients who received treatment were unlikely to have been enrolled. In AstraZeneca's response to the MTA Assessment Group report, we presented a recent study by Shields et al. (61), at that point under peer-review but has now since been published. Shields et al. 2022 assessed the impact of vaccination on hospitalisation and mortality from COVID-19 in patients with primary and secondary immunodeficiency in the UK, which aligns closely with the target population for the submission – as noted in the MTA committee slides on slide 8(62). The study included a cohort of 140 patients infected between January 2021 and March 2022. Study participants represents patients infected after the deployment of vaccination and the routine use of antiviral and monoclonal antibody treatments in inpatient and outpatient settings. Furthermore, the majority of infections occurred later in the pandemic, after patients had received at least two vaccine doses, after the more transmissible B.1.1.529 (Omicron) SARS-CoV-2 variant became dominant, and after legal restrictions on social interactions had been lifted.

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	For patients who were not treated with antivirals or neutralising monoclonal antibodies by the COVID-19 Medicine Delivery Units during the Omicron period, the rate of hospitalisation was reported as 15.9%. We are confused why NICE would not consider this study relevant, or even comment on its applicability in the MTA committee slides or the ACD, but did consider the PANORAMIC study relevant for decision making despite the significant limitations and confounding noted. We would like to reiterate by again underlining the importance of using an appropriate measure for hospitalisation. Given that the underlying risk of hospitalisation is a key driver of the cost-effectiveness, it is crucial that the latest available evidence is used. Shields et al. demonstrates that the currently used value range of 0.77% to 2.79% is a considerable underestimation. This hypothesis is supported when considering evidence presented on page 282 of the Committee papers (Committee papers *Table 1: Literature Review Search Results*), reflecting even higher risks in certain subgroups of the McInnes population, during Omicron dominated periods. The following proportions of patients hospitalised from McInnes populations were identified: • **Chinnadurai et al. 2022**(63) (Haemodialysis): 0.0% • **Parry et al. 2022**(64) (chronic lymphocytic leucaemia): 7.7% - **Gleeson et al. 2022**(65) (immunosuppressed kidney transplant recipients): 20.8% - **Bradwell et al. 2022**(66) (haematological malignancy): 26.4% In addition, a targeted literature review undertaken by AstraZeneca identified three additional sources, reporting crude rates of hospitalisation for COVID-19 positive, predominantly vaccinated high-risk patients during Omicron waves: • **Ashby et al. 2022**(67) (haemodialysis): Ranging from 16.1% (one vaccine dose) to 9.8% (three vaccine doses) • **Trindade et al. 2022**(68) (lung transplants): 17.9% • **Anjan et al. 2022**(69) (solid organ transplants): 31.9% These reviews clearly show that there are large variations within the McInnes high-risk clinical subgroups, with certain rates as high as >30%(69). This warrants that the economic modelling should at consider a lower bound of 5.48%, as presented on slide 8 in the MTA

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	committee presentation(62), and an upper bound of 15.9%, as evidenced by Shields et al.(61)
7	**AstraZeneca again reiterates a response to the EAG assessment report, as the mortality assumptions and approach remain counter-intuitive and results in clinically implausible estimates.** The way the model developed by the EAG currently implements all-cause mortality means that patients who receive outpatient treatment and subsequently end up hospitalised, have a much higher risk of inpatient death compared to hospital patients who did not receive treatment. In some low-efficacy scenarios, this leads to 121 times higher inpatient mortality for some treatments compared to standard of care. As a consequence, in the current model, Evusheld is associated with increased all-cause and inpatient mortality compared to standard of care, based on a relative risk of all-cause death at 28 days greater than one (RR=1.18) and a multiplier for Evusheld inpatient mortality of 2.92. This is an implausible assumption which contradicts all available clinical trial data. Phase III, randomised, double-blind, clinical trial TACKLE, which evaluated the efficacy and safety of Evusheld for early outpatient treatment of COVID-19 demonstrated a statistically significant reduction in the relative risk of all-cause mortality compared with placebo; at treatment initiation within five days of symptom onset, the relative risk was 0.33 (95% CI 0.03–3.15).(19) Therefore, AstraZeneca stands by the view that it is inappropriate for the EAG and NICE to accept this inherently flawed modelling approach, which significantly biases the ICER estimates in favour of standard of care, despite contrary evidence. The assumption that Evusheld is associated with increased all-cause and inpatient mortality is perverse in the context of the robust randomised clinical trial data available. The EAG themselves acknowledge that the assumption is unreasonable (page 36 and 61 of the EAG report): • *"…it may be seen as unlikely that an intervention that causes a statistically significant reduction in the composite endpoint of hospitalisation or death would cause an increase in the number of deaths…" and* • *"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."*

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<table>
<tr><td></td><td>AstraZeneca appreciates the time-limitation, but it is not reasonable that this should be allowed to impact the robustness of the assessment. We are furthermore surprised that this comment made during AstraZeneca's response to the EAG report was not even discussed during the committee meeting, or raised in the ACD.

As a solution to the modelling issue, we suggested that the inpatient mortality multiplier be set to 1.0 for all treatments, which in the case of Evusheld still biases in favour of standard of care in light of the available evidence – but not to the extent currently modelled.

This should be implemented moving forwards, and while not an optimal solution (such as using the actual robust and peer reviewed clinical trial data), would at least remove the unreasonable assumption that a statistically significant reduction in all-cause death and all-cause hospitalisation or death would translate to an increased risk of death.</td></tr>
<tr><td>8</td><td>In Table 1 below we have reproduced the base case ICER as per the MTA report and the analysis presented by the EAG for reference.

Table 1: EAG base case
<table><tr><th>Model assumptions</th><th>Low efficacy</th><th>Mean efficacy</th><th>High efficacy</th></tr><tr><td>• Seven days from symptom onset:
o FAS: Relative risk of all-cause death: 1.18
o mFAS: Hospitalisation and all-cause death: 0.52
• Risk of hospitalisation: 2.79%
• Inpatient mortality relative risk: 2.92</td><td>Dominated</td><td>£485,067</td><td>£17,380</td></tr></table>
AstraZeneca has proposed that Evusheld be restricted to a population where nirmatrelvir plus ritonavir is unsuitable, and treatment is administered within 5 days of symptom onset. We maintain that in this positioning, Evusheld should be compared to standard of care using the modified full-analysis set from the TACKLE study, considering data within 5 days of symptom onset (Issue 5). In addition, given that the relevant comparator is standard of care, and data are available which supports the efficacy of Evusheld for different variants of concern, this implies that low and high efficacy scenarios are not relevant and the mean efficacy scenario is most appropriate for decision making.

In Table 2 we present economic analyses for this population, and we also show the impact using a more plausible range of hospitalisation rates from 5.48% to 15.9% (Issue 6), and the impact of not assuming Evusheld leads to increased inpatient mortality (Issue 7). Results using the low and high efficacy scenarios are presented for completeness.</td></tr>
</table>

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Table 2: Economic analyses relevant to the target positioning for Evusheld

Model assumptions	Low efficacy	Mean efficacy	High efficacy
• ***Five*** days from symptom onset: o mFAS: Relative risk of all-cause death: ***0.64*** o mFAS: Hospitalisation and all-cause death: ***0.33*** • Risk of hospitalisation: 2.79% • Inpatient mortality relative risk: 2.30	**Dominated**	**£26,146**	**£12,729**
• ***Five*** days from symptom onset: o mFAS: Relative risk of all-cause death: ***0.64*** o mFAS: Hospitalisation and all-cause death: ***0.33*** • Risk of hospitalisation: 2.79% • Inpatient mortality relative risk: **1.00**	**£36,168**	**£18,122**	**£13,574**
• ***Five*** days from symptom onset: o mFAS: Relative risk of all-cause death: ***0.64*** o mFAS: Hospitalisation and all-cause death: ***0.33*** • Risk of hospitalisation: **5.48%** • Inpatient mortality relative risk: **1.00**	**£16,841**	**£7,653**	**£5,337**
• ***Five*** days from symptom onset: o mFAS: Relative risk of all-cause death: ***0.64*** o mFAS: Hospitalisation and all-cause death: ***0.33*** • Risk of hospitalisation: **15.9%** • Inpatient mortality relative risk: **1.00**	**£3,704**	**£537**	**Dominates**

Abbreviations: FAS – Full analysis set; mFAS – Modified full analysis set

The analyses above report that the ICER varies between £537 and £18,122 depending on the hospitalisation rate used in the economic model. Given that AstraZeneca have presented robust data which supports a hospitalisation rate of 15.9%, the most plausible base case ICER for Evusheld as a treatment for COVID-19 is £537 versus standard of care.

In addition, even in scenarios where overly conservative or inappropriate assumptions are used (i.e. hospitalisation rate of 2.79% and inpatient mortality of 2.30), the ICER is still below a cost-effectiveness threshold of £30,000 per QALY.

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As a result, Evusheld represents a cost-effective treatment and should be recommended by NICE within AstraZeneca's proposed positioning as a treatment for COVID-19.

Additional information:

[redacted] 3[redacted].

Table 3: Economic analyses using the PAS price

Model assumptions	**Low efficacy**	**Mean efficacy**	**High efficacy**
EAG base case with PAS price			
• Seven days from symptom onset: o FAS: Relative risk of all-cause death: 1.18 o mFAS: Hospitalisation and all-cause death: 0.52 • Risk of hospitalisation: 2.79% • Inpatient mortality relative risk: 2.92	[redacted]	[redacted]	[redacted]
Economic analyses relevant to the target positioning for Evusheld with PAS price			
• ***Five*** days from symptom onset: o mFAS: Relative risk of all-cause death: ***0.64*** o mFAS: Hospitalisation and all-cause death: ***0.33*** • Risk of hospitalisation: 2.79% • Inpatient mortality relative risk: 2.30	[redacted]	[redacted]	[redacted]
• ***Five*** days from symptom onset: o mFAS: Relative risk of all-cause death: ***0.64*** o mFAS: Hospitalisation and all-cause death: ***0.33*** • Risk of hospitalisation: 2.79% • Inpatient mortality relative risk: **1.00**	[redacted]	[redacted]	[redacted]
• ***Five*** days from symptom onset: o mFAS: Relative risk of all-cause death: ***0.64***	[redacted]	[redacted]	[redacted]

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	○ mFAS: Hospitalisation and all-cause death: ***0.33*** • Risk of hospitalisation: **5.48%** • Inpatient mortality relative risk: **1.00**			
	• ***Five*** days from symptom onset: ○ mFAS: Relative risk of all-cause death: ***0.64*** ○ mFAS: Hospitalisation and all-cause death: ***0.33*** • Risk of hospitalisation: **15.9%** • Inpatient mortality relative risk: **1.00**	[redacted]	[redacted]	[redacted]

Abbreviations: FAS – Full analysis set; mFAS – Modified full analysis set

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NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

Draft Guidance comments form

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Gilead Sciences Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

Draft Guidance comments form

Comment number	Comments
1	Gilead acknowledges the unique and inherent challenges of carrying out an assessment of the clinical and cost-effectiveness of medicines for COVID-19 in a pandemic and post-pandemic setting. However, we have significant concerns about the conduct of this technology appraisal, primarily regarding robustness, fairness, and a lack of methodological transparency. We believe that NICE has not acted fairly and that, depending on the outcome to this consultation process, there is a risk that NICE may make unreasonable recommendations regarding the use of remdesivir (Veklury®) and other therapeutics for the treatment of COVID-19. If so, this would be detrimental to patients, both in the UK and internationally, given that NICE guidance is extremely influential globally. Gilead believes that NICE has not acted fairly and that NICE's recommendation in respect of remdesivir is unreasonable based on the evidence submitted to NICE, for the following reasons (these are further elaborated in our detailed response): • By failing to follow its own published process and methods, NICE has acted unfairly: for example, companies did not have the opportunity to make a full evidence submission (including a de novo cost effectiveness analysis). In addition, the Evidence Assessment Group (EAG) did not conduct its own independent literature review (for lack of time) and did not validate the input from an outsourced provider. • The living network meta-analysis (NMA) methodology used to inform decision-making has significant limitations and excluded important clinical evidence without clear justification. For example, the living NMA methodology / process does not take all available evidence into account, and does not align with published and preferred NICE manual relating to systematic identification of evidence (section 3) (1). COVID-19 is now comprised of 11 variants, all of which are being monitored by WHO, and we need a comprehensive evidence base that monitors this thoroughly. Without this, the appraisal of the benefit, is inequitable and unbalanced. • The Committee's adoption of the low efficacy scenario for remdesivir and its reliance on the resulting cost-effectiveness estimates to develop recommendations is unreasonable and flawed. The Committee choses to adopt an extreme position on the evidence for remdesivir in its deliberation on the cost-effectiveness estimates by choosing to consider only the low- and mean- efficacy scenarios. According to the NICE methods guide, these data should be used instead to inform a probabilistic analysis in order to generate mean expected incremental cost-effectiveness ratios (ICERs) that reflect the uncertainty with regards to remdesivir. The approach taken departs so significantly from established NICE methods that Gilead respectfully requests this be referred to the Decision Support Unit (DSU) for independent review. • Key economic evidence has been excluded from the appraisal and the EAG model is not a reliable basis for decision-making, with significant errors identified following

	the first committee meeting. Companies were not permitted to submit their own *de novo* cost-effectiveness analyses, and instead the EAG model was used to inform all decision making. There are significant areas of concern relating to the EAG model, including the multiple errors that were not corrected before the Committee deliberated on the evidence at the Appraisal Committee Meeting. • Important evidence relating to time to discharge (TTD) from hospital and mortality for remdesivir has been overlooked and should be incorporated into the economic model to inform decision making. In particular, the EAG does not consider data from the ACTT-1 trial on TTD, which clearly shows that remdesivir patients have a reduced TTD compared to placebo (8). • The Committee has not taken all the clinical evidence into account, including the SOLIDARITY trial. The Draft Guidance does not reflect the full body of data available, nor is it in line with the broad range of evidence-based guidelines from around the world. Because of this, the clinical benefits of antivirals across the disease spectrum of COVID-19 have been underestimated. Remdesivir is an important anti-viral option for helping hospitalised patients to recover significantly faster and reduce the likelihood of disease progression and mortality. • If the Draft Guidance is published in its current form, it will create considerable equality challenges for multiple groups, including those with protected characteristics, because of limited access to anti-viral treatment in the hospital setting. For example, this includes hospitalized patients (especially those requiring supplemental oxygen), paediatric patients under 12 years of age, and patients with co-morbidities and contraindications relating to renal and hepatic impairment. Gilead considers that the Draft Guidance has resulted from a process that has not been robust or methodologically sound. Gilead requests that the Committee modifies its decision to reflect the issues raised in the consultation. We request that NICE: • Fully considers the additional clinical evidence submitted by Gilead, which is important to produce an evidence-based recommendation for remdesivir. • Re-considers the inclusion of SOLIDARITY, which as stated in the Draft Guidance itself "*would have likely impacted the final conclusions for remdesivir*". • Develops the guidelines for remdesivir based on the best available evidence and an appropriate measure of uncertainty, by applying a consistent approach across all treatments to the consideration of the low-, medium- and high- efficacy scenarios, rather than applying an arbitrary low-efficacy scenario inconsistently to remdesivir. • Re-evaluate data that has informed international guidance on the use of COVID-19 antivirals across the spectrum of disease, and in combination with immunomodulators, to rectify the gaps in treatments available for hospitalised patients in the Draft Guidance. • Refers the approach taken by the EAG to the DSU for consideration as this departs so significantly from NICE established methods, and could be considered as setting

	a precedent for future MTAs. Gilead therefore requests an external independent review of the methodology used for the COVID-19 MTA. • Gives detailed reasons for inclusions and exclusion of sources of evidence, as well as the rationale for selecting certain outcomes from each study selected. The information should be presented in a PRISMA diagram, and the appraisal should adhere to the NICE Reference Case.
2	**Failure to follow NICE's published process and methods** Gilead believes that NICE has failed to act fairly by not following its own published process and methods for technology appraisals. NICE has adapted and re-sequenced the steps of the MTA to such an extent that deviates materially from the normal MTA process. This is unfair to Gilead and other stakeholders and also undermines the robustness of the Committee's decision-making and credibility of the Draft Guidance. In particular: 1. The EAG was commissioned, and the Evidence Assessment Report (EAR) was published, before NICE started the technology appraisal process. (1) Nonetheless, the EAG, using the justification of lack of time, did not conduct its own independent, systematic literature review, instead relying on an outsourced provider whose input the EAG did not validate or subject to quality control. This is contrary to the principles for evidence collation reflected in the Manual, and in particular, section 5.5. 2. Companies, including Gilead, were not given the opportunity to make a *full* evidence submission (including a de novo cost effectiveness analysis) before the development of the EAR but instead were only asked to comment on the EAR, without being able to submit additional evidence. This contradicts – for example - sections 1.3.1 and 5.5-5.6 of the Process and Methods Manual (the Manual**)** (1). Gilead's request to submit a de novo cost-effectiveness model was rejected by NICE which we believe to be unfair. As a result, Gilead lost the opportunity to fully participate in the appraisal and inform the Committee. The fact that the EAG did not consider all the relevant data sources has led to subsequent shortcomings in the application of assumptions and methodology. 3. Relevant evidence has been excluded by the EAG and was not considered by the Committee. For example, the SOLIDARITY trial (2) was excluded from the EAR without a clear justification due to a lack of systematic approach. This decision was unreasonable and unfair, as further described in section 3.3 of this response. (1) 4. Companies did not have an opportunity to discuss commercial in confidence patient access schemes (PAS) net price discounts or commercial access agreements before the start of the evaluation. Given that the usual process was not followed, there was also a lack of clarity over whether and when commercial discussions would take place. This contradicts 5.5.6 section of the Manual (1). With less opportunities to settle on an appropriate commercial arrangement, it means that Gilead's participation in the technology appraisal was unfairly constrained. 5. In section 5.5.6 of the Manual NICE states that it "*aims to make sure that companies bringing technologies forward for possible use in the NHS can make the best plausible case for its product, to the ultimate benefit of the NHS and patients*" (1). However, in addition to not having the opportunity to make an evidence submission, companies

	were not able to make a meaningful contribution in the Committee meeting: for example, each company was only given the opportunity to answer one question in the whole Committee meeting, despite the complexity of the topic, attendant uncertainties, number of products involved, and clear contention over some of the assumptions. (1) 6. The Draft Guidance is based on flawed economic modelling which deviates from NICE's methods and processes. For example, not all of the economic evidence has been taken into account. 7. The economic model produced by the EAG and discussed by the Committee was later admitted containing errors. The model was updated only after the Committee meeting and a further corrected version was issued after the Draft Guidance was published. This demonstrates a lack of quality control that would normally be expected before an economic model is submitted to the Committee. It also raises the risk that the Committee made its recommendations on the basis of an incorrect model. 8. NICE did not provide sufficient justification for its conclusions and approach on a number of issues, such as: the rationale for excluding certain sources of evidence, or the Committee's adoption of the low efficacy scenario for remdesivir. 9. The recommendations made in the Draft Guidance cannot be justified by the evidence presented; the rationale of selection of certain sources of evidence are unclear and lack full transparency. Section 3.2.1 section of the Manual states that the evidence must be "*Assembled systematically and synthesised in a transparent way that allows the analysis to be reproduced*". This has not happened with this appraisal to date. Gilead has previously highlighted to NICE its concerns about the fairness of this appraisal process. Given the extensive differences between this process and NICE's published process and methods, we question if NICE may have exceeded its powers.
3	**The living NMA methodology excludes key clinical evidence without clear justification, resulting in significant limitations of the evidence presented to the committee and ultimately to unreasonable conclusions being made in the Draft Guidance** The methodology used to identify and synthesise evidence that underpins the Draft Guidance has the following limitations: • The approach is not in line with established methods for the systematic and transparent identification and synthesis of evidence as the inclusion and exclusion of clinical evidence is not justified (as outlined in section 3.2.1 of the Manual (1)). • As a result of unclear inclusion criteria for evidence, high quality information is disregarded in favour of low-quality evidence with high risk of bias. • The excluded evidence includes robust data sources such as SOLIDARITY AND ACTT-1, that are relevant and important for NICE's recommendations.

3. 1 <u>The approach is not in line with established methods for the systematic identification and synthesis of evidence as the inclusion and exclusion of clinical evidence is not justified</u>

- The most relevant or applicable data has not been selected for many of the interventions, including remdesivir, with key trials such as SOLIDARITY (2) and CATCO (Canadian sub study of SOLIDARITY) (3) excluded from the EAG analyses without a clear justification due to a lack of systematic approach.
- A full systematic literature review was not deemed feasible in the EAG report given the timescale of the project, and so instead a pragmatic, alternative approach was undertaken where evidence was sourced from two living systematic reviews (COVID-NMA and metaEvidence (4,5)). However, this approach has compromised the quality and robustness of the assessment resulting in a biased evaluation.
- For the development of the NMA, a mathematical model was constructed that used the data from these living systematic reviews to simulate the experiences of patients in hospital, requirement for supplemental oxygen, until discharge or death.
- The dynamic nature and regular update of the living systematic review and subsequent NMA is extremely valuable in a rapidly evolving landscape such as in the context of COVID-19.
- However, the EAG state in their report that "*checking of the extracted data by the EAG against the original RCT publications for accuracy could not be undertaken within the timescales of the project*" (EAG report, v3, page 28), which undermines the reliability of the evidence.

3.2 <u>As a result of unclear inclusion criteria for evidence, high quality information is disregarded in favour of low-quality evidence with high risk of bias</u>

- It is unclear from the information provided why certain sources of evidence were not included in the evidence base for this appraisal. This lack of transparency regarding data selection is unsystematic and contrary to the normal NICE methods, as outlined in section 3.3 of the Manual (1).
- Trials with methodology that was not robust, such as Wang et al. (2020) (6), and Mahajan et al. (2021) (7) were included. In the risk of bias analysis conducted by the COVID-NMA initiative, Wang et al. (2020) (6) is categorised as having "some concerns", and Mahajan et al. (2021) (7) is considered to have a high risk of bias. In contrast, SOLIDARITY is considered to have a low risk of bias in the same analysis (4).
- There was also no clear rationale for the inclusion of some trial outcomes over others. An example is the inclusion of the pivotal study ACTT-1 (8) to look at time to death outcomes, even though the primary endpoint was time to recovery. The inclusion of mortality data from SOLIDARITY (2) would have made more sense to be included given its status as a primary endpoint in a much larger population.
- Similarly, the EAG discount the outcome of time to discharge for remdesivir, which is an outcome that could easily be retrieved from ACTT-1 (8).
- Furthermore, the choice to include a study that was halted early due to the lockdown in China and was therefore underpowered (Wang et al., 2020 (6)) is concerning

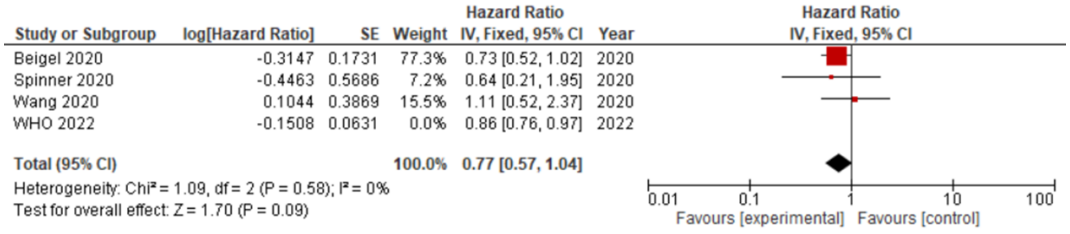
given that this study was selected to assess the outcomes time to death and clinical improvement. Therefore, the outcome has no statistical significance, and should not have been included in the NMA.

3.3 The excluded evidence includes robust data sources such as SOLIDARITY AND ACTT-1 that are relevant and important for NICE's recommendations.

- There is no justification for the exclusion of clinical evidence provided in the EAG report. Both ACTT-1 (8) and SOLIDARITY (2), amongst others constitute more robust data sets from which to retrieve the aforementioned outcomes for assessment.
- Other sources that could strengthen the evidence base for decision-making, but were not considered by the living NMA methodology include Garibaldi et al., 2021 (9) and Mozaffari et al., 2022 (10)
- With regard to SOLIDARITY in particular, this is the full data set for which DISCOVERY is a sub study and was included (see table 23 of the EAG report), so it is not clear why the EAG has not used the full data set, which would enable a more comprehensive appraisal of the available evidence.
- In addition, NICE has recently updated the living guidelines for the management of COVID-19 (11) using the SOLIDARITY data set which confirms the relevance of this source of evidence.
- It is acknowledged in the Draft Guidance that the inclusion of SOLIDARITY in the NMA would have likely changed the recommendation for remdesivir. The SOLIDARITY trial found there was no significant difference in in-hospital mortality at Day 28 between remdesivir and control [remdesivir 14.5%, control 15.6% (RR 0.91; 95% CI 0.82-1.02, P=0.12)] (2). However, there was significant mortality benefit associated with remdesivir in patients who were on oxygen (low or high-flow) but not ventilated [remdesivir 14.6%, control 16.3% (RR 0.87; 95% CI 0.76-0.99, P=0.04]; which is consistent with the findings in ACTT-1 of mortality benefit in the group on low-flow oxygen (2,8).
- To reflect the importance of the SOLIDARITY trial data Gilead has updated the NMA used to derive the time to death summary outcome for remdesivir. Previously the NMA for the time to death outcome included three studies which – altogether – had less than 2,000 patients combined (6,8,12). SOLIDARITY adds roughly another 8,000 patients, therefore bolstering the significance of the analysis. In this additional analysis Gilead considered the overall population, the oxygen no ventilation population as well as the no oxygen population:
  - Overall population – RR 0.86 (0.76–0.98)
  - Oxygen no ventilation population – RR 0.87 (0.76–0.99)
  - No oxygen population – RR 0.76 (0.46–1.28)

  In a first step Gilead has recreated the original forest plot from the COVID-NMA, which shows a summery outcome of HR of 0.77 (0.57-1.04) for time to death using a fixed effects log hazard model (viz. Figure 1).

Figure 1: Updated NMA results – time to death – as reported in the EAG report



The updated NMA results are presented below in Figure 2, Figure 3 and Figure 4 respectively.

Figure 2: Updated NMA results – time to death – overall population from SOLIDARITY

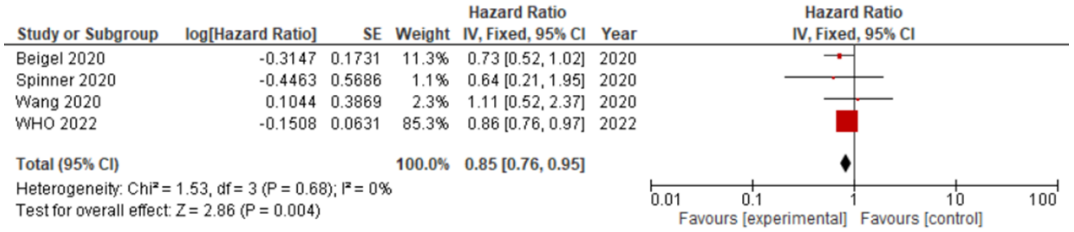


Figure 3: Updated NMA results – time to death – oxygen no ventilation population from SOLIDARITY

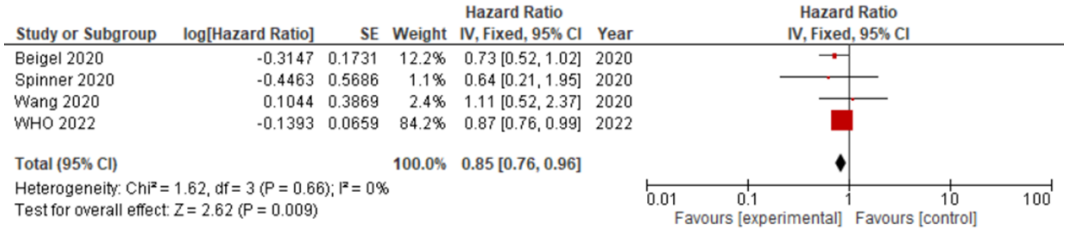
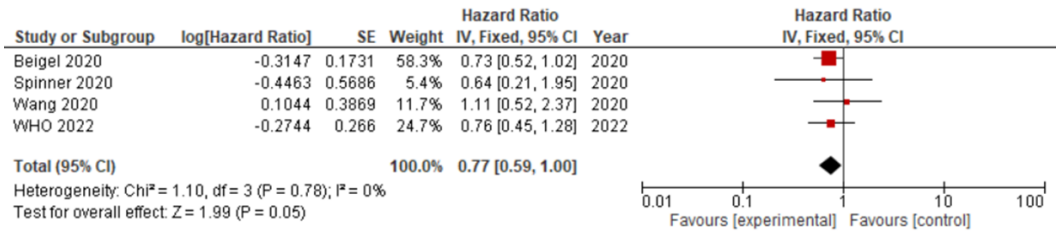


Figure 4: Updated NMA results – time to death – no oxygen population from SOLIDARITY



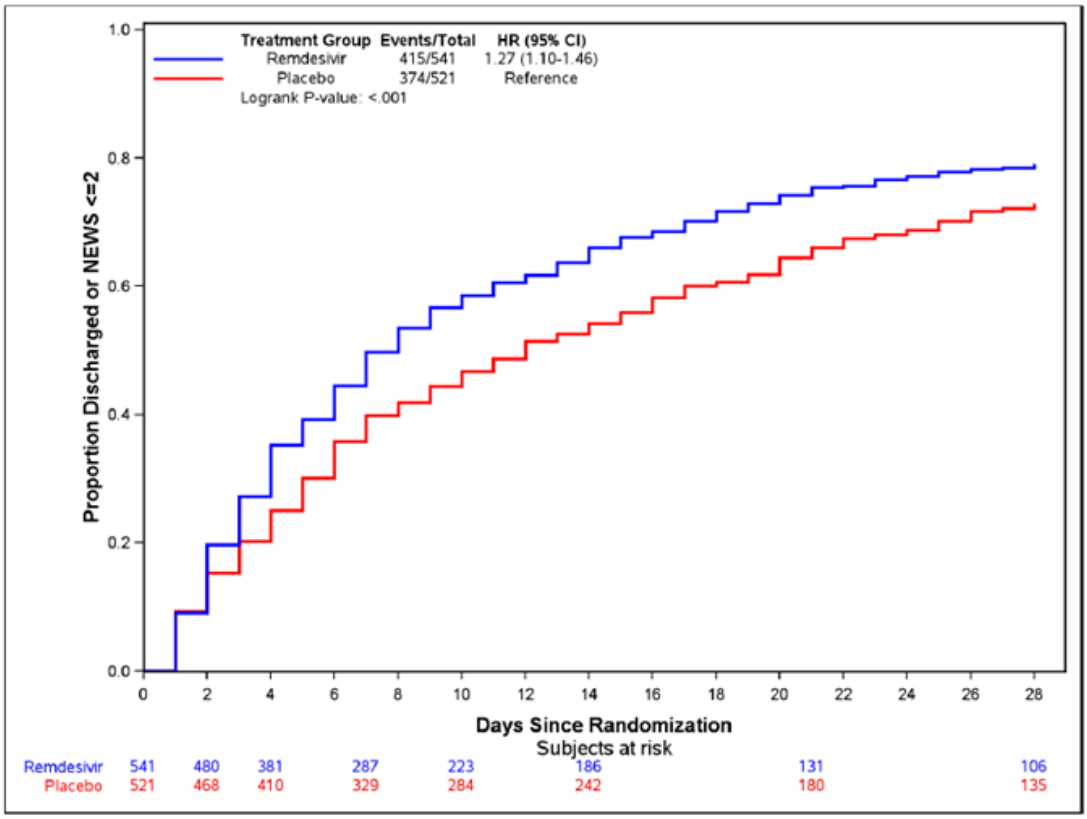
- As can be seen from the updated NMA results the summary outcome now reports an upper confidence interval below 1 for both the total population as well as the oxygen no ventilation population, suggesting a clear clinical benefit of treatment with remdesivir. Even in the no oxygen population subgroup the upper CI now goes down to 1, while still showing less deaths on remdesivir versus the control (i.e. 25 vs. 33 deaths) (2). Arguably, the upper CI from the no oxygen population would drop further given the lower patient numbers in the subgroup compared to the oxygen no ventilation population.

	• Given the updated NMA results for the oxygen/non ventilated patients align with the findings of ACTT-1 (which is a randomised controlled trial), these results are robust and reliable enough to support an assessment of clinical effectiveness in this specific population, supporting its inclusion as a source of data. Furthermore, the full dataset from SOLIDARITY is more applicable than DisCoVeRy data included in the assessment report, for the reasons outlined in sections 3.1- 3.3 of this response. • Although these real-world evidence sources were not included in the living systematic review and NMA due to not being randomised, they are useful in contextualising the results from SOLIDARITY and ACTT-1. • For example, the mortality benefits of remdesivir are also reflected in a recently published RWE trial (13) which compared 24,856 remdesivir-exposed patients against 24,856 propensity score–matched control patients, finding a statistically significant 17% reduction in inpatient mortality among patients hospitalized with COVID-19 (hazard ratio: 0.83 [95% CI, 0.79-0.87]). • Similar results are also reported by Mozaffari et al. (10), which report that remdesivir was associated with a reduction in mortality at 14 days (hazard ratio [95% confidence interval]: 0.76 [0.70–0.83]) and 28 days (0.89 [0.82–0.96]) In view of the significant limitations of the evidence presented to the Committee (some of which were highlighted by the EAG itself), it was unreasonable for NICE to draw the conclusions made in the Draft Guidance (including ranking of therapies against each other) from the evidence presented. Gilead requests that NICE fully considers the additional clinical evidence submitted by Gilead, which is important to produce an evidence-based recommendation for remdesivir. In particular, Gilead requests that NICE re-considers the inclusion of SOLIDARITY, which as stated in the Draft Guidance itself "would have likely impacted the final conclusions for remdesivir".
4	**The Committee's adoption of the low efficacy scenario for remdesivir and its reliance on the resulting cost-effectiveness estimates to develop recommendations is unreasonable and flawed** • In section 3.12 of the Draft Guidance (14), the Committee notes that it considers remdesivir's mechanism of action may not fit the stated treatment aims, because antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation (as discussed in section 7.2). No clinical evidence to support the Committee's view is put forward. • Nonetheless, the Committee then proceeds to adopt an extreme position on the evidence for remdesivir in its deliberation on the cost-effectiveness estimates, choosing to consider only the low- and mean- efficacy scenarios. The limitations of this approach are outlined below. • Section 3.9 of the Draft Guidance (14) chooses to consider the EAG scenarios using the upper and lower confidence limits of each efficacy estimate from the NMA rather than using probabilistic sensitivity analysis (PSA) to assess uncertainty. Scenarios

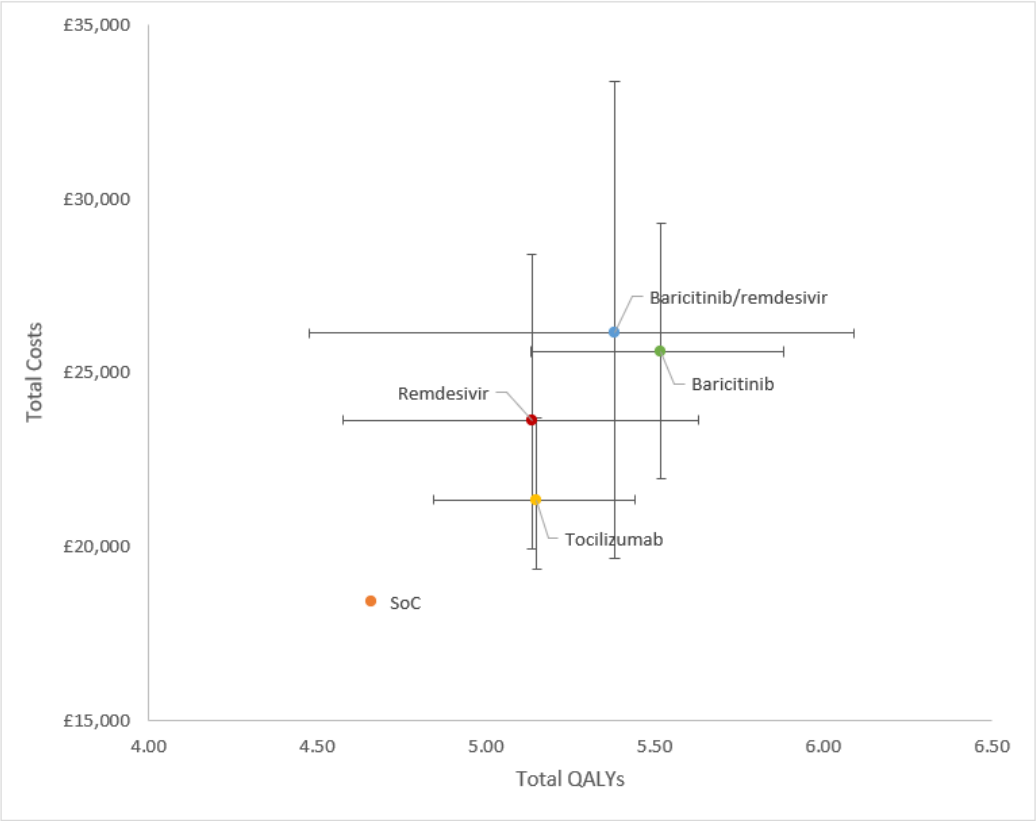
	were therefore developed to represent 'lower efficacy' and 'higher efficacy' estimates. We note that the EAG cautioned the Committee that these efficacy scenarios had limitations because they represented additional uncertainty to that in the evidence base and are not grounded in clinical evidence. • Ignoring this advice, the Committee determined that these low, mean, and high efficacy scenarios can be used to explore uncertainty in relation to the generalisability of evidence to the newer COVID-19 variants. • In section 3.21 of the Draft Guidance (Hospital setting without supplemental oxygen), the ICERs for remdesivir compared to standard of care (SoC) are reported as £10,114 (mean-efficacy estimate) and dominated (low-efficacy estimate). The Committee states that because of uncertainty about the clinical effectiveness of remdesivir in this setting, it preferred the low-efficacy scenario. • Uncertainty in the available evidence is reflected by the range of efficacy estimates with a mean estimate and upper and lower estimates. Typically, and according to section 4.7.12 of the Manual (1), these data would be used to inform a probabilistic analysis, generating mean expected ICERs that reflect the uncertainty in the evidence. However, in this appraisal, and without providing a justification, the Committee has determined to arbitrarily select the 'low-efficacy' scenario to reflect its uncertainty with regard to remdesivir. This is an extreme position and lacks any credibility, as the decision to do so is not underpinned by clinical evidence and, as stated, is not aligned with the published methodology. In the low-efficacy scenario, SoC is associated with greater QALYs and lower costs compared to remdesivir – remdesivir is therefore dominated by SoC. In other words, the model estimates that supportive care without treatment intervention will generate superior clinical outcomes compared to remdesivir. Relying on this as the basis for decision making is absurd and unreasonable.
5	**Important economic evidence has been excluded from the appraisal and the EAG model does not reliably enable an incremental analysis of COVID-19 therapeutics** There are limitations in the economic model developed by the EAG that result in concerns over its appropriateness for decision making. This section focuses on the limitations of the economic model developed by the EAG. 5.1 <u>Low confidence in the EAG model resulting from multiple corrections to the model following consideration of its results</u> • Gilead lacks confidence in the economic modelling, as corrections were made to the model and outputs following the identification of errors after the Committee meeting, and after Draft Guidance was published. Important errors of this sort are typically identified in a proper quality control of the model considerably in advance of Committee.

	5.2 <u>Limitations of the EAG model</u> • As well as previously discussed limitations relating to the choice of scenarios, other issues identified include length of stay assumptions (assumed equal for remdesivir and standard of care, leading to a higher length of stay (LOS) cost for remdesivir and lower quality-adjusted life years (QALYs) due the model structure). This is in direct contrast to the clinical picture, where remdesivir has demonstrated improvements in time to discharge, as outlined below. • Where relative treatment effects for certain comparators are not available the model adopts the arbitrary assumption that there is equivalence between active therapies and standard of care (SoC). This appears to be based on the conclusion that where treatment effects are available, they are close to unity relative to SoC and have little impact within the analyses. Gilead believes that this assumption is not justified as additional evidence to inform outcomes – such as time to discharge for remdesivir for example – was available and would have been identified by the EAG if a systematic review of the published literature had been conducted, rather than relying on external, unvalidated data sources. • As an example, within the EAG economic model, in the hospitalised context, the hazard ratios for mortality for remdesivir and tocilizumab are 0.7791 and 0.7718 respectively, with those for clinical improvement being 1.0404 and 1.0403 respectively. Not only might such differences in point estimates be considered spurious, but the assumption applied for remdesivir for discharge is that there is no effect versus SoC whereas the effect for tocilizumab is 1.05. This implies a benefit for tocilizumab versus remdesivir in the current model based entirely on the arbitrary assumption that remdesivir has no impact on discharge despite having a virtually identical effect to tocilizumab in terms of clinical improvement. • Furthermore, data is available for remdesivir from the ACTT-1 trial which demonstrates that the time to discharge (TTD) benefit is 1.27 over placebo, (8) which implies that remdesivir has superior TTD compared with the recommended tocilizumab.

Figure 5: Kaplan-Meier Curves of Time to Discharge or to a National Early Warning Score (NEWS) of ≤2 by Treatment Group (ITT Population) (8)



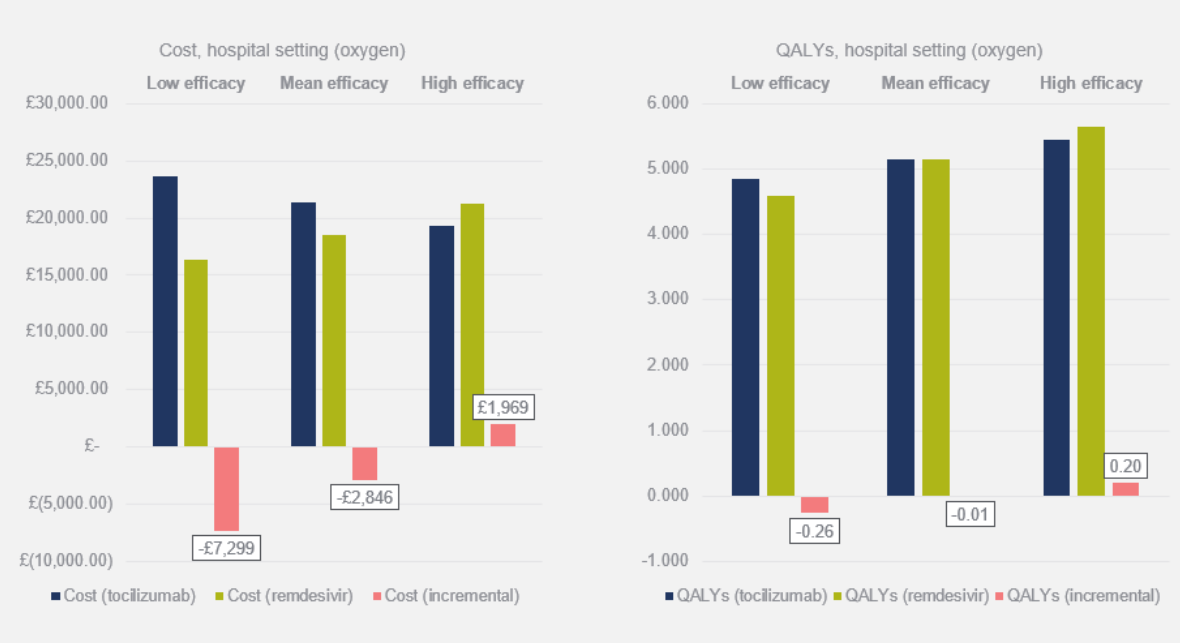
- In one instance the hazard ratio for remdesivir relative to placebo is applied as 1.00 with a confidence interval of 0 – 50 based purely on application of a continuity correction in both arms, due to zero events. Set against the other evidence both for remdesivir and other therapies this is implausible
- In the example of remdesivir versus tocilizumab it is apparent that minor rounding of point estimates and an assumption of the discharge HR then being in line with other parameters (rather than being dismissed as inconsequential and arbitrarily assumed equal to SoC), would remove any QALY difference between these active therapies.
- The comparison between remdesivir and tocilizumab is merely illustrative of the general point that arbitrary assumptions and minor numerical differences may overstate any apparent differences between therapy options.
- As a result of the limitations of the analyses, even though tocilizumab, baricitinib and remdesivir are similarly cost-effective the Committee does not recommend remdesivir. The similarity in cost-effectiveness between the three treatments can easily be seen when looking at **Figure below, which shows that no meaningful differentiation can be made between tocilizumab, baricitinib and remdesivir regarding cost-effectiveness when all efficacy scenarios are considered.**

	Figure 6: Cost-effectiveness comparison of baricitinib, tocilizumab, remdesivir and baricitinib/remdesivir across efficacy scenarios using the EAG model version 5 – hospital setting, with oxygen 
6	**Important evidence relating to time to discharge (TTD) from hospital and mortality for remdesivir has been overlooked and should be incorporated into the economic model to inform decision making** 6.1 Time to discharge The EAG model does not consider data from the ACTT-1 trial (8) on time to discharge (TTD) which clearly shows that remdesivir patients have a reduced TTD compared to placebo (median difference = 4 days earlier discharge). Instead, the EAG model assumed that time to discharge (TTD) for remdesivir was equal to SoC in hospitalised patients. This is especially confusing as the EAG applied a hazard ratio (HR) to the SoC TTD curve in their model, thereby conferring an advantage in costs and quality adjusted life years (QALYs) for one treatment, while ignoring this for others. Gilead has therefore amended version 5 of the EAG model to account for the improved TTD for remdesivir over SoC. This has been done by modifying P10:P2511 in the "Trace_Hosp_Oxy_Rem" as well as the "Trace Hosp NoOxy Rem" sheet to apply the hazard ratio (i.e. "HR_Rdv_TTDischarge") so that:

=MIN(1-(OFFSET(INDIRECT("Ttdischarge_SoC"&A2),E10,0)^HR_Rdv_TTDischarge),N10)

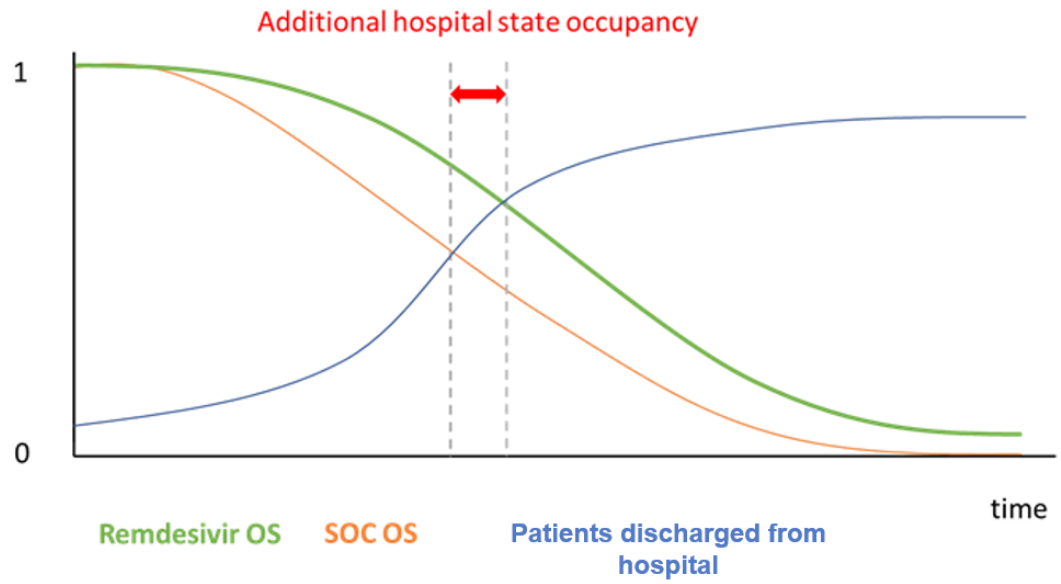
Applying the favourable HR (=1.27) for remdesivir from the ACTT-1 trial (8) in the EAG model improves both costs and QALYs for remdesivir. As visualized in Figure below applying a HR for TTD yields lower cost for remdesivir compared to tocilizumab in two out of three scenarios whereas efficacy in terms of QALYs seems even between the two treatments, with a marginal difference in favour of tocilizumab in the low efficacy setting and a similar marginal difference in favour of remdesivir in the high efficacy scenario.

Figure 7: Comparison of costs and QALYs for remdesivir and tocilizumab across efficacy scenarios in the hospital setting (with oxygen) using the amended EAG model



The way in which the EAG decided to model TTD also raises some concerns with regards to the validity of the cost-effectiveness model, due to the interaction between TTD and survival in the hospitalised setting. Assuming patients are discharged from hospital equally across treatments means that patients receiving treatments with better survival outcomes stay in hospital for longer due to the way in which health state occupancy is set up in the EAG model. This results in an assumption that having patients die quicker is beneficial (as it saves costs due to reduces health state occupancy in costly hospital states), therefore penalizing treatments with better survival outcomes.

Figure 8: Interaction between hospital discharge and survival in the EAG model (illustrative)



6.2 Mortality / time to death

As explained in section 3.3 of this response, Gilead has recreated the meta-analysis results used to inform the time to death outcome for remdesivir. Furthermore, Gilead has incorporated these updated meta-analysis results into the latest version of the EAG model (v5.1) and shared this amended model with NICE as additional evidence.

As can be seen from Figure 9 below remdesivir is already highly cost-effective in 5 out of 9 scenario & setting combinations using the EAG model v5.1, indicating a strong likelihood of representing good value for money.

Figure 9: ICER (remdesivir against SOC) across efficacy scenarios and settings

Efficacy scenario	Community	Hospital (no oxygen)	Hospital (with oxygen)
High	£25,475.77	£7,442.90	£10,287.43
Medium	£96,485.01	£10,113.61	£10,995.68
Low	Dominated	Dominated	Dominated
Source: EAG model v5.1 (no Gilead amendments)			

When applying the updated NMA analysis for time to death, the results for remdesivir become even more favourable, as now 6 out of 9 scenario & setting combinations demonstrate high cost-effectiveness against SOC, with one more scenario & setting combination being reasonably cost-effective as shown in Figure 10 below. In the hospital setting (with oxygen) remdesivir is now cost-effective across all efficacy scenarios.

Figure 10: ICER (remdesivir against SOC) across efficacy scenarios and settings, using updated NMA results

Efficacy scenario	Community	Hospital (no oxygen)	Hospital (with oxygen)
High	£25,475.77	£9,615.45	£10,702.80
Medium	£96,485.01	£13,196.43	£12,630.49
Low	Dominated	£33,274.32	£25,235.00
Source: EAG model v5.1 EAG model v5.1 (with Gilead amendments) - includes updated meta-analysis			

Combining the results of the updated meta-analysis with the reasonable assumption that remdesivir patients are being discharged earlier from hospital compared to SOC patients, results for remdesivir against SOC become extremely cost-effective across efficacy scenarios in both hospital settings (no oxygen and oxygen) as demonstrated in Figure 11 below.

Figure 11: ICER (remdesivir against SOC) across efficacy scenarios and settings, using updated NMA results (SOLIDARITY overall population) and time to discharge hazard ration (1.27) for remdesivir

Efficacy scenario	Community	Hospital (no oxygen)	Hospital (with oxygen)
High	£25,475.77	£2,180.12	£524.42
Mean	£96,485.01	£2,290.05	Dominant
Low	Dominated	£3,318.92	Dominant
Source: EAG model v5.1 (with Gilead amendments) - includes updated meta-analysis and updated time to discharge assumptions			

As can be seen in Figure 11 above, remdesivir is dominant compared to SOC in the hospital setting even when considering the low efficacy scenario.

Similar results can be seen when considering subgroups from the SOLIDARITY trial (i.e. “Oxygen no ventilation” and “No Oxygen”) and re-running the meta-analysis using these estimates. A more detailed summary of the cost-effectiveness results compared to SOC has been provided to NICE in an Excel file.

6.3 Reduced hospital length of stay & lower costs with remdesivir

Various studies have shown that the use of remdesivir significantly reduces the hospital LOS which translates to cost-savings for national healthcare systems. (15,16)

As pointed out by Ruggeri et al. (17) in their conclusion “*remdesivir has the potential to reduce the negative effects of the Coronavirus disease, improving patient conditions and reducing death tolls, and can also save scarce healthcare resources during this pandemic, resulting in a shorter hospital stay and fewer ICU admissions*”.

7	**The committee has not taken all the clinical evidence into account** This Draft Guidance does not reflect the full body of data available, nor is it in line with the broad range of evidence-based guidelines from around the world including the European Society of Clinical Microbiology and Infectious Diseases (18), the World Health Organisation (WHO) (11), the U.S. National Institute of Health (19), and the NICE COVID-19 Rapid Guideline. (20) As part of this response to the Draft Guidance we are submitting additional analyses to cover aspects of cost-effectiveness as well as clinical effectiveness (intervention/comparators/ outcomes). NICE's Draft Guidance states that remdesivir's efficacy is uncertain or no better than the Standard of Care is erroneous and inappropriate given remdesivir's marketing authorisation and the clinical evidence submitted by Gilead to date. According to its licensed indication (21), remdesivir is approved for the treatment of both patients with non-severe and severe disease, for adult patients requiring supplemental oxygen (low-or high-flow oxygen or other non-invasive ventilation) and for paediatric patients below 12 years. Remdesivir is the only anti-viral treatment approved for these indications. Remdesivir is an important anti-viral option for helping hospitalised patients to recover significantly faster and reduce the likelihood of disease progression and mortality. 7.1 <u>NICE has misinterpreted the phases in the natural history of COVID-19 and underestimated the clinical benefits of antivirals across the disease spectrum of COVID-19</u> Gilead considers that the summaries of clinical effectiveness in the Draft Guidance are not reasonable. NICE has given insufficient consideration to segmenting the patient population according to oxygen use within the hospital setting. This split does not reflect sequencing in clinical practice or recognise the key stages of disease progression. It also does not reflect the correct wording of the regulatory labels of the various interventions, despite signposting to these at the beginning of the document. The use of the different therapies considered in this MTA at different stages of disease progression is important to understand. For example, the use of therapies with an immunomodulatory mode of action too early (such as in a patient not yet requiring supplementary oxygen support) could be detrimental to a patient's outcomes as outlined in the RECOVERY trial for dexamethasone (22). NICE sees these treatments as mutually exclusive in the Draft Guidance, and discounts this clinically important point when assessing clinical and cost effectiveness of the therapies, even though NICE's living guidelines for the management of COVID-19 splits patient groups in hospital by oxygen usage. In section 3.12 of the Draft Guidance, the Committee notes that it considers remdesivir's mechanism of action may not fit the stated treatment aims, because antiviral activity would

be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation.

The natural history of progression with SARS-CoV-2 includes a viral replication phase and an inflammatory phase, as demonstrated by this graphic. Contrary to the inference made by the Draft Guidance, these phases overlap – that is, they do not stop at the point of hospitalization. Given that viral replication is a key driving factor for the systemic inflammatory response among patients with severe COVID-19, the antiviral mechanism of action of remdesivir is a critical component of the multifaceted care of patients with severe disease. (23–25)

We acknowledge the majority of clinical benefit for antivirals will be felt in the early phases of COVID-19 infection, as evidenced by the PINETREE phase 3 study in which remdesivir vs placebo led to 87% relative risk reduction in hospitalisation or all cause death (26). However, there is a significant group of individuals for whom access to antivirals in hospital settings has proven efficacy in preventing mortality and disease progression, and an increasing body of evidence regarding prevention of 'long COVID' sequelae. Those patients who are hospitalised at high risk of disease progression are not accommodated equitably, or given due consideration within the current draft NICE guidance.

In addition, Gilead requests that the Committee reconsiders including the results from the SOLIDARITY trial, which – as stated in the Draft Guidance itself – "*would have likely impacted the final conclusions for remdesivir*".

7.2 Combination therapies which include remdesivir are recommended for treating patients with severe COVID-19

Infection with SARS-CoV-2 includes a viral phase and an inflammatory phase. Patients with severe and critical COVID-19 can have prolonged viral phase (24) with uncontrolled inflammatory response. Combination therapies are recommended by guidelines for treating patients with severe COVID-19 (11,18–20,27) – RCTs and RWE also demonstrate that remdesivir provides additional benefits when used in combination with immunomodulators – these treatments appear mutually exclusive in the NICE Draft Guidance, which negates evidence-based practice.

7.2.1 Remdesivir in combination with Dexamethasone demonstrates better outcomes than Dexamethasone alone

- Remdesivir provides significant survival benefits in patients on low-flow O_2 when used in combination with Dexamethasone (Dex) compared to Dex alone. This is based on a retrospective, multicenter study of remdesivir in hospitalized adults (28)

- Prospective, sequential controlled cohort study of remdesivir + DEX vs DEX alone in patients requiring non-invasive O2 support - Remdesivir/dexamethasone treatment is associated with significant reduction in mortality, length of

	hospitalization, and faster SARS-CoV-2 clearance, compared to dexamethasone alone. (29) • Nationwide, population-based cohort study of 30-day mortality among 1,694 patients treated with remdesivir+DEX+SoC compared to 1,053 patients who received SoC alone - Treatment of moderate to severe COVID-19 with remdesivir and dexamethasone was associated with significantly reduced 30-day mortality and need of MV compared to SoC treatment. (30) • Additional observational data which shows that treatment with remdesivir, dexamethasone, or both, in patients hospitalized with COVID-19 was associated with a reduction in mortality and a reduced incidence of neurological complications in an additive manner (31) • In hospitalized patients with COVID-19 pneumonia receiving low-flow oxygen and dexamethasone, in-hospital death rates and rates of transfer to the intensive care unit or death were 8.9 and 17.8% (HR: 0.46, 95% CI: 0.21–1.02, p = 0.06) and 20.0 and 35.6% with and without remdesivir, respectively (HR: 0.45, 95% CI: 0.23–0.89, p = 0.015) (32) • In a retrospective, cohort study - remdesivir + DEX was associated with faster time to clinical improvement, faster development of IgG antibodies, & decreased in-hospital death when initiated prior to, or simultaneously with Dex vs late introduction or no remdesivir exposure (33) 7.2.2. <u>Benefits of remdesivir + Immunomodulator vs remdesivir only or SoC</u> • ACTT-2 (34), an adaptive Phase 3 randomized, double-blind, PBO- controlled, multicenter global trial demonstrated remdesivir in combination with Baricitinib in hospitalized patients with COVID-19 not requiring ventilation (moderately ill) or those requiring non-invasive or invasive ventilation (severely ill), compared to remdesivir alone, significantly improved time to recovery from 8 days to 7 days. The greatest impact was seen in patients requiring high flow oxygen or non-invasive ventilation (shorter time to recovery from 18 days to 10 days) • Padilla et al. 2022 (35) – A cohort study of hospitalised patients who received Dex and Tocilizumab alone or Tocilizumab + remdesivir demonstrates that remdesivir decreases the risk of mortality and need for invasive mechanical ventilation (IMV) in patients with high viral loads and low-grade systemic inflammation • In a study of Baricitinib (36) with or without remdesivir in hospitalised patients with COVID-19, a retrospective sub-group analysis demonstrated Baricitinib + remdesivir was associated with a reduction in risk of death vs usual care RR 0.87 (95% CI 0.77-0.98, p-0.026)

7.3 The Committee ignored variant stability of remdesivir and inappropriately disregarded evidence that remdesivir is effective in treating COVID-19 variants, including Omicron

In section 3.10 of the Draft Guidance, the Committee acknowledges that *"Most of the clinical evidence is from studies done before the Omicron variant of SARS-CoV-2 (the virus that causes COVID-19). So there are significant uncertainties in the clinical evidence."* The Committee then arbitrarily (and without justification) introduces an approach for considering different mechanisms of action separately, (for anti-inflammatories, antivirals, and others), without supporting evidence for this approach.

The Committee notes that most evidence for the anti-inflammatories (baricitinib and tocilizumab) was generated during the earliest waves of the pandemic. It then concludes, without supporting evidence, that the relative benefit for anti-inflammatories can be generalised to later waves of the pandemic.

For antiviral treatments (molnupiravir, nirmatrelvir plus ritonavir, remdesivir), the Committee notes that there is observational data to support antiviral efficacy against later variants. Surprisingly, this evidence is apparently disregarded owing to a lack of systematic assessment. However, contrary to its approach with anti-inflammatory treatments, which are afforded an assumption of generalisability without supporting evidence, the Committee concludes that the evidence on antivirals is uncertain for newer variants. This piecemeal approach to the interpretation of available evidence is entirely at odds with NICE's preferred methods for decision making and is unfair and unreasonable.

In fact, Remdesivir has consistently been shown to have excellent stability to COVID-19 variants of concern (including Omicron), as highlighted in the publications below. Unlike some other therapies, which are affected by changes in the virus's spike protein, remdesivir targets the highly conserved viral RNA-dependent RNA polymerase (RdRp). No genetic changes in the RdRP region have been identified that are associated with remdesivir resistance.

7.3.1 Remdesivir as a candidate to treat future variants of concern:

- The Draft Guidance emphasises that key evidence for remdesivir cannot be considered as there is uncertainty around the effectiveness of remdesivir to treat the Omicron variant
- Given that it is impossible to predict which variant might rise to become the next big variant of concern it is unreasonable to exclude evidence on these grounds alone
- Both in vitro and RWE data support the claim that remdesivir is effective in treating variants of concern – remdesivir therefore is an ideal candidate to treat unknown future variants of concern

7.3.2 Supporting in vitro data:

- In vitro analyses support remdesivir's activity against variants of concern (VOC) including Alpha, Beta, Gamma, Delta and Omicron specific variants (37–39)
- Evidence that suggests that BA2.12.2, BA.4 and BA.5 share a similar level of susceptibility to remdesivir as the ancestral strains of SARS-CoV2 remdesivir retains antiviral potency against clinical isolates of all known SARS-CoV-2 variants in vitro (21,38,40–42). Figure 12 demonstrates that remdesivir is effective against all VOCs, with all VOCs showing no reduction in susceptibility.

Figure 12: Remdesivir antiviral activity against clinical isolates of SARS-CoV-2 variants

SARS-CoV-2 Lineage	Country First Identified	WHO Nomenclature	Key Substitutions	Remdesivir EC_{50} (nM)	Fold Change in Susceptibility	Change in Susceptibility
A	USA	-	-	110	1.0	
B.1.1.7	UK	Alpha	P323L	192	1.58	No change[a]
B.1.351	South Africa	Beta	P323L	141	1.19	No change[a]
P.1	Brazil	Gamma	P323L	97	0.82	No change[a]
B.1.617.2	India	Delta	P323L, G671S	70	0.59	No change[a]
B.1.429	USA	Epsilon	P323L	210	1.94	No change[a]
P.2	Brazil	Zeta	P323L	151	1.17	No change[a]
B.1.526	USA	Iota	P323L	258	2.33	No change[a]
B.1.617.1	India	Kappa	P323L	77	0.63	No change[a]
C.37	Peru	Lambda	P323L	175	1.37	No change[a]
B.1.1.529 BA.1 BA.2	South Africa	Omicron	 P323L P323L	 44 25	 0.45 0.23	 No change[a] No change[a]

a Fold-change: < 2.5- is not significant. All variants show no reduction in susceptibility.

7.3.3 Real world evidence during Omicron phase:

- A retrospective cohort study by Piccicacco et el. 2022 (43) showed that high risk patients receiving remdesivir had significantly lower likelihoods of a hospitalization and/or emergency department visits during the Omicron surge than those treated with sotrovimab (11% versus 23.3%; OR = 0.41, 95% CI = 0.17–0.95)
- A prospective cohort study showed that early outpatient treatment with remdesivir significantly reduces hospitalization or death by 84% in high-risk, majority immunosuppressed patients with Omicron variant COVID-19 compared to patients treated with SoC (44)
- In a prospective cohort study (45) in outpatient adult solid organ transplant recipients (n=192) during the Omicron BA.2 wave (April-May 2022), early remdesivir significantly decreased the hospitalisation rate compared with patients

	treated with SoC: adjusted hazard ratio 0.12 (95%CI: 0.03 to 0.057). The adjusted number needed to treat to prevent one hospitalization was 15.2 (95%CI: 13.6 to 31.4). No patient that received early remdesivir needed ICU admission or died. 7.4 Preliminary data shows treatment with remdesivir during the acute phase might lead to reduction in post-acute COVID-19 sequalae • In a prospective study of 449 hospitalised COVID-19 patients with at least 6 months follow up, analysis of the prevalence of risk factors for long COVID-19 syndrome demonstrated remdesivir treatment led to a 35.9% reduction in LCS rate (OR=0.641; 95% CI 0.413-0.782, p<0.001) (46) 7.5 Emerging studies are evaluating the potential impact of remdesivir on readmission rates in hospitalised patients • A multicentre cohort study (n=2062) demonstrated patients were less likely to be readmitted within 30 days if they received remdesivir relative to not receiving remdesivir; associations were strongest for those with mild disease (RR: 0.31; 95% CI: 0.13,0.75). Overall, being treated with remdesivir was associated with a 35% decrease in risk of dying in the 30-days following discharge (HR: 0.65; 95%: 0.49,0.85) (47)
8	**If published, the Draft Guidance will create treatment gaps and equality challenges** Because NICE has misunderstood the phases in the natural history of COVID-19, the Committee has failed to evaluate and make recommendations for treatment options across patient groups in hospital by oxygen use. The absurd gaps in treatment available for vulnerable patient groups demonstrates that NICE's conclusions are unreasonable. 8.1 The lack of any routine recommendation of antiviral provision in the hospital setting (especially for those requiring supplemental oxygen) goes against evidence based clinical practice and international guidelines, particularly for those at high risk of disease progression • If approved, the Draft Guidance would result in a clear treatment gap in the hospitalized setting for access to antivirals in appropriate patients in Ordinal scale categories 4 and above. • Gilead is concerned that the draft guidance from NICE does not recommend a treatment option for hospitalised patients who do not require supplemental oxygen. Tocilizumab is specifically recommended for patients who need supplemental oxygen or mechanical ventilation which therefore creates a treatment gap in the hospital setting. 8.1.1 Supporting evidence • Patients with severe COVID-19 can have prolonged viral replication (up to 4 weeks after symptom onset) and therefore require an anti-viral intervention. Studies such as the one conducted by Ali et al., 2022 (3) demonstrate that remdesivir has a significant effect on outcomes of importance to patients and health systems.

- As evidenced by the SOLIDARITY study (2), those treated with remdesivir who required oxygen (low or high flow) without mechanical ventilation, had a statistically significant reduction in mortality [remdesivir 14.6%, control 16.3% (RR 0.87; 95% CI 0.76-0.99, P=0.04]; this is consistent with the finding in ACTT-1 of mortality benefit in the group on low-flow oxygen (8). The SOLIDARITY data led to the WHO guidelines being updated to conditionally recommend remdesivir for both non-severe and severe COVID-19 patients. (11)
- Results of a systematic review and individual patient data meta-analysis showed reduced mortality with remdesivir in hospitalized COVID-19 patients requiring no or conventional oxygen support (48)

8.1.1 Real world data demonstrating the use of early remdesivir in hospitalized patients prevents progression/ reduces mortality:

- Remdesivir initiated upon hospital admission was associated with improved survival among patients with COVID-19, Multi-centre observational cohort in USA. (10)
- Paranjape et al., 2021 (49) – retrospective observational study (USA) of 475 patients hospitalized with COVID-19, concluded that early treatment led to improved clinical outcomes (shortened length of stay, reduced risk of MV and death). This effect was more pronounced in patients on lower oxygen requirement at baseline and was seen both with and without the use of corticosteroids.
- Wong CKH et al., 2022 (33) – nationwide retrospective cohort analysis of remdesivir vs control demonstrated significantly shorter time to clinical improvement, shorter length of hospital stay, lower risk of in-hospital death, reduced time to achieving low viral load and IgG antibody positivity.
- Garcia-Vidal C et al., 2021 (50) - Remdesivir was associated with 62% reduced odds of death versus SoC and its survival benefit increased with shorter duration of symptoms.

8.2 The Draft Guidance will create equality challenges for multiple groups, including those with protected characteristics, because of limited access to anti-viral treatment in the hospital setting

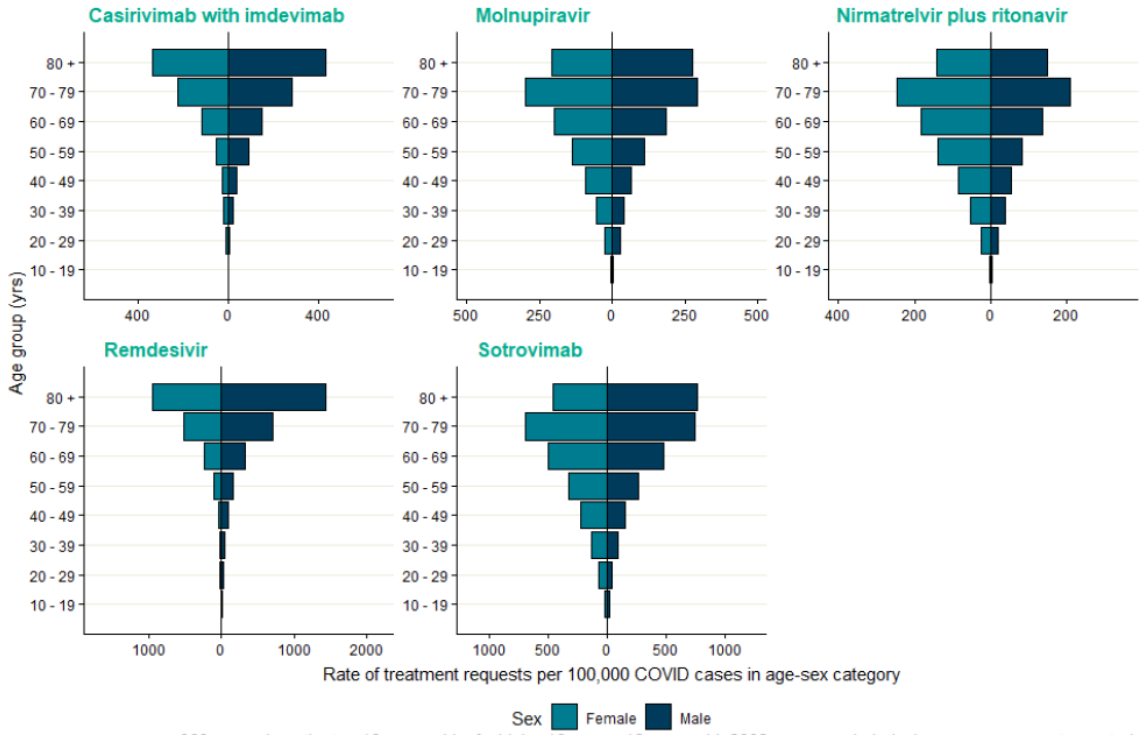
The NICE Draft Guidance implies that there may be no anti-viral COVID-19 therapies available for paediatric patients under 12 years of age. Given that age is a protected characteristic, not enabling access to the only antiviral licensed for this population will create an equality issue, because there will be no alternatives available to this group of patients.

In addition, Gilead is concerned about NICE recommending Paxlovid – a drug which has been found to have high contraindications (up to 15% of patients as reported by Lim et el. 2022 (51) and >37% for patients with comorbidities and 27% in older patients according to Hoertel et al. 2022 (52). According to Blueteq data there are higher rates of requests for remdesivir than other antivirals in patients >80 years of age (per 100,000 COVID-19 cases). This is the age with the highest death rates, which are likely to have high rates of co-morbidities, such as renal and hepatic impairment. Co-medications would likely prevent the

use of Paxlovid due to contra-indications. Gilead is concerned that these patients with potential contraindications to Paxlovid will not have appropriate access to COVID-19 antivirals if Paxlovid is the only recommended antiviral.

Gilead agrees with NICE's assessment that there are important equality considerations in this appraisal – many people are at an increased risk of hospitalisation and death, including people from Black, Asian and other minority ethnic family backgrounds. Importantly, data from ESPAUR (53) report that treatments used in hospitals, such as remdesivir, had a higher percentage of requests for patients in the most deprived IMDs (index multiple deprivation deciles). However, should the Draft Guidance be finalised, some patients will have no antiviral treatment option, creating equality and fairness challenges. It is NICE's obligation to treat people fairly and consider this alongside clinical and cost-effectiveness data when making a recommendation, consistent with section 3.1.4 of the Manual (1).

Figure 13: Rate of requests in Blueteq (per 100,000 COVID-19 cases) by therapeutic, age group and sex, from the English surveillance programme for antimicrobial utilisation and resistance ESPAUR Report 2021 to 2022



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NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

Draft Guidance comments form

Consultation on the Draft Guidance document – deadline for comments 5pm on Tuesday 6 December 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[GlaxoSmithKline]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted]
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The draft guidance only recommends nirmatrelvir/ritonavir for treating COVID-19 in adults with an increased risk for progression to severe COVID-19. The draft guidance does not recommend any other antiviral or antibody therapies, including sotrovimab. This guidance, if implemented, could result in significant health inequality and unmet need in vulnerable patient populations, by denying them access to sotrovimab – an efficacious and cost-effective therapy which has provided significant patient and public health benefits since being approved for use in this indication in late-2021. To date, over 38,000 doses of sotrovimab have been administered by COVID Medicines Delivery Units (CMDUs) in England in the past 11 months (NHS 2022a), demonstrating clinical confidence in sotrovimab's effectiveness, tolerability, and safety. Denying alternative COVID-19 therapeutics risks a lack of options for early treatment against future variants of the SARS-CoV-2 virus. GSK is concerned that the protective value of therapeutics with alternative and additional mechanisms of action to oral antivirals has not been considered. A pre-print publication by an academic group considers the possibility of a future 'Omicron-like event' resulting in the emergence of a brand-new variant (Peacock et al. 2022). They conclude that it is not clear how likely or commonly we should anticipate such events, but that it would seem prudent to have strategies in place in the event they do occur. GSK believes that having a range of medicines available for the early treatment of COVID-19 is one part of a strategy to

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	plan for any future Omicron-like disruptive evolutionary event where population health could be at significant risk. In addition, GSK is concerned that this specific MTA is out of process for NICE and has resulted in draft guidance that does not reflect the values and process that NICE typically follows for evaluations of health technologies. Our response to this consultation on the Draft Guidance document breaks down our concerns and comments into the following key topics: 1. Evidence for sotrovimab's sustained clinical effectiveness not being appropriately considered 2. Inequality and unmet need for patients at the highest risk of severe COVID-19 disease 3. Consideration of the most recent evidence for hospitalisation rates in those patients at the highest risk of severe COVID-19 disease 4. Validity of the External Assessment Group's low effectiveness scenario 5. Use of the CMDU micro-cost to estimate the administration costs for community treatments We also cross-reference to additional evidence and data presented in Appendix A, as requested by NICE. We believe these data and evidence are highly pertinent and request that they are carefully reviewed and considered by the NICE Committee and External Assessment Group to ensure that all high-quality and recent evidence are considered as part of this appraisal in a robust, transparent and systematic way. GSK requests that the Committee considers recommending sotrovimab in patients who are ineligible for (or contraindicated to) treatment with nirmatrelvir/ritonavir. These patients are at the highest risk of severe COVID-19 outcomes, including hospitalisation, and therefore sotrovimab offers an effective, well-tolerated, and cost-effective therapeutic option for these patients with significant unmet need and with no other community COVID-19 treatment options.
2	**GSK does not believe that all relevant evidence has been considered in producing this draft guidance**. <u>Clinical effectiveness of sotrovimab</u> While acknowledging that most of the clinical evidence is from studies that pre-date the Omicron variant, GSK does not agree that it is highly uncertain whether sotrovimab is effective against the Omicron variant. While the committee believed that the WHO's and FDA's recommendation against the use of sotrovimab was reasonable, this conclusion does not take into account the totality of available evidence. A recent independent publication from the Francis Crick Institute, the National Institute of Health Research, and University College London (UK) has challenged the negative assessment of sotrovimab by the WHO and urged a reassessment based on limitations and variability of in vitro data and lack of correlation to clinical effectiveness

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	in emerging real-world evidence (Wu et al. 2022). A subsequent publication has further underscored the need for care when extrapolating between neutralizing assays and the clinical efficacy of monoclonal antibodies (Cox et al. 2022). The correspondence in The Lancet by Owen and colleagues elaborate on the reasoning behind the WHO Therapeutics and COVID-19: Living Guideline's strong recommendation against sotrovimab which appears to be predominantly based on clinical pharmacology modelling approaches (Owen et al. 2022). GSK would like to reinforce the lack of a validated pharmacology model that can consistently and reliably correlate in vitro neutralization to predicted clinical efficacy. In the absence of a reliable correlation between in-vitro neutralization and efficacy, other data modalities – including pre-clinical in vivo and observational – are of particular relevance and importance. While recognising that observational studies can be subject to confounding bias, there are well established methodologies for removing and testing for confounding bias such as those employed by Zheng et al, using the OpenSAFELY data source in the UK (Zheng, Green, et al. 2022). To help inform the Appraisal Committee and the External Assessment Group of the latest real-world evidence supporting the continued clinical effectiveness of sotrovimab, GSK has conducted a systematic literature review of emerging observational data obtained during the Omicron BA.2 variant wave. This indicates that sotrovimab 500 mg IV retains clinical effectiveness in preventing severe outcomes, despite moderate reductions in in-vitro neutralization with Omicron BA.2. A recent pre-print publication of a study of the Discover Database in North-West London (Patel et al. 2022) reports clinical outcomes associated with sotrovimab by periods of Omicron BA.1, BA.2, and BA.5 (post-hoc exploratory analysis) predominance. These data, in conjunction with preclinical data supporting in vivo antiviral activity of sotrovimab against Omicron BA.2 and Omicron BA.5 viral variants in a hamster model of infection, reinforce the lack of validated models to predict correlates of efficacy based solely on in-vitro neutralization. This systematic literature review, and the preclinical data, are provided in Appendix A. The variability of in-vitro results based on cell lines and assay systems and a lack of models to incorporate the role of Fc effector function, which triggers the body's own innate immune cells to fight SARS-CoV-2 infection, may also contribute to inconsistency between clinical effect and in-vitro results. As of 30 November 2022, sotrovimab continues to neutralize all tested variants with moderate reductions in in-vitro neutralization for Omicron BA.2 sub-lineages; this contrasts with other clinical stage mAbs in which substitutions found in circulating variants are associated with significant reductions in susceptibility or a loss of activity. GSK continues to investigate the role of sotrovimab against viral variants with moderate reductions in susceptibility to better understand its ongoing role in early treatment of appropriate high-risk patients with COVID-19. It should also be noted that the recent increase in Omicron BA.2 sub-lineage variants suggests that the near future may be a mix of sub-lineage variants (sometimes referred to as the 'variant soup'), as opposed to one dominant variant. Therefore, assessing the effectiveness of an early-treatment in just one specific sub-lineage variant may be of limited value when considering the effectiveness of treatments across the population who are at risk of COVID-19 from many sub-lineage variants. This speaks again to the

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	importance of well-conducted and recent observational studies which do not discriminate by sub-lineage type. GSK asserts that the current WHO and FDA guidance, which advises against sotrovimab, disadvantages patients who have a high unmet need and are at high risk of COVID-19 progression. This includes those living with liver disease, renal disease, solid organ transplants, solid cancers, haematological diseases, and immune-mediated inflammatory disorders.(Green et al. 2022). [redacted] Consideration of neutralisation in-vitro assays, in isolation, does not provide a necessary robust and established causal relationship with clinical effectiveness. While in-vitro data has a role to play in estimating the possible effectiveness of antibody therapies in neutralising current variants of SARS-CoV-2, GSK notes the complexity of the evolving variant landscape and the difficulty in establishing a feasible clinical trial design, and the lack of a validated pharmacology model that could consistently and reliably correlate in-vitro neutralization to predicted clinical efficacy. Consequently, GSK continues to generate and monitor preclinical and RWE data to inform the ongoing benefit-risk assessment of sotrovimab. GSK is concerned that not all available evidence on the effectiveness of sotrovimab has been taken into consideration using formal systematic methods. This is contrary to NICE's clinical evidence hierarchy and guidance for the methodology of evidence synthesis. Further, we note the latest "NICE Health Technology Evaluations; The Manual" and agree that Real World Evidence is an important source of data when a randomised controlled trial (RCT) is not available or appropriate. <u>Dual Functionality of sotrovimab</u> As expressed in its Summary of Product Characteristics (SmPC) (GSK 2021), sotrovimab, unlike other COVID-19 therapeutic monoclonal antibodies (mAbs), is a dual-action, engineered human IgG1 mAb that binds to a conserved epitope on the spike protein receptor-binding domain of SARS-CoV-2. It was derived from a parent antibody (S309) isolated from memory B cells of a survivor of severe acute respiratory syndrome coronavirus (SARS-CoV) from 2003. Sotrovimab contains an "LS" mutation in the Fc region to prolong serum half-life. Furthermore, this mutation in the Fc region allows it to activate CD8+ T lymphocytes for immune destruction of infected cells. In Appendix A (Section 2.2), a full description with references to preclinical studies is provided to describe how the effect change associated with the cell-mediated immune response of sotrovimab's mechanism of action is not captured in in-vitro assays. As referenced in WHO and FDA recommendations, this is a plausible reason why in-vitro assays, in isolation, do not align with the RWE on sotrovimab's effectiveness. <u>Real World Evidence</u>

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	Consequently, we request that the EAG and Appraisal Committee carefully consider the importance and relevance of a study by the OpenSAFELY academic collaboration recently published in the BMJ on the continued effectiveness of sotrovimab versus molnupiravir in the Omicron-variant era (Zheng, Green, et al. 2022). The authors concluded that in routine care of adults in England with COVID-19 in the community and at high risk of severe outcomes from COVID-19, those who received sotrovimab were at a substantially lower risk of severe outcomes of COVID-19 compared with molnupiravir. The study was conducted at a time where BA.1 and BA.2 were the dominant variants and where moderate fold change in in-vitro neutralisation for BA.2 was observed, suggesting a lack of robust and predictable correlation between in-vitro neutralisation and clinical outcomes. A retrospective cohort study of individuals treated with sotrovimab with either BA.1 or BA.2 variant classification was recently published as a pre-print manuscript by a team from the UK Health Security Agency (Harman et al. 2022). A stratified Cox regression model was used by Harman and team to estimate the hazard ratios (HRs) of hospital admission with a length of stay of two or more days. The results suggest that the risk of hospital admission is similar between BA.1 and BA.2 cases treated with sotrovimab in the community. Additional evidence on sotrovimab clinical effectiveness provided by GSK, includes a pre-print publication of a study of the Discover Database in North-West London (Patel et al. 2022). This is a retrospective cohort study of non-hospitalized adult (≥18-year-old) patients who received early treatment for or were diagnosed with COVID-19 between December 1, 2021, and May 31, 2022. Outcomes (hospitalisation or death) were reported for 28 days after the COVID-19 diagnosis. Subgroup analyses were conducted in patients with advanced renal disease, those aged between 18–64 and ≥ 65 years, and by periods of Omicron BA.1, BA.2, and BA.5 (post-hoc exploratory analysis) predominance. Based on robust and consistent emerging observational data obtained during the Omicron BA.2 variant wave, sotrovimab retains clinical effectiveness, despite moderate reductions in in-vitro neutralization, against Omicron BA.2 and likely other similar Omicron BA.2 sub-lineage variants such as Omicron BA.5. These data, in conjunction with other preclinical data in Appendix A supporting in vivo antiviral activity of sotrovimab against Omicron BA.2 and Omicron BA.5 viral variants in a hamster model of infection, reinforce the lack of validated models to predict correlates of efficacy based solely on in-vitro neutralization. Furthermore, in vitro experiments have demonstrated sotrovimab's ability to induce antibody-dependent cellular cytotoxicity and antibody- dependent cellular phagocytosis which may contribute to overall antiviral activity in vivo (Cathcart et al. 2022; Case et al. 2022; Bruel et al. 2022). The variability of in-vitro results based on cell lines and assay systems and a lack of models to incorporate the role of Fc effector function may also contribute to inconsistency between clinical effect and in-vitro results. A total of 696 patients were prescribed sotrovimab, 337 were prescribed nirmatrelvir/ritonavir, 470 were prescribed molnupiravir, and 4,044 eligible high-risk untreated patients were included. Patients receiving sotrovimab were mostly older than 65 (36.9%), had at least three high-risk comorbidities (47.6%), and had severe renal disease (29.3%). The study shows, in total, 5/696 (0.7%) patients on sotrovimab,

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	<5/337 (0.3–1.2%) patients on nirmatrelvir/ritonavir, 10/470 (2.1%) patients on molnupiravir, and 114/4,044 (2.8%) untreated patients were hospitalised with COVID-19 as the primary diagnosis. Similar results were observed across all subgroups and during Omicron subvariant periods. A new study (Zheng, Campbell, et al. 2022), published as a pre-print on December 4, 2022, and hence not captured in our SLR, identified patients on kidney replacement therapy (KRT; dialysis and kidney transplantation) as being at the highest risk of severe outcomes from COVID-19. Using OpenSAFELY-TPP linked to the UK Renal Registry (UKRR) as a data source to identify patients on KRT, the author compared the clinical effectiveness of sotrovimab against molnupiravir in preventing severe outcomes in KRT patients in non-hospitalised settings. The author identified 2367 individuals as renal patients, of whom 1852 received sotrovimab treatment and 515 received molnupiravir treatment between December 16, 2021, and August 1, 2022, spanning the BA.2 and BA.5 predominance period. The study authors also conducted a complementary analysis using data from patients in the Scottish Renal Registry (SRR) treated with sotrovimab or molnupiravir, following similar analytical approaches. In England, over the 28 days of follow-up following the start of treatment, there were 38 cases (1.6%) of COVID-19-related hospitalizations or deaths, with 21 (1.1%) in the sotrovimab group and 17 (3.3%) in the molnupiravir group. Sotrovimab compared to molnupiravir was linked to a significantly decreased incidence of 28-day COVID-19-related hospitalisation or mortality in multiple-adjusted analyses (hazard ratio, HR=0.35, 95% CI: 0.17 to 0.71; P=0.004), with results remaining robust in sensitivity analyses. In the SRR cohort, over the 28 days of follow-up following the start of treatment with sotrovimab (n = 723) or molnupiravir (n = 270), there were 19 cases (1.9%) of COVID-19 related hospitalizations or deaths. In multiple-adjusted analyses, sotrovimab showed a trend toward lower risk of 28-day COVID-19 related hospitalisation/death than treatment with molnupiravir (HR=0.40, 95% CI: 0.13 to 1.21; P=0.106). In both datasets, sotrovimab had no evidence of association with other hospitalisation or death compared with molnupiravir (HRs ranging from 0.73-1.20; P>0.05). GSK also conducted a retrospective cohort study (data on file, see summary on section 2.4.1 of Appendix A) using data from the Hospital Episode Statistics (HES) database in England. This study provides useful data on the clinical characteristics and hospitalisation rates over time of people who have received sotrovimab and were hospitalised due to COVID-19. [redacted]

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3	Inequality and Unmet Need The Committee's decision, as indicated in the draft guidance, results in no therapeutic options being available to patients for whom nirmatrelvir/ritonavir cannot be prescribed. **This will disadvantage people who are the most vulnerable to experiencing the severe outcomes of COVID-19.** As per the latest SmPC for nirmatrelvir/ritonavir (Pfizer 2021), treatment is contraindicated in patients with severe renal impairment and contraindicated in patients with severe hepatic impairment. It is also contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions. Nirmatrelvir/ritonavir is also contraindicated with medicinal products that are potent CYP3A inducers where significantly reduced plasma nirmatrelvir/ritonavir concentrations may be associated with the potential for loss of virologic response and possible resistance. The clinical experts at the Committee meeting stated that patients are often prescribed mAbs when oral antiviral therapy is contraindicated or because drug interactions are likely. Generally, this arises in the most vulnerable patients and was similarly reflected in an OpenSAFELY observational study, which reported the clinical characteristics of recipients of COVID-19 therapeutics in non-hospitalised settings (Green et al. 2022). According to this study, sotrovimab is more frequently administered than nirmatrelvir/ritonavir in patients with immune-mediated inflammatory disorders, solid cancer, haematological diseases, stem cell transplant recipients, renal disease, liver disease, and immunosuppression due to HIV or AIDS. Table 1 within Green et al. 2022 shows that, holistically, sotrovimab is prescribed for 55% of this highest-risk group, while nirmatrelvir/ritonavir is only prescribed in 18% of cases and molnupiravir in 27%. Another published observational study (Gahir et al. 2022) conducted by a team at University College London Hospital (UCLH), UK, and presented at the British Infection Association (BIA) identified 872 COVID-19 treatment-eligible patients who attended the COVID Medicine Delivery Unit (CMDU) in North Central London (NCL) between 10 February and 2 May 2022. It was estimated that 36% of treatment-eligible patients could not take nirmatrelvir/ritonavir due to contraindications, and 5% of those who began treatment with nirmatrelvir/ritonavir had to discontinue the treatment. Research shows that key patient groups for whom nirmatrelvir/ritonavir is contraindicated are at the highest risk of experiencing severe COVID-19, for instance, kidney replacement therapy (KRT; dialysis and kidney transplantation) patients were identified (Zheng, Campbell, et al. 2022) as having the worst prognosis for COVID-19 infections. As a result, this draft guidance may increase health inequalities compared with the current situation where several treatment options are available through the Interim Clinical Commissioning Policy (NHS 2022b). It is important to acknowledge that though the epidemiology of the COVID-19 pandemic has changed in the general population over time, the risks of severe outcomes for groups of people considered to be at the highest risk of severe infection remain very high. According to a retrospective study (Nab et al. 2022) conducted for NHS England, standardised death rates in transplant recipients remained constant across successive waves at 10 per 1,000 person-years. There was also only a small decrease in the mortality rate between the waves of cases in people with kidney

	disease, haematological malignancies or other conditions associated with immunosuppression. Another observational study (Zerbit et al. 2022) found that of the 57 COVID-19 vaccinated patients with haematological malignancies diagnosed with SARS-CoV-2 infection, 22.8% (n = 13) were hospitalised for a severe form of COVID-19 and 23% (n = 3) of the hospitalised patients died. Further analysis shows patients receiving T-cell or B-cell immunotherapy accounted for the totality of hospitalisation cases (*n* = 13). It has also been shown by (Tenforde et al. 2021)), that vaccine effectiveness is lower in the immunocompromised group (59.2%; 95% CI: 11.9 to 81.1%) than in those without immunosuppression (91.3%; 95% CI: 85.5 to 94.7%). People who are immunocompromised are four times more likely to die of COVID-19 and have prolonged symptoms that can last longer. The UKHSA publication on the risks and outcomes of COVID-19 (PHE 2020) indicated that the outcomes due to COVID-19 are largely influenced by ethnic and socioeconomic disparities. According to the data, people of ethnic minorities and those living in deprived areas have higher rates of diagnosis and death. People of Bangladeshi ethnicity had around twice the risk of death as people of white British ethnicity. When compared to White Britons, people of Chinese, Indian, Pakistani, Other Asian, Black Caribbean, and other black ethnicities had a 10 to 50% higher risk of death. The data also showed that mortality rates from COVID-19 in the most deprived areas were more than double those in the least deprived areas, for both males and females. This is greater than the inequality seen in mortality rates in pre-pandemic years, indicating greater inequality in outcomes of COVID-19. A more recent UKHSA pre-print publication validating the QCovid4 risk prediction algorithm (Hippisley-Cox et al. 2022) reports significantly elevated mortality hazard ratios (versus high-risk patients prioritised for COVID-19 therapeutics) for men for several conditions. These include the following conditions: kidney transplant (6.1-fold increase); Down's syndrome (4.9-fold); radiotherapy (3.1-fold); type 1 diabetes (3.4-fold); chemotherapy grade A (3.8-fold), grade B (5.8-fold); grade C (10.9-fold); solid organ transplant ever (2.4-fold); dementia (1.62-fold); Parkinson's disease (2.2-fold); liver cirrhosis (2.5-fold). Other conditions associated with increased COVID-19 mortality included learning disability, chronic kidney disease (stages 4 and 5), blood cancer, respiratory cancer, immunosuppressants use, oral steroids use, COPD, coronary heart disease, stroke, atrial fibrillation, heart failure, thromboembolism, rheumatoid/SLE, schizophrenia/bipolar disease sickle cell/HIV/SCID; type 2 diabetes. Results were similar in the model in women, and also when evaluating the risk of COVID-19 hospital admission. Treatment with nirmatrelvir/ritonavir may be contraindicated for a significant number of patients living with many of these conditions. A large proportion of the deprived community and black, Asian, and minority ethnic people are more likely to suffer from co-morbidity, putting them at the highest risk of severe COVID-19. An academic study using NHS data concluded that *"…individuals from a BAME background are more likely to be diagnosed with COVID-19 and more likely to be admitted to hospital and intensive care, compared to the general population of England."* (Alaa et al. 2020). It should be noted that the UKHSA study (Hippisley-Cox et al. 2022) suggests that health inequalities due to COVID-19 attributed to ethnicity may be decreasing, due to improved vaccination status and public health services.

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	Not recommending sotrovimab has the potential to disadvantage those who are most vulnerable to COVID-19 infection, as well as most vulnerable to the outcomes of COVID-19 infection Therefore, we request that the Committee recommends sotrovimab to ensure that the most vulnerable patient groups continue to be protected from the severe outcomes associated with COVID-19. Future sub-group analysis in a nirmatrelvir/ritonavir ineligible population should account for the additional increased risk of severe outcomes that these highest-risk patients can experience. Also, GSK asks the Committee to give particular consideration to the fact that recommending more than one treatment for COVID-19 will help reduce health inequalities due to COVID-19, a key principle that is considered important for all NICE guidance (NICE).
4	<u>Hospitalisation rate</u> GSK is aligned with the Committee on the definition of a high-risk population being those as defined in the McInnes report (DHSC 2022), instead of the inclusion/exclusion criteria for study participants in the PANORAMIC study (Butler 2022). The patient population as defined in the McInnes report represents those who have most to benefit from monoclonal antibodies due to the severity of their clinical outcomes if not treated once symptomatic with COVID-19. We do not believe that the outcomes from the PANORAMIC trial should be the referenced base case hospitalisation rate when evaluating this high-risk group. The hospitalisation rate in PANORAMIC is artificially low, as noted by the Committee, because the study excluded participants at the higher end of the risk group. Consequently, conducting cost effectiveness analyses based on the PANORAMIC-defined high-risk definition undervalues treatments used in patients with the highest risk of hospitalisation and other severe outcomes from COVID-19 infection. Furthermore, such patients are often ineligible for nirmatrelvir/ritonavir (Green et al. 2022). It is notable that the hospitalisation rate in the highest-risk sub-groups, where sotrovimab is primarily used, is consistently higher than in both the general population and the PANORAMIC-defined "high-risk" populations. The relevant hospitalisation rates in these patient groups range from 7.69% in chronic lymphocytic leukaemia patients to 26.42% in haemato-oncology patients (see the targeted literature review, section 2.5 of Appendix A). According to an OpenSAFELY study (Nab et al. 2022), the prognosis for the highest risk groups (McInnes population) is much poorer regardless of variants, particularly for immunocompromised or transplant recipients, and has not changed since the pandemic began. We request that the Committee reconsiders these elevated risks and especially for people ineligible for nirmatrelvir/ritonavir. In particular their baseline hospitalisation rates merit closer reconsideration. The targeted literature review (section 2.5. of Appendix A) reports high baseline hospitalisation rates in Omicron-era studies with a sample size greater than 30 for untreated patients with COVID-19 and who are in long term care (4.51% hospitalisation rate, (Krutikov et al. 2022)); kidney transplant recipients (20.83%, (Gleeson et al. 2022)); chronic lymphocytic leukaemia patients (7.69%,(Parry et al. 2022)); and haematological malignancy patients (26.42%,(Bradwell et al. 2022)). A more recent published observational study that was not identified in the targeted review (Zerbit et al. 2022) found that of the 57 COVID-19 vaccinated patients with haematological malignancies diagnosed with SARS-CoV-2

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	infection, 22.8% (n = 13) were hospitalised for a severe form of COVID-19 and 23% (n = 3) of the hospitalised patients died. **Based on these published studies during the Omicron-era in relevant clinical sub-groups at the highest-risk of hospitalisation, a baseline hospitalisation rate of at least 4.51% is warranted.** Future sub-group analysis in a nirmatrelvir/ritonavir ineligible population should account for the significantly increased risk of severe outcomes that these highest-risk patients can experience, including the high baseline hospitalisation rates demonstrated in the targeted literature review and reported above (see Section 2.5 in Appendix A).
5	<u>Validity of the EAG's low effectiveness scenario</u> The EAG conducts a low effectiveness scenario to inform the Committee regarding the sensitivity of the model results to key parameter inputs, but acknowledges the limitations associated with these scenarios in terms of how they are modelled. The low effectiveness scenario is informed from the upper end of the confidence intervals for the two clinical trial endpoints used in the model – hospitalisation and mortality. However, many of the studies were not powered to detect a statistically significant difference in mortality, and therefore low numbers of events can result in a very large confidence interval for this endpoint. It should be noted that RWE for sotrovimab has demonstrated a reduction in COVID-19 related mortality (Zheng, Green, et al. 2022; Cheng et al. 2022). For several treatments, including sotrovimab, the low effectiveness scenario results are an illogical scenario where sotrovimab reduces hospitalisation but increases mortality, when compared to standard of care. We believe this scenario is invalid and does not appropriately inform the Committee of the uncertainty associated with the clinical endpoints. If these scenarios are necessary for Committee consideration, then we recommend that in all modelled scenarios the effectiveness in terms of a hazard ratio for mortality is capped at 1 (e.g., equivalent to standard of care) to avoid counter-intuitive results where a scenario may be simulated with a treatment reducing hospitalisation but increase mortality.
6	<u>Use of CMDU micro-cost for the administration cost for community treatment</u> We disagree with the Committee's assumption that the CMDU micro-cost, as opposed to an NHS reference cost, is a more accurate reflection of the cost to be borne by the NHS when community treatments are implemented as part of routine NHS practice in 2023. The latest NHS England Commissioning policy (NHS 2022b) explicitly states that the CMDU's will be decommissioned and models of care will be established so recommended community treatments for COVID-19 are administered as part of routine NHS delivery. We do not agree that the true cost to the NHS of delivery of intravenous treatments will be close to £800, and this high cost reflects the resources required to design, establish and staff a new service during the height of the pandemic (which represents a sunk cost). GSK believes that regular NHS reference costs for intravenous administration of treatments will much more accurately reflect the true cost of intravenous community COVID-19 therapies. Alternatively, it may be appropriate to consider the variable cost of each treatment administration by the CMDUs in the most recent months, in effect removing the sunk cost associated at the start of the pandemic with staffing and scaling up the CMDUs.

Insert extra rows as needed

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Merck Sharp & Dohme (UK) limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Executive summary	Thank you for the opportunity to comment on the appraisal consultation document (ACD). MSD acknowledges the challenge facing NICE: to make a timely, future-proof, endemic-setting recommendation for a high-risk population - that is still being defined - based on limited, yet highly heterogenous early pandemic data from different geographies, variants, vaccination statuses and patient populations. **Unfortunately, the draft guidance is not a sound and suitable basis for guidance to the NHS on COVID-19 treatments.** Should nirmatrelvir with ritonavir be the only treatment option recommended in the community setting, some highly vulnerable, high-risk patients will be left without any effective treatment option. The pragmatic methodology employed in this MTA impacts the technologies differently, leading to inconsistent and biased estimates against some, but not all, treatments. Additionally, equality and equity challenges in the UK health system are likely to be amplified, not mitigated, by the current guidance. Not recommending a treatment option for the many patients in the community setting who are contraindicated or have unmanageable drug–drug interactions (DDIs) with the other community-based oral treatment option, leaves some of the highest-risk patients with no community-based treatment option. This includes patients that are older, disabled, or from an ethnic minority background as is described in 2.34 of the ACD. MSD's product molnupiravir (Lagevrio) is not recommended in this ACD, despite evidence presented on its clinical and cost effectiveness in the management of COVID-19, particularly in those at highest risk of progression to severe disease. Recent real-world data from Australia, in a population of 27,000 COVID-19 patients aged 70 years and older, report molnupiravir substantially reduced risk of hospitalisation (26%) and risk of death (54%).[1] PBAC has offered to share with NICE what information it has on this dataset (personal communication). The inclusion of the PANORAMIC data in this Technology Appraisal (TA) drives this negative decision. While PANORAMIC is a well-designed and well-conducted study, it collected data in a fundamentally different patient population to that of relevance to this TA. Specifically, the patient population in PANORAMIC is not at high-risk of developing severe disease. **PANORAMIC should not be included in this TA either to estimate (background) hospitalisation rates or provide efficacy estimates for molnupiravir**. The application of the same high administration costs for molnupiravir and nirmatrelvir with ritonavir in the economic model unnecessarily increases the cost and, therefore, cost-effectiveness of molnupiravir, a treatment that is straightforward to prescribe, is not associated with any DDIs, and could easily be deployed in the primary care setting. In assigning this high cost, the value of molnupiravir is not accurately captured. Equally, the cost of prescribing nirmatrelvir with ritonavir is underestimated due to the time needed to ensure it is not prescribed to patients that are contraindicated or might have drug–drug interactions (DDIs). The patient population relevant to this TA were predominantly treated by the COVID Medicines Delivery Units (CMDUs), therefore data and insights from these centres are more appropriate. Applying a hospitalisation rate (2.79%) with the mean efficacy estimate for molnupiravir from the meta-analysis excluding PANORAMIC results in an estimated ICER of £[redacted] (Appraisal Committee's [AC]) or £[redacted]/QALY gained versus SoC (company's preferred assumptions; reduced administration costs and mean efficacy only). The cost-effectiveness of molnupiravir versus SoC increases when higher hospitalisation rates are explored based on CMDU expert opinion. [redacted]

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	Based on the above analyses, described in more detail below, molnupiravir is cost-effective in a number of plausible scenarios, especially when no alternative treatment options exist for high-risk patients. On this basis, we request the AC reviews its decision and so prevents highly vulnerable patients, including those with disabilities and those from different ethnic backgrounds, losing access to a well-tolerated and effective COVID-19 treatment with a straightforward prescribing and dosing regimen that could be deployed in the primary care setting. **Some patients require rapid treatment in the community setting due to clinical considerations including older aged (as example >65years), immunosuppression, diabetes, those with chronic kidney disease (CKD), those receiving treatment for cancer, those vaccinated but not mounting an immune response, and those who are vaccine contraindicated. These high-risk patients may be left without viable treatment options for mild/moderate COVID-19 treatment as per the current draft guidance recommendations.** The economic model excludes all social benefits associated with oral treatments administered in the community, as discussed in 3.23 of the ACD. For example, reduced sickness amongst the NHS workforce, avoiding the requirement for patients to travel to the hospital and patient preference for treatment at home. The model fails to accurately cost DDIs associated with nirmatrelvir with ritonavir. It has been clinically validated that prescribing nirmatrelvir with ritonavir safely (taking account of contraindications and DDIs) would take substantially longer than prescribing molnupiravir. The current model also omits any (rare) DDI events. These omissions disadvantage molnupiravir, which has no known DDIs or contraindications. We disagree that consideration of these factors is outside the NICE Reference Case, as discussed in issue 9 below. The draft guidance fails to consider that future variants might be associated with higher hospitalisation rates, which has a considerable impact on cost-effectiveness. The company reports scenarios within the economic model varying hospitalisation rates that are more representative of the high-risk population. These scenarios should be considered in any final NICE guidance to prevent the guidance being redundant. MSD has carried out alternative exploratory analyses to ascertain the cost-effectiveness of molnupiravir across a range of different assumptions. The company has demonstrated how realistic deployment costs for molnupiravir impact cost-effectiveness (See Appendix 2). It is clear that the deployment cost applied has a large impact on the cost-effectiveness in alternative scenarios and we advocate for its change prior to issuing any final guidance. We therefore urge the AC to reconsider the evidence and make a positive final guidance recommendation for molnupiravir to ensure that high-risk patients can benefit from multiple alternative community treatment options.
Clinical evidence considerations	
1: Patients in PANORAMIC are at lower risk of developing severe disease compared with the McInnes high-risk population	The ACD concludes that the definition for high-risk of progressing to severe disease with COVID-19 presented in the McInnes report should be used to define the relevant patient population for this MTA. The McInnes definition does not include age as a risk factor, despite clear evidence demonstrating increasing risk of hospitalisation and severe disease with increasing age.[2] McInnes is the definition used operationally in the UK in the CMDUs to triage the highest-risk patients for treatment. The MTA, in line with usual NICE methods, should only include studies

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or the population in the MOVe-OUT RCT.	that report data for a similar population at high risk of disease progression, or statistical methods should be used to adjust for the considerable clinical heterogeneity in study populations. Molnupiravir was granted its marketing authorisation based on the results of the MOVe-OUT clinical trial.[3] The inclusion criteria for the PANORAMIC[4] study do not align with either the inclusion criteria for MOVe-OUT or with the marketing authorisation for molnupiravir: inclusion criteria for MOVe-OUT and PANORAMIC are available in Appendix 1. In brief, to be eligible for enrolment into PANORAMIC, a patient had to be aged 50 years or over, or 18 years or over with a specified pre-existing condition. By contrast, presence of a risk factor for progression to severe disease, irrespective of age, was an inclusion criterion for MOVe-OUT, with one factor defined as age of 60 years or over. The difference between the inclusion criteria from the two studies means that patients at lower risk of developing severe COVID-19 were eligible for enrolment in PANORAMIC and could be classified as 'high-risk' patients. The inclusion criterion of "*Judged by recruiting clinician or research nurse to be clinically vulnerable"* is subjective and vague, and allows for the healthcare practitioner to enrol anyone they think might be vulnerable, even if they are not necessarily at high-risk of progressing to severe COVID-19. The consequence of applying the criteria above may result in a population less likely to progress to severe disease and, consequently, an artificially low rate of hospitalisation in both the molnupiravir and standard of care (SoC) groups. **During the consultation period, MSD contacted UK clinical experts for input, who fed back that those patients at highest risk of progression continued to receive treatment via the CMDUs. Consequently, patients eligible for inclusion in PANORAMIC were at a lower risk of progression than the target population for treatment with molnupiravir. Clinical experts also confirmed that patients not qualifying for treatment via the CMDUs, and therefore a population that is at lower risk of disease progression, were diverted to PANORAMIC for screening and potential enrolment.[5]** Additionally, people randomised to SoC in PANORAMIC were able to obtain molnupiravir and other treatments through the NHS, outside of the study, which confounds the estimates of effect from the SoC group from PANORAMIC, and likely results in lower rates of hospitalisation and death, both of which contribute to the underestimation of the comparative clinical effectiveness of molnupiravir. In Section 3.14 of the ACD, clinical experts suggested that, given the committee's preferred definition of high-risk, the highest-risk group **is underrepresented** in PANORAMIC, a view which was supported by clinical experts contacted by MSD during the consultation period. Overall, **MSD is extremely concerned that crucial clinical heterogeneity across study populations is not being adequately addressed.** In brief, study key population baseline characteristics for MOVe-OUT[3] and PANORAMIC[4] were; • Mean participant age: 43.7 years (standard deviation 13.7) in MOVe-OUT versus 56.6 years in PANORAMIC; • Proportion of people with one or more comorbidities at risk for progression to severe illness from COVID-19: 99.4% in MOVe-OUT versus 69% in PANORAMIC; • % BMI > 30: ~75% in MOVe-OUT versus ~15% in PANORAMIC • % Diabetic: ~16% across both arms in MOVe-OUT versus ~12% in PANORAMIC • Level of vaccination: 0% in MOVe-OUT versus 99% having received at least one dose of a SARS-CoV-2 in PANORAMIC.

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	While MOVe-OUT patients are younger on average, it is clear that the PANORAMIC study recruited a population that was highly vaccinated and at lower risk of progressing to severe disease, and, based on the timing of the study, was affected by the Omicron variant, which is acknowledged to associated with lower rates of hospitalisation compared with earlier variants. The inclusion of the PANORAMIC trial in the meta-analysis is likely to lead to bias and uncertainty in estimates of comparative effectiveness versus SoC, due to the introduction of additional clinical heterogeneity into the analysis. As noted earlier, the population enrolled in PANORAMIC has a lower risk of progression compared with population from other studies included in the analysis, and, therefore, inclusion of results derived from PANORAMIC are likely to introduce bias against molnupiravir, and underestimate its true clinical effect. Given the recognised presence of heterogeneity, data were synthesised using a random effects model, and, due to the size of the population enrolled in PANORAMIC, the results from PANORAMIC are likely to have a higher weight in the analysis than results from other studies, which exacerbates the underestimation of the effect of molnupiravir in a population at high risk of progression. Inclusion of results from PANORAMIC in any meta-analysis is likely to increase uncertainty in effect estimates and their generalisability to the target high risk population. It would seem perverse if a negative recommendation were made with respect to molnupiravir largely on the basis of the results from the PANORAMIC trial, given the lack of trial evidence for the other treatments in a highly vaccinated population. Alternatively, all suitable sources of evidence should be incorporated into the NMA as in a typical NICE HTA. MSD is aware of RWE studies from similar geographies to the UK that were conducted during the Omicron variant COVID-19 wave in vaccinated patients more like the McInnes definition of the population at high-risk of developing severe disease. Whilst we acknowledge the limitations of retrospective studies, given the rapidly evolving nature of the clinical data, RWE should be taken into consideration. We enclose this evidence, which is in press or published, in a separate appendix for consideration by the Committee. **Given the aspects described above, MSD considers that results from PANORAMIC are not relevant for the purposes of this appraisal.**
2. Additional RWE to PANORAMIC provides critical evidence on the activity of MOV in high-risk patient populations, especially in older patients and those with clinical considerations that may not be able to receive nirmatrelvir with ritonavir.	The clinical programme underpinning the effectiveness estimates for molnupiravir is comprehensive, with several clinical studies reporting positive results, as is currently evidenced in the ERG report. By comparison, the efficacy and safety of other agents are predominantly derived from a single RCT. **Evolution of COVID-19 and changes in vaccination rates over time not only impact the assessment of molnupiravir but also all other oral antivirals and monoclonal antibodies; for example, EPIC-HR recruited unvaccinated patients pre-Omicron variant.** RWE provides additional evidence of the clinical benefit of molnupiravir in treating a broad range of patients with mild-to-moderate COVID-19 both those at low risk of hospitalisation or death and those who are clinically vulnerable and at very high risk of hospitalisation or death due to COVID-19. The pivotal Phase 3 trial, MOVe-OUT, showed that molnupiravir was effective in high-risk, unvaccinated non-hospitalised patients infected with early variants of COVID-19. Given the changing epidemiology of SARS-CoV-2, RWE provides additional useful insights into the clinical efficacy and safety of molnupiravir for treating newer variants.

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	MSD systematically surveyed the literature for reports of RWE studies that include molnupiravir (see Appendix 3 for a tabular summary of RWE studies available as of 29th September 2022). The identified real-world data, collected largely when Omicron was the predominant SARS-CoV-2 variant alongside a range of vaccination rates, provide evidence of the safety and effectiveness of molnupiravir in treating patients across a continuum of risk. Whilst RWE sources may have limitations, they remain important for consideration for COVID-19, which continues to evolve over time. Results from a selection of RWE studies are summarised here. We report the larger, territory wide or national databases, the full list of RWE sources is provided in appendix: • Observational, retrospective assessment of data collected from 19,868 electronic medical records of Clalit Health Services in Israel (Arbel et al 2022[6]), molnupiravir was shown to be associated with a reduced risk of hospitalisation or death in high-risk patients with COVID-19 who were 65 years and older.[6] In this group, the adjusted HR for hospitalisation was 0.55 (95% CI, 0.34 to 0.88). Most patients (92%) in this study had previous COVID-19 immunity (i.e., by vaccination, prior COVID-19 infection, or both) and received molnupiravir during the Omicron wave.[6] • Observational, retrospective cohort study conducted by Wong et al,[7] data from the Hong Kong Hospital Authority were used to identify a territory-wide cohort of non-hospitalised patients with an officially registered diagnosis of SARS-CoV-2 infection during a period in which the Omicron variant was dominant.[7] After propensity score matching, 54,217 patients (4,983 who received molnupiravir and 49,234 matched controls) were analysed for study outcomes. After matching, the mean age of participants treated with molnupiravir was 71.4 years. Study vaccination rate was ~17%. Molnupiravir use was associated with lower risks of death and in-hospital disease progression.[7] The risk of hospitalisation for molnupiravir-treated patients was similar to the risk in the matched controls (crude incidence rate of 107.6 vs 104.0 per 100,000 person-days, respectively: HR 0.98 [95% CI 0.89 to 1.06]. However, treatment with molnupiravir was associated with a lower risk of all-cause mortality (crude incidence rate of 17.9 vs. 22.1 per 100,000 person-days, respectively: HR 0.76 [95% CI 0.61 to 0.95]).[7] ○ An evaluation of the clinical effectiveness of molnupiravir (by the same authors) in patients in Hong Kong who were hospitalised due to their high risk of progression to severe disease showed that molnupiravir was associated with a lower risk of death compared with matched controls (HR: 0.48 [95% CI 0.40 to 0.59]).[8] It should be noted that the mean age after propensity score matching in the molnupiravir arm was 80.7 years. • In a retrospective cohort study conducted by Bruno et al[9] in southern Italy, 719 high-risk patients received treatment for COVID-19 during a period when Omicron and subvariants were dominant.[9] Of the trial population, 554 patients received molnupiravir whereas 165 patients received nirmatrelvir and ritonavir – 93% of the total trial population had been fully vaccinated. The mean age for molnupiravir was 73 years, whereas for nirmatrelvir and ritonavir mean age was 62 years. Overall, 43 all-cause hospitalisations (5.9%) and 13 (1.8%) deaths were observed at 30 days. No differences between the two antivirals were observed. Both antivirals helped to limit hospitalisation and deaths at 30 days among patients who were at high-risk of disease progression in the period when Omicron was dominant, and most of the population was vaccinated. Amongst others, age ≥75 years was associated with higher risk for hospitalisation.

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	• A retrospective study conducted in Israel by Najjar-Debbiny et al[10] examined the effectiveness of molnupiravir in patients who were at high-risk for severe COVID-19 and had no contraindications for molnupiravir use.[10] Overall 2,661 molnupiravir patients were propensity score matched to 2,661 controls. The composite outcome was progression to severe COVID-19 or COVID-19 specific mortality. Molnupiravir was associated with a nonsignificant reduced risk of the composite outcome (HR, 0.83 [95% CI, 0.57 to 1.21]). However, subgroup analyses showed that molnupiravir was associated with a significant decrease in the risk of the composite outcome in older patients (HR: 0.54 [95% CI, 0.34 to 0.86]), females (HR: 0.41 [95% CI, 0.22 to 0.77]), and in patients with inadequate COVID-19 vaccination (HR: 0.45 [95% CI:0.25 to 0.82]); the vaccination status in the study was ~77%.[10] Authors report that adequate vaccination was associated with significant decrease in number of events for all examined outcomes. • A retrospective study, conducted by Flisiak *et al.* 2022,[11] assessed the efficacy of molnupiravir in patients hospitalised for COVID-19 in a real-world clinical practice during the wave of Omicron infections. Of the 203 patients that received molnupiravir, 9.9% died during the 28-day follow up compared with 16.3% of the 387 patients that did not receive anti-viral treatment (p=0.03). The reduction in 28-day mortality was particularly evident in the population of patients over 80 years of age treated in the first 5 days of the disease (14.6% vs 35.2%, p=0.016).[11] Data are not available on the vaccination status of participants included in the study. • MSD is aware of the Australia Victoria Government dataset that is being prepared for publication and may provide a valuable source of evidence for the use of molnupiravir in the real-world setting. Top-line results have been reported by the authors who note that the risk of hospitalisation reduced by 26% and the risk of death reduced by 54% for molnupiravir-treated patients in patients over 70 years of age.[1] MSD kindly requests NICE utilises its relationship with the PBAC in Australia, who we understand have access to some of this data, to source this large and relevant dataset. [redacted] These RW studies consistently report positive effectiveness of molnupiravir with evidence of benefit in higher risk populations (including older ages and unvaccinated patients). Interesting routes requiring further research also emerge: patients hospitalised after molnupiravir treatment require less intensive treatment and a measurable benefit in rapid treatment with an antiviral. The rapid evolution of the COVID-19 pandemic has made it necessary to consider data from randomized-controlled trials (RCTs) **and** RWE studies to understand the true efficacy of COVID-19 antiviral treatments and the populations with greatest potential to benefit. These studies vary in inclusion/exclusion criteria (e.g., vaccination status), outcomes, and predominant circulating variant, which makes simple cross-trial comparisons of reported efficacy results challenging and baseline hospitalisation rates is not appropriate as it would not account for such differences. An internal MSD study by Maas *et al*. 2022[12] used a multivariate logistic regression model of influential factors (developed based on the MOVe-OUT study) to predict the baseline event rates for hospitalization/death in populations from nine recently published studies given the COVID-19 evolution under the assumption that alternative RWE sources can be used to carry out such adjustments on the current clinical literature (abstract submitted to ECCMID 2023 for publication and shared in confidence). The analysis demonstrated that baseline rates of hospitalisation or death were highest in studies involving unvaccinated populations and carried

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out pre-Omicron variant. The analysis also showed variations in baseline hospitalisation risk across RCTs, with the MOVe-OUT trial enrolling the highest risk population, with a predicted mean event rate of [redacted], while the UK PANORAMIC study population was associated with the lowest baseline event rate (predicted mean: [redacted]) based on the different adjustments conducted. The baseline event rates for studies conducted in vaccinated participants, while the Omicron variant was the predominant variant, were much lower compared to studies of unvaccinated participants conducted pre-Omicron with alternative adjustments and models providing a mean range of baseline hospitalisation rates across the different studies included in the analysis .

Notably, **in RWE studies, higher risk patients tended to receive molnupiravir, while lower risk patients tended to receive nirmatrelvir with ritonavir or SoC (Figure 1).** Clinical characteristics, such as patient risk factors, vaccination status, and virus variant, had a substantial impact on hospitalisation rate or death. The data presented add further support to the company's position that it is inappropriate to use the PANORAMIC trial alongside the other RCT evidence to model the clinical effectiveness of molnupiravir within the economic assessment (i.e., the meta-analysed treatment effects), without further consideration of underlying risk and how this impacts the cost-effectiveness results.

Figure 1: Predicted baseline risk of published COVID-19 studies

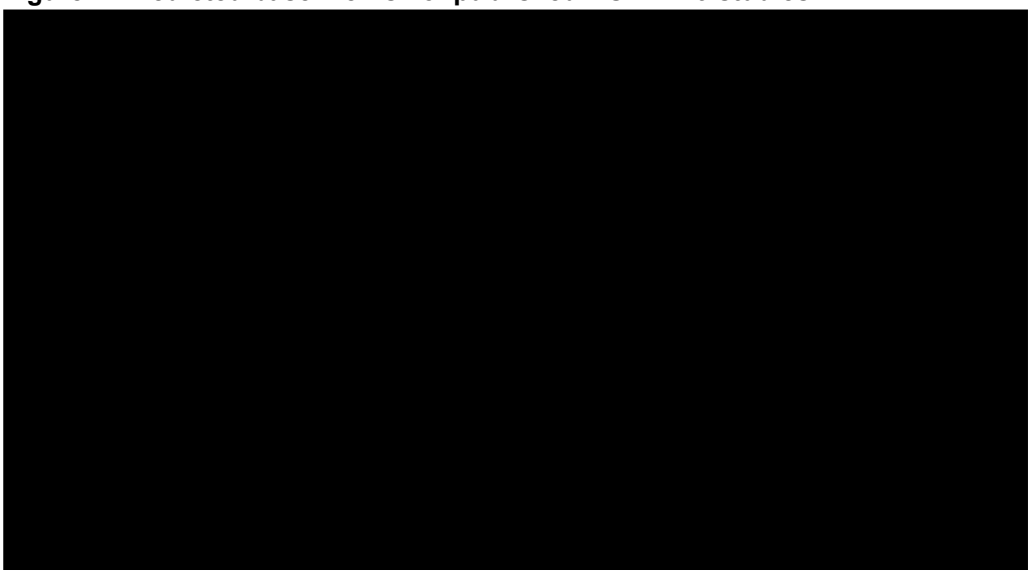

Figure 1 Abbreviations: MOV – molnupiravir; nrt/r – nirmatrelvir/ritonavir
Note: Model A reflects the previously developed logistic regression model based on MOVe-OUT. Model B and C reflect different assumptions to account impact of vaccination status and vaccination status plus Omicron variant, respectively, on the predicted rate of hospitalisation/death.

The RWE described above offers additional evidence of the clinical benefit of molnupiravir that is generalisable in the Omicron variant across a range of populations and vaccination rates, which could be of relevance in those with inadequate immune response. However, the unconventional MTA process means that these additional, potentially relevant, studies have not been included, however, results from the PANORAMIC study *have* been included, despite the population heterogeneity with MOVe-OUT and the McInnes population highlighted under Issue 1 above.

Molnupiravir's comprehensive evidence base, compared to that of other treatments in the community setting, has not been taken into account as a strength in this appraisal process and instead the inclusion of data from PANORAMIC for a low-risk, vaccinated population exposed to the Omicron variant, unfairly penalises the treatment.

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	MSD is aware that the clinical effectiveness of nirmatrelvir with ritonavir is currently being assessed within the PANORAMIC trial as noted in the draft guidance. It is unclear from the ACD when or how the results for nirmatrelvir with ritonavir will be incorporated into clinical and cost effectiveness analyses? MSD requests that NICE transparently states how it plans to revisit any guidance following the release of the PANORAMIC data for nirmatrelvir with ritonavir. We urge the Committee to consider the totality of the evidence presented above which is strongly supportive of the effectiveness of molnupiravir in vaccinated, Omicron-infected, **high-risk patients.** **Additional RWE supports the effectiveness of molnupiravir in high-risk patient populations, especially older patients and those with clinical considerations who may not be able to receive nirmatrelvir with ritonavir, due to contraindication or potential DDIs, and patients requiring rapid treatment in the community setting. MSD reiterates its request for the Committee to consider the additional evidence presented. Only at that stage can it be certain that any final guidance issued by NICE may continue to remain relevant for the NHS.** We note section 3.6 in the ACD states, "the committee considered a single definition of high risk should be used because of the model limitations. Additional functionality would be required to make differential subgroup recommendations and this would not be practical or proportionate to the decision problem". It is not true to say additional functionality would be required to make subgroup recommendations, all that is needed is an estimate of the background hospitalisation (and mortality rate) for the relevant subgroup. The consequence of not considering subgroups, which is apparent in this draft guidance, is that high-risk populations, including those with relevant protected characteristics around race and disability, are left without any treatment option. We request the AC reconsider if this situation is proportionate.
3. A significant number of patients will be unable to receive treatment for COVID-19 due to drug-drug interactions and contraindications. Their impact is excluded from the economic evaluation.	**A significant number of high-risk patients are ineligible for treatment with nirmatrelvir plus ritonavir, due to the potential for DDIs and contraindications with existing treatments for co-morbid conditions. As no alternative treatments have been recommended for use in the community, these patients will have no access to treatment for COVID-19. DDIs should be included in the economic model. DDIs have an impact on the cost-effectiveness of interventions that is currently omitted.** In the ACD, nirmatrelvir plus ritonavir is the only COVID-19 treatment recommended for use in the community setting. Ritonavir (in the nirmatrelvir and ritonavir combination) is a potent CYP38 inhibitor and interactions with other medicines may lead to severe, life-threatening, or fatal events.[13] Contraindications for nirmatrelvir plus ritonavir include severe renal and hepatic impairment. Furthermore, ritonavir is known to have interactions with many treatments used in the management of other conditions, including interactions with anticoagulants, anticonvulsants and antiarrhythmics, which are common treatments for the comorbid conditions the presence of which defines a high-risk patient. **A UK clinical expert consulted by MSD fed back that approximately 20% of patients could be contraindicated to nirmatrelvir plus ritonavir and will therefore require access to alternative treatment options.** MSD therefore explored various scenarios using age as a proxy for increasing severity and assuming that patients with severe renal and hepatic impairment are at higher-risk of progressing to severe disease with COVID-19. Simply

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	adjusting the model starting age to 65 with a 2.79% hospitalisation rate using MSD's preferred assumptions resulted in an ICER of £[redacted]For patients aged 70 or older the ICER was £[redacted]. It should be noted that the background hospitalisation rates in these patients is likely to be higher than the 2.79% and alternative values informed by expert opinion or clinical literature (such as Vo et al 2022) only improve the cost-effectiveness of molnupiravir in this patient population with ICERs between £[redacted] and £[redacted] depending the efficacy selection and hospitalisation input explored; refer to full cost-effectiveness results provided by MSD in confidential appendix). Several analyses have been conducted exploring the potential risks of administering a ritonavir-containing COVID-19 treatment, which are discussed in further detail below: • In an analysis of the Optum claims database of 1.2 million US patients diagnosed with COVID-19 from 1st January 2020 to 30th June 2021,[14] it was estimated that approximately 43% of all COVID-19 patients were receiving at least one concomitant medication that had a potential contraindication to or major DDI with ritonavir-containing COVID-19 treatment. The prevalence of potential DDIs increased in high-risk populations for severe illness from COVID-19, including patients >60 years of age (62%), those with diabetes (72%), with any type of cancer (62%), with chronic kidney disease stage 3–5 (74%), or residing in a long-term care facility (68%).[14] • A similar analysis conducted with data derived from the 2015–2019 National Health and Nutrition Examination Surveys database[15] estimated that 29.3% of all US adults had a potential contraindication or major DDI with a ritonavir-containing COVID-19 treatment.[15] The prevalence rose to 60% among those aged at least 60 years, 78% among individuals with diabetes, and 88% among those with serious heart conditions. Thus, a vast number of high-risk patients will be without an effective COVID-19 treatment if only nirmatrelvir plus ritonavir is approved.[15] • An analysis of the Pharmaceutical Benefits Scheme 10% sample (PBS10) claims data found that over 40% of the Australian adult population were at risk of potential DDIs that would be classified as major or contraindicated with ritonavir-containing treatment.[16] Patients at higher risk for severe COVID-19 symptoms had the highest prevalence of contraindications or major potential DDIs. These were highest in patients with cancer (79%), dementia and/or Alzheimer's (77.2%), and diabetes (73.8%). The study further demonstrates patients with the highest risk of developing severe COVID-19 symptoms, and therefore most likely to require hospitalisation, will be without an effective COVID-19 treatment if only nirmatrelvir with ritonavir is recommended.[16] • A retrospective analysis was conducted using the statutory health insurance (SHI) claim data from 2019 in database of Gesundheitsforen Leipzig GmbH (Germany) (abstract submitted to the DOAK conference for publication and share in confidence). Contraindicated medications and medications being subject to physician's decision were defined according to either SmPC or Mikus 2022. The study showed that combined potential DDI among those using ritonavir-containing regimen for contraindicated medications and those requiring a physician's decision was 56.0% according to SmPC, and 44.3% according to Mikus's approach. • A cohort study conducted by Hoertel et al (2022)[17] examined the prevalence of contraindications to nirmatrelvir with ritonavir in patients hospitalised with COVID-19. A review of the health records of 62,525 patients identified that 14.6% had a medical contraindication to nirmatrelvir plus ritonavir. Rate of contraindications increased to 26.9% in patients aged over 65 years and to over 37.0% in people with comorbidities,

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	which included diseases of the skin and subcutaneous tissue (45.5%), neoplasms (38.2%) and diseases of the nervous system (39.4%).[17] Section 3.24 in the ACD acknowledges that the current recommendations may exclude some people in certain risk groups who are included in the marketing authorisation and who have a disability. People with disabilities are more likely to be taking a medicine in the list of nirmatrelvir plus ritonavir contraindications. These patients are already at increased risk for progression to severe COVID-19, therefore not recommending an alternative COVID-19 treatment unfairly discriminates against people with a high unmet need for an effective treatment. The same section also highlights that people from ethnic minority family backgrounds are more likely to be diagnosed with COVID-19 and have a higher risk of dying from COVID-19 than the white British population (black people: HR 1.71; 95% CI, 1.44 to 2.02: Asian people: HR 1.62; 95% CI, 1.43 to 1.82).[18] Furthermore, the ACD acknowledges that the prevalence of hepatic and renal impairments is high in people from ethnic minority family backgrounds. Nirmatrelvir plus ritonavir is contraindicated in patients with severe hepatic and renal impairments.[19] Offering no alternative COVID-19 treatment for non-hospitalised patients indirectly discriminates against patients from an ethnic minority family background. These patients are already at an increased risk of suffering fatal COVID-19 and are now being denied access to effective COVID-19 treatments. There is compelling evidence in the scientific literature that highlights the implications of DDIs in optimal treatment selection for specific patient groups, and these concerns are also supported by clinicians whom MSD engaged during the appraisal consultation process. The evidence demonstrates that, in some patient groups, the risk of DDIs is considerable due to the nature of their conditions. Interruption of regular treatment schedules for some comorbid conditions to facilitate treatment for COVID-19 with nirmatrelvir with ritonavir is considered clinically inappropriate, especially as there are existing COVID-19 treatments that may be prescribed concomitantly with treatments for comorbid conditions, such as molnupiravir. With regards to the economic evaluation, before prescribing nirmatrelvir plus ritonavir, a full medication review is required to evaluate potential for DDIs. As such, administration costs for nirmatrelvir plus ritonavir are likely to be higher than other comparators but this is not reflected at all in the economic analyses run to date. For example, the cost of a pharmacist per hour is valued at £352.49,[20, 21] which underscores that administration costs could rapidly accumulate should only ritonavir-based treatment be recommended. Additional costs associated with DDIs include GP and pharmacist costs, as well as hospital visits. DDIs complicate the ability of the pharmacist to easily prescribe additional medication due to the requirement for a full medication review, which is resource intense. If patients in the UK can be treated within the community with molnupiravir, an easy-to-administer drug with no known DDIs, then considerable time and resource use is saved compared with the use of other community drugs for high-risk patients with COVID-19. The sensitivity analysis provided by the Committee demonstrates 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 hospitalisation admission proportion increase in the standard of care arm. Figure 23 in the Committee papers shows that, as the hospitalisation risk increases, the ICER for molnupiravir reduces. As such, the likelihood of molnupiravir being a cost-effective treatment for people with disabilities or from ethnic minority family backgrounds is increased, as these groups have an increased risk of hospitalisation. For example, a study carried out by Imperial College London (April 2022) has identified people with

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	long-term conditions, such as severe mental illness and learning disabilities, as the groups with the highest risk of hospitalisation.[22] Furthermore, as there are no known DDIs or contraindications associated with the use of molnupiravir, making it an ideal alternative treatment for high-risk patients ineligible to receive nirmatrelvir plus ritonavir. To avoid excluding a significant number of high-risk patients from COVID-19 treatment, in particular people with disabilities and people from ethnic minority family backgrounds, the Committee needs to address the significant unmet need for an effective alternative agent that can be quickly administered in the community for patient groups with various clinical considerations at high risk of progressing to severe disease which may require urgent care in the community setting. **It is clear that from the evidence above that the impact of DDIs is important and relevant and should be considered formally in the appraisal process to avoid disadvantaging any patient groups indirectly.** **Unlike its comparators, molnupiravir has no known drug-drug interactions and the full cost-effectiveness implications of this have not been explored.** **Currently the cost-effectiveness of molnupiravir is underestimated significantly, especially for patient groups that cannot receive alternatives recommended within the draft guidance.**
Evidence synthesis considerations	
4. The current evidence synthesis methodology is flawed. Using low-efficacy estimates for molnupiravir is both inappropriate and disadvantageous.	**MSD has serious concerns regarding the approach to the evidence synthesis and its ability to inform decision making. There are key differences across studies that have not been adjusted for and that may affect the validity of the results considered by the AC. MSD conducted some additional analyses that attempt to quantify the impact of study differences and adjust trial outcomes to demonstrate the likely impact of differences on the estimates of clinical and cost effectiveness of molnupiravir.** Due to the limited time available, a pragmatic approach was adopted by the EAG to identify and collate information on COVID-19 for non-hospitalised patients to provide evidence for decision-making. The estimates of comparative effectiveness presented in Table 5 (p31) of the EAG report were derived from the two living systematic reviews (COVID-NMA initiative and the metaEvidence initiative). The COVID-NMA initiative was used as a third-party source to identify relevant trials and synthesise data from these trials. The EAG report does not list the source trial data included in the synthesis and does specify which trials are included in the synthesis for patients at risk of hospitalisation. Most of the studies included in the evidence synthesis were conducted in an unvaccinated population and pre-Omicron, with the exception of the PANORAMIC study, the data from which became available a few working days before the ACM. Of treatments under consideration within PANORAMIC and the MTA, only results for molnupiravir results have read out to date. However, we understand that whilst nirmatrelvir with ritonavir is undergoing assessment, it will be some time before results will be available, particularly given the slower than expected recruitment of the study to date. In contrast to the other pivotal RCTs included in the review, as noted earlier, the **PANORAMIC study recruited a highly vaccinated population at a low risk of progressing to severe disease and affected by the Omicron variant (see Issue 1 above).** Despite the high level of clinical heterogeneity identified when comparing PANORAMIC with other included studies,

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	results from PANORAMIC were synthesised with those from other trials identified from the COVID-NMA initiative, in effect "adjusting" the relative treatment effect reported from the other pivotal RCTs to that of an "less risk, Omicron exposed, highly vaccinated population". **It should be noted that no comparable evidence in a highly vaccinated population was considered with respect to any of the other treatments under consideration and no attempts were made to adjust the other data in any other way.** In the draft ACD, the Committee also noted that: *"the mean efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were likely to overestimate the benefits of molnupiravir."* This is factually incorrect, and we request it is corrected to "*the mean efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were likely to* ***underestimate*** *the benefits of molnupiravir.* ***This is because PANORAMIC recruited a population that is generally perceived to be at lower risk for progression to severe disease if left untreated"*** The estimates of relative effectiveness from the PANORAMIC trial are likely to be biased due to patients in the usual care arm receiving molnupiravir and other treatments through the NHS, as commented on by the authors of the PANORAMIC trial: "*Participants randomised to molnupiravir would not have received additional molnupiravir through the NHS; however, those randomised to usual care may have received molnupiravir through the NHS and this was recorded in the online diary".* MSD is concerned about the preference for considering the low efficacy estimates from the evidence synthesis to inform decision making. **Use of the low efficacy estimate does not capture the effectiveness of molnupiravir in the real-world setting and disproportionately disadvantaged against molnupiravir.** Furthermore, inclusion of the results from PANORAMIC disproportionately disadvantages against molnupiravir because of the lower rate of hospitalisation derived from a population at lower risk of progression, which leads to an underestimation of the clinical effect of molnupiravir in its target population. There is no reason to believe that the confidence interval (CI), which is used to generate the low efficacy scenario from the meta-analysis represents, a reasonable estimate of the efficacy in the contemporary population, and it should be clearly noted that a 95% CI is an arbitrary level. Further, the lower limit of the 95% CI estimates should be viewed with extreme pessimism. **For these reasons MSD does not believe that the low efficacy values should be considered by the Committee when evaluating the cost-effectiveness of treatments in the non-hospitalised setting.** Specific to the evidence synthesis, the estimated QALYs from the cost-effectiveness model, based on evidence synthesis results are presented in Table **1** (from Erratum dated 25/10/22). As demonstrated, there is a high degree of uncertainty in both the comparability of results from different studies and the relevance of the study results to a contemporary population given that the studies evaluated patients from an unvaccinated population and did not include patients infected with the Omicron variant. **As a result, any judgement as to the ranking of molnupiravir relative to nirmatrelvir with ritonavir is highly uncertain.** These uncertainties notwithstanding, molnupiravir was estimated to be the second most effective treatment. The mean estimated QALYs were 0.03 less than nirmatrelvir with ritonavir, which was recommended in the draft guidance. MSD has extracted the forest plots from the living COVID-NMA to demonstrate the inappropriateness of ranking treatments (Figures 2 and 3); molnupiravir's assessment included a larger number of studies, which informs the point estimate, including the PANORAMIC study (Butler et al 2022[4]). This is not the case for EPIC-HR informing the evaluation of nirmatrelvir

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with ritonavir with effect size estimates extracted from a single RCT. Multiple studies and the evolution of COVID-19 would contribute to the upper level estimate of molnupiravir's effectiveness crossing the line of no difference. However, as explained, this is not fully reflective or relevant because the analysis below includes a lower risk population, which biases the results.

Figure 2: Forest plot from COVID-NMA for meta-analysis of RCTs evaluating molnupiravir

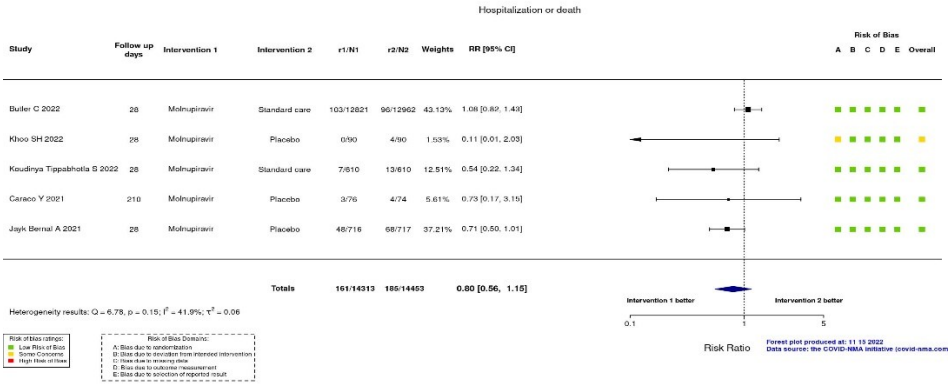

Figure 3: Forest plot from COVID-NMA for analysis of RCT evaluating nirmatrelvir with ritonavir

Table 1: *Extract from Table 21 of updated AG report (Erratum dated 25/10/22)*

Intervention	QALYs		
	Mean	Low	High
SoC	13.42	13.42	13.42
Nirmatrelvir/ritonavir	**13.54**	**13.49**	**13.56**
Sotrovimab	13.49	13.38	13.56
Remdesivir	13.46	13.28	13.56
Casirivimab/imdevimab	13.48	13.39	13.55
Molnupiravir	**13.51**	**13.44**	**13.54**
Tixagevimab/cilgavimab	13.42	13.26	13.52

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	<table><tr><td>**Incremental difference Mov vs Nir/Rit**</td><td>**-0.03**</td><td>**-0.05**</td><td>**-0.02**</td></tr></table> As recommended in a recent publication by Thom *et al.* (2022),[23] decision-making should not be based on deterministic analysis due to the uncertainty in model parameters. Basing the final recommendations on probabilistic sensitivity analysis would better capture the uncertainty in certain model parameters, such as efficacy values, as well as future-proofing the guidance. **Assuming low efficacy estimates for molnupiravir is both inappropriate and disadvantageous considering the extensive RCT and RWE evidence base available for molnupiravir, in contrast to all other agents under assessment.** The AC may continue to consider conservative assumptions in efficacy estimates for other agents to account for their limited evidence base when informing final recommendations. The current methods bring severe implications in the validity of the comparative effectiveness estimates used for molnupiravir's assessment. The impact of clinical heterogeneity is not captured, and attempts have not been made to adjust the results to account for the differences. To do this adequately, a full assessment of uncertainty, primarily based on clinical heterogeneity in the patient population and on the disparity across the studies in other factors (i.e., standard of care, variant type, pandemic development) would be required rather than on pure statistical heterogeneity from an aggregate level meta-analysis, where selected studies are pooled together without any adjustment. **Simply pooling the results of these studies to inform the decision making is therefore flawed.** Given these aspects MSD strongly urges the Committee to only **consider the results of the meta-analysis excluding the PANORAMIC trial versus SoC, as these will provide the least biased estimates of comparative effectiveness versus SoC as suggested by clinical experts.** A more robust meta-analysis could alternatively be performed if the PANORAMIC research team made available the patient level data to the EAG for the purposes of identifying the "true high-risk" sub-group population to ensure a more robust basis for evidence synthesis before drawing conclusions for decision making. Given information available, we would expect this to be a small proportion of the PANORAMIC study population. Adjustments to the remaining clinical evidence should also be carried out to reflect the ongoing evolution of clinical evidence base.
Model input considerations	
5. Alternative hospitalisation rates need exploring.	**Hospitalisation rates were extensively discussed at the ACM, and different sources were cited as proxies of the true background hospitalisation rate for patients who are at high risk of progressing to severe disease. It is also acknowledged within the ACD that the PANORAMIC hospitalisation rate of 0.77% could be an underestimation for the target population at 'high-risk'.** In Section 3.6 of the ACD, the Committee concluded that the definition of high-risk in the McInnes report is the most robust. Using the DISCOVER-NOW database[24] interim analysis and McInnes high-risk population definition results in a hospitalisation rate of 2.79%.[25] Given the Committee's preferred definition of "high-risk", the hospitalisation rate should be sourced from data using the high-risk definition for consistency. In Section 3.14 of the ACD, clinical experts suggested that, given the Committee's preferred definition of high-risk, the highest-risk group may have been under-represented in the PANORAMIC trial given that the hospitalisation rate was 0.77%, which is significantly lower than all the other reported estimates: 2.79% for the original estimate used by the EAG for their base case, 1.45% in the OPENSAFELY study,[26] and 18.4% in the Shields *et al.* 2022 publication.[27]

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	Despite acknowledging that the hospitalisation rate from PANORAMIC is likely to be an underestimation of the true rate for high-risk patients, the Committee presented scenario analyses in Section 3.20 of the ACD utilising the low, likely underestimated, hospitalisation rate. Additionally, the Committee states that the results for molnupiravir are over NICE's £30,000 per QALY willingness-to-pay threshold. However, there is no acknowledgement that scenario analysis using the low-efficacy measure and 0.77% hospitalisation rate generates an ICER for nirmatrelvir plus ritonavir that is also over the standard willingness-to-pay threshold at £60,415 per QALY gained, with nirmatrelvir plus ritonavir being recommended as a treatment option in the ACD. MSD engaged with clinical experts and patient organisations during the consultation period to collect more insights around the appropriateness of the parameters applied in the economic model. Experts and patient organisation representatives **agreed that the PANORAMIC baseline hospitalisation rate does not reflect the patients at true high risk of progressing to severe disease. Experts note that COVID-19 continues to evolve, and it is unclear how future variants will affect patients.** One clinical expert closely affiliated with a CMDU provided further insights noting that as: "*a minimum, a 3%-5% hospitalisation rate is realistic for true high-risk patients who had an immune response with COVID-19 vaccination. But this rate could perhaps increase to 7% or even 8% for those who do not mount an adequate immune response after COVID-19 vaccination. To put this into perspective, from the 28% treated at a CMDU, approximately 20% of patients do not mount an immune response.*" Including patients with a lower risk for progression to severe COVID-19 than in the identified target population (such as those included in PANORAMIC) will translate into a lower rate of hospitalisation and rate of mortality. Any decisions made using parameters from a trial population unreflective of the target population will lead to a spurious final recommendation. Considering that the hospitalisation rate parameter is a key model driver, MSD asks that a full systematic review is conducted to capture all randomised and non-randomised data sources, in line with the NICE evaluation methods, **in the correct high-risk of severe disease population**. Consulting clinical experts would also generate and/or validate more accurate rate of hospitalisation for high-risk patients. MSD has run some additional analyses using the hospitalisation rates provided by clinical experts, alongside some estimates reported in the clinical literature (please see Table 3 in Appendix 2). The analyses reflect comments that PANORAMIC underestimates the true hospitalisation rate and illustrates the impact this parameter has on the ICER. MSD has also run alternative scenarios to ascertain what hospitalisation rates result in ICERs below £30,000/QALY for molnupiravir versus SoC. These analyses demonstrate that the hospitalisation rate needs to be between [redacted] depending on the assumptions feeing into the economic analysis. Importantly, these analyses validate the clinical expert values for hospitalisation ("*range of 3% to 5% as minimum and perhaps a 7%-8% for some patient groups*)". MSD's analyses demonstrate the importance of exploring alternative hospitalisation rates for all interventions, given the uncertainty in disease evolution over time, as supported by expert feedback. **MSD asks that the Committee takes into consideration the expert insights and a range of estimates around rate of hospitalisation for its final guidance to ensure future proofing of the recommendations.**

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6. Unjustified administration cost for oral antiviral treatments	Once delivery of oral antivirals is moved to the primary care setting, in the future, the current deployment costs for oral therapies (£410) will reduce substantially. Molnupiravir is easy to prescribe, with no known DDIs, which means that deployment costs for most patients should proxy those of community NHS prescription plus postage costs for timely treatment delivery. Under these considerations, the application of a £410 administration cost for oral antiviral treatments is unjustified and should be removed or, at minimum, reduced to align with the cost of prescribing drugs in the community. MSD acknowledges that a percentage of patients may still require a more formal review, based on clinical expert discussions held during the appraisal process and, therefore, has adjusted deployment costs to reflect true routine commissioning reality. We note that the draft guidance page 27 states; **"***NHS England provided Covid Medicines Delivery Unit (CMDU) deployment costs for the administration of oral antivirals (£410) and neutralising monoclonal antibodies (£820). Some companies disagreed with using CMDU deployment costs because these include costs based in secondary care.* ***However, future delivery is anticipated to be in primary care, which would reduce these costs. The NHS England representative explained that the delivery of service is subject to change. In future, integrated care boards will be responsible for treatment delivery currently done by the CMDUs****"*. It was also noted that costs were calculated before implementation of nirmatrelvir plus ritonavir as an additional antiviral treatment. Nirmatrelvir plus ritonavir is expected to increase resource use because of the expected requirements to assess contraindications. We therefore request that deployment costs applied to this agent are proportionally adjusted to reflect clinical reality in line with emerging literature on this subject. Section 3.18 of the ACD explains the EAG's rationale for including an administration cost for oral COVID-19 treatments. MSD disagrees with the Committee's decision to include a £410 administration cost for oral COVID-19 treatments for the following reasons: • The Position Statement from the CMDU, included in the committee papers, highlights the difficulty CMDUs participating in the costing exercise encountered in estimating the staff time spent on administration, triage, and treatment. As such, the estimated administration cost is uncertain and has the potential to include the cost of staff time spent on both triage and treatment. • The £410 administration cost applied in the economic analysis includes deployment costs based in secondary care. The ACD suggests that "*future delivery may be in primary care*", which would likely reduce deployment costs. Molnupiravir is administered in the community as an outpatient treatment, therefore, including secondary care deployment costs in the CMDU's oral administration cost estimate will unnecessarily inflate the administration cost for primary care treatments. Comparing the CMDU's estimated administration cost for oral treatments with the NHS prescription charge highlights the disparity between the costs. A £410 administration cost is approximately equivalent to three hours of GP time (£140 per hour GMS activity[20]), which is high for an oral drug with no contraindications. Furthermore, the PSSRU 2021 reported a prescription cost per consultation as £33.10, which is considerably lower than the £410 administration cost applied in the model.[20] The cost of £33.10 is more appropriate for molnupiravir, because the risk of contraindications is understood to be minimal.[14] • Furthermore, MSD has engaged with clinical experts to understand if CMDUs (or their future transformation) could still be used to deploy access of antivirals in specific patient populations (primarily those with polypharmacy due to comorbidities). Experts

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	noted that between **7% and 8% (maximum value of 10% reported used)** of patients that are at high risk of progressing to severe disease and may therefore require COVID-19 therapeutics will need a more detailed assessment due to DDIs and comorbidities. For the purposes of this assessment, we used the maximum value of 10% that would require a complex assessment in similar facility of the CMDU. Therefore, the Committee considered an alternative cost of £41.00 for molnupiravir alone, 10% of the £410 administration cost used in the economic analysis. The administration costs for nirmatrelvir with ritonavir should differ to account for the higher assessment time required to ascertain patient fitness based on DDIs. The rapidly changing nature of the pandemic and the speed at which CMDUs were established meant that the structure and resourcing needs of the CMDUs evolved with the progression of the pandemic. The Position Statement explained how deployment costs have continued to change throughout the pandemic. As the treatment pathway becomes established and patient needs are more predictable, administration costs for oral COVID treatments are likely to fall due to increased efficiency when administering treatments within the CMDU. In the ACD, a representative from NHS England explained how the delivery of the service is subject to change with integrated care boards responsible for treatment delivery currently done by the CMDU. To future-proof the guidance, MSD believes the best approach would be to either exclude administration costs for oral treatments or adjust them accordingly as outlined above, to ensure estimates used in the economic model have face validity. In Appendix 2, MSD have run some additional analyses which include a DDI cost for nirmatrelvir/ritonavir and the elimination of administration costs for an oral drug in the community. Applying these assumptions results in total discounted costs of [redacted] and total discounted QALYs of [redacted] for molnupiravir and an overall ICER of [redacted] for molnupiravir vs SoC. This is compared to an overall ICER of £10,251 for nirmatrelvir/ritonavir vs SoC (MSD has applied costs for DDIs in its preferred assumptions). **Using alternative plausible administration costs results in improved estimates of cost-effectiveness for molnupiravir versus SoC.**
7. Omissions from the economic model	It is also worth noting that other aspects from PANORAMIC in addition to the hospitalisation rate that benefit molnupiravir are currently not factored in the economic assessment. For example, the PANORAMIC study demonstrates a significant improvement in the time to resolution of symptoms for patients treated with molnupiravir. The median time to first recovery was 9 days in molnupiravir and 15 days in usual care, resulting in an estimated benefit of 4.2 days with molnupiravir treatment. Therefore, a faster return to health will result in a greater incremental QALY for patients treated with molnupiravir compared to usual care. Additionally, reduced healthcare resource use is associated with molnupiravir. Of the patients in the PANORAMIC study, 19.6% of those receiving molnupiravir contacted a GP, compared with 23.7% receiving usual care, which leads to reduced costs with use of molnupiravir **Whilst hospitalisation rates for SoC have been included from PANORAMIC, other relevant endpoints, such as time to recovery and health care resource use, have not been included in the assessment by the EAG. It can therefore be concluded that the cost-effectiveness of molnupiravir is currently underestimated within the current economic model.**
Uncaptured value for molnupiravir	

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9. Uncaptured clinical and societal value of molnupiravir	**MSD continues to remain concerned with the current technology appraisal process and the evaluation framework followed for COVID-19 therapeutics. The rigidity of the current framework means that clinical and societal value are not captured for antivirals, including molnupiravir, with a resulting negative impact on the cost-effectiveness analyses.** Some aspects of additional value could had been easily introduced without requiring excessive model structure changes. We note that section 3.23 in the ACD discusses elements of uncaptured value including, for example, transmission to healthcare professionals and concludes these either fall out of the reference case or there is limited evidence to support them. We disagree that these fall outside of the reference case. While it is generally understood that the current NICE evaluation framework may be restrictive in capturing wider societal benefits, these factors have been discussed extensively on a number of occasions: • Recent anti-microbial assessments (cefiderocol and ceftazimide/avibactam for severe drug-resistant, gram-negative bacteria);[28] • Other antiviral HTAs (notably in Hepatitis C [TA430,[29] TA499,[30] TA507;[31] focusing on latest TAs] and Influenza [TA158[32] and TA168[33]]); • Direct societal and economic impact to the NHS of sickness in the NHS workforce. Drawing from the examples listed above, MSD restates that areas of uncaptured value relevant for decision-making are excluded from this MTA. This includes some elements of transmission, diversity of products and insurance (antimicrobial assessments)[25,26] and transmission (Hepatitis-C appraisals (TA507,[31] TA499[30])). **Relevance for COVID-19:** During the appraisal committee meeting, extensive time was dedicated to discussing the effectiveness of technologies under consideration across different COVID-19 variants. We welcome the Committee's apparent conclusions that AVs are more likely to maintain their effectiveness over time. MSD considers that the Committee's deliberations on the above matter attempts to capture qualitatively the following "STEDI" aspects of the antimicrobial assessment framework that would enable to capturing of wider health benefits: • spectrum of action (antibiotics specific); • transmission disruption (applicable to COVID); • enablement value for the NHS (applicable to COVID); • diversity of products (applicable to COVID); • insurance value (applicable to COVID). With regards to the COVID-19 therapeutics appraisal, the EAG model and assessment report exclude all social benefits associated with approving oral treatments that can be administered in the community. These include reduced sickness amongst the NHS workforce, avoiding the requirement for patients to travel to the hospital and patient preference for treatment at home. Due to the patient-facing nature of the role, front-line healthcare workers are at a higher risk of contracting COVID-19 than the general public, which will result in significant costs to the health service through staff absenteeism and, consequently, delayed or cancelled treatments. Such

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	costs would be reduced by preventing hospitalisation in high-risk patients with COVID-19, which would, therefore, result in the reduction of transmission to front-line healthcare workers. As a treatment that is delivered entirely in the community, and that has been shown to reduce rate of hospitalisation compare with placebo, molnupiravir can reduce the exposure of the NHS workforce to COVID-19.[3] The reduction in transmission to key healthcare workers, a key benefit of molnupiravir, is not considered in the economic model. **MSD continues to advocate that such aspects should be formally modelled as part of the ongoing MTA or at least be explored in scenario analyses considering their relevance, although we acknowledge that some restructure in the economic model may be necessary to capture the aspects outlined above.**

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Appendix 1: Inclusion criteria for MOVe-OUT and PANORAMIC

The inclusion criteria for MOVe-OUT were:[3]

- Documented Polymerase Chain Reaction (PCR)-confirmed SARS-CoV-2 infection within ≤5 days of randomisation;
  - AND has initial onset of signs/symptoms to COVID-19 for ≤5 days prior to randomisation and at least one sign/symptom on the day of randomisation;
  - AND has mild or moderate COVID-19, with one of the following risk factors:
    - Age >60 years;
    - Active cancer;
    - Chronic kidney disease (CKD);
    - Chronic obstructive pulmonary disease (COPD);
    - Immunocompromised from solid organ transplant;
    - Body mass index (BMI) ≥30;
    - Serious heart conditions;
    - Diabetes mellitus.

The inclusion criteria for PANORAMIC were:[4]

- Experiencing COVID-19 symptoms, beginning in the last 5 days
  - AND have had a positive Polymerase Chain Reaction (PCR) or Lateral Flow test for COVID-19;
  - **AND are aged 50 or over**, **or aged 18 or over** with a **LISTED** pre-existing condition:
    - Chronic respiratory disease;
    - Chronic heart or vascular disease;
    - CKD;
    - Chronic liver disease;
    - Chronic neurological disease;
    - Severe and profound learning disability;
    - Down's syndrome;
    - Diabetes mellitus;
    - Primary or secondary immunosuppression;
    - Solid organ, bone marrow and stem cell transplant recipients;
    - BMI >35;
    - Severe mental illness;
    - Care home resident;
    - Judged by recruiting clinician or research nurse to be clinically vulnerable.

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Appendix 2: Alternative assumptions & cost-effectiveness estimates explored during the MTA process followed by MSD's exploratory analyses

Appendix 2.1: Alternative hospitalisation rate estimates explored and rationale

Alternative sources of hospitalisation rates have been discussed already within the MTA. The DISCOVER-NOW data, provided by Glaxo Smith Kline (GSK) as a stakeholder response, assessed 3,865 high-risk non-hospitalised patients in North-West London, with a COVID-19 diagnosis or positive polymerase chain reaction test between the 1st of December 2021 and the 30th of April 2022 who did not receive treatment with a monoclonal antibody or an antiviral. The high-risk conditions considered in this analysis were aligned with those defined as the highest-risk group in the Department of Health and Social Care commissioned Independent Advisory Group Report.

The targeted literature review conducted by GSK found that the hospitalisation rate varied from 0 to 26.4% (p 281 of committee papers). When pooling the data across the five studies identified, the "all-cause hospitalisation rate" for the aggregated high-risk population was estimated as 5.48%. Three out of the five studies reported COVID-only hospitalisation which resulted in a COVID-related hospitalisation rate of 5.05%. The 2.79% hospitalisation rate, reported by the EAG, is calculated using a population with a median baseline age of 52 years (p581 of committee papers). As highlighted in Section 3.5 of the ACD, clinical experts considered age an important risk factor for progression to severe COVID-19. Patients used to calculate the hospitalisation rate of 2.79% are significantly younger than patients in the RWE data presented as part of Issue 2, and this rate is, therefore, unlikely to reflect the hospitalisation rate of a true high-risk population.

The hospitalisation rate of COVID-19 will be higher in the true high-risk patient group than the upper bound 2.79% hospitalisation rate used by the Committee in their scenario analyses, which should be reflected in the current cost-effectiveness analysis. This is in line with clinical expert feedback received from MSD during the consolation period. **Clinicians informed MSD that the true hospitalisation rate for patients at high risk of progressing to severe disease could be between 3% and 5% for the increasing to 7% or 8% for those that mount inadequate immune response following vaccination. Molnupiravir's utilisation from real word evidence is primarily in older patient groups with higher likelihood for DDIs due to comorbidities. MSD therefore used the Vo et al 2022 publication to**

proxy the baseline hospitalisation rate as a scenario analysis(6.7 fold increase in 2.79% rate used currently)**. We also explored the impact of higher hospitalisation rate estimates based on clinical expert opinion (**for 65+ 5% was applied, for 70+ 8% was applied). Table *2* presents the literature and expert opinion estimates explored in subsequent scenario analyses by MSD. Full description of C/E analyses explored and assumptions formulating these are also included below.

Table 2: Summary of hospitalisation rates explored within scenario analyses

Hospitalisation rate (%)	Reference
0.77	Butler *et al.* 2022[4] (PANORAMIC); MSD considers this as unrealistically low for high risk patients
[redacted]	[redacted]unrealistically low for high risk patients
2.79	The EAG's preferred assumption
3.0	Based on clinical expert opinion
5.0	Based on clinical expert opinion
8.0	Based on clinical expert opinion (not mounting immune response)
18.7	Vo *et al.* 2022[2]; 17,756 US veterans and who were aged ≥65, non-IC and with no booster or which 3,328 were hospitalised with infections following vaccination

Appendix 2.2: Summary of alternative assumptions explored & impact on the C/E results for molnupiravir

Table 3 below presents the EAGs original and updated preferred assumptions, followed by those understood to be preferred by the Committee. It also presents the Company's preferred assumptions and scenarios explored in alternative cost-effectiveness analyses appropriate for the economic assessment of molnupiravir.

MSD has replicated the cost-effectiveness estimates generated from the EAG that informed the draft guidance recommendations. These are provided below alongside some MSD exploratory analyses to demonstrate the conservatism of some key assumptions that informed draft recommendation in MSD's preferred base-case assumptions include:

- Exclusion of PANORAMIC, use of mean evidence synthesis estimates
- A minimum hospitalisation rate of 2.79%
- An outpatient starting age of 56.5 similar to that of PANORAMIC
- Application of DDI costs of £352.49 to nirmatrelvir/ritonavir; assumed based on the cost of a pharmacist for 1 hour.

- Administration costs of £41 (an oral drug in the community) applied to molnupiravir; 10% proportion of the £410 administration cost applied by the EAG.

Alternative scenarios and permutations of these as outlied Table 3 above are explored to ascertain the impact on the cost-effectiveness results (presented in **Error! Not a valid bookmark self-reference.**). When PANORAMIC is excluded, and more appropriate hospitalisation rates are used and revised oral administration applied, molnupiravir is a cost-effective use of NHS resources. The higher rates of hospitalisation required for molnupiravir to be C/E under these conditions [redacted] fall well within the rates of hospitalisation provided by UK clinical experts to MSD during the consultation period. Using MSD's assumptions the [redacted] hospitalisation rates under [redacted] would result in molnupiravir being a C/E intervention. These hospitalisation again fall well within the range of hospitalisation estimates provided by UK clinical experts to MSD during the consultation period although below the value reported by Vo et al 2022 (18.7%).

Table 4 below. ICERs for molnupiravir versus standard of care across a wide range assumptions. The conservatism of the current AC assumptions negatively impacts the C/E of molnupiravir versus standard of care. **Molnupiravir has the potential to be a highly cost-effective use of NHS resources under a wide range of plausible alternative assumptions and scenarios explored by MSD.**

Table 3: Summary of base-case assumptions adopted by the EAG and the Company

	EAG base-case (updated analysis)	Committee Preferences	Company base-case
Outpatient population starting age	56.6 (PANORAMIC)	56.6 (PANORAMIC)	**56.6 (PANORAMIC)** Scenarios: • 65+ • 70+
Hospitalisation rate for SoC (%)	• Original 1.8%, • Updated 2.79% • PANORAMIC: 0.77% explored	• 2.79% • 0.77% (PANORAMIC) [redacted]	**2.79%** Scenarios: • 0.77% • 3% (expert opinion) • 5% (expert opinion) • 8% (expert opinion) • 18.7% (Vo et al 2022; as proxy scenario)

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Administration costs for oral drug in the community	£410	£410	**£41.00**[a] Scenarios: • £33.1 (PSSRU pharmacist time) • £0 (complete exclusion)
DDI costs associated with nirmatrelvir/ritonavir	£0	£0	**£352.49 applied** (does not affect SoC comparison)
Inclusion of PANORAMIC study	Yes	Yes	**No, justification provided**
Evidence synthesis estimates explored for MOV (RR for hospitalisation)	Mean: 0.68 Low: 0.50 High: 0.94	Mean Low	**Mean only** **Scenarios:** • Low (pessimistic) • High (optimistic)

Abbreviations: DDI – drug-drug interactions; SoC – standard of care
[a] this is taken as a 10% proportion of the administration costs adopted by the EAG.

MSD's preferred base-case assumptions include:

- Exclusion of PANORAMIC, use of mean evidence synthesis estimates
- A minimum hospitalisation rate of 2.79%
- An outpatient starting age of 56.5 similar to that of PANORAMIC
- Application of DDI costs of £352.49 to nirmatrelvir/ritonavir; assumed based on the cost of a pharmacist for 1 hour.
- Administration costs of £41 (an oral drug in the community) applied to molnupiravir; 10% proportion of the £410 administration cost applied by the EAG.

Alternative scenarios and permutations of these as outlied Table 3 above are explored to ascertain the impact on the cost-effectiveness results (presented in **Error! Not a valid bookmark self-reference.**). When PANORAMIC is excluded, and more appropriate hospitalisation rates are used and revised oral administration applied, molnupiravir is a cost-effective use of NHS resources. The higher rates of hospitalisation required for molnupiravir to be C/E under these conditions [redacted] fall well within the rates of

hospitalisation provided by UK clinical experts to MSD during the consultation period. Using MSD's assumptions the [redacted] hospitalisation rates under [redacted] would result in molnupiravir being a C/E intervention. These hospitalisation again fall well within the range of hospitalisation estimates provided by UK clinical experts to MSD during the consultation period although below the value reported by Vo et al 2022 (18.7%).

Table 4: Cost-effectiveness results for Molnupiravir under different assumptions using AG, or AC key assumptions alongside alternative scenarios – including MSD's exploratory analyses (disaggregated results below)

Description	Efficacy selection		
EAG	**Mean**	**Low**	**High**
Hospitalisation 2.79%	[redacted]	[redacted]	[redacted]
Hospitalisation 0.77%	[redacted]	[redacted]	[redacted]
MSD scenario: *goal seek hospitalisation < ICER £30K (2.79% starting rate)*	[redacted]	[redacted]	[redacted]
Committee; NMA efficacy estimate including PANORAMIC for MOV			
Hospitalisation 2.79%	[redacted]	[redacted]	[redacted]
Hospitalisation [redacted] ([redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation 0.77% (as per EAG's analysis above)	[redacted]	[redacted]	[redacted]
MSD scenario: *No Administration costs applied, 2.79% hospitalisation rate*	[redacted]	[redacted]	[redacted]
Hospitalisation 0.77%, molnupiravir acquisition costs £0 for first two years	[redacted]	[redacted]	[redacted]
Hospitalisation 2.79%, molnupiravir acquisition costs £0 for first two years	[redacted]	[redacted]	[redacted]
MSD scenario: *goal seek hospitalisation < ICER £30K (2.79% starting rate)*	[redacted]	[redacted]	[redacted]
Committee; NMA efficacy estimate excluding PANORAMIC for MOV			
Hospitalisation 2.79%	[redacted]	[redacted]	[redacted]
Hospitalisation 0.77%	[redacted]	[redacted]	[redacted]
No Administration costs applied, 2.79% hospitalisation rate	[redacted]	[redacted]	[redacted]
MSD scenario: *goal seek hospitalisation < ICER £30K (2.79% starting rate)*	[redacted]	[redacted]	[redacted]
Company preferred base case and associated scenarios[#]			
Hospitalisation 2.79%	[redacted]	[redacted]	[redacted]
Hospitalisation 0.77%	[redacted]	[redacted]	[redacted]
Hospitalisation of 3%	[redacted]	[redacted]	[redacted]
Hospitalisation of 5%	[redacted]	[redacted]	[redacted]
Hospitalisation of 8%	[redacted]	[redacted]	[redacted]
Hospitalisation of 18.7% as upper estimate from Vo et al 2022	[redacted]	[redacted]	[redacted]
Starting age 65+	[redacted]	[redacted]	[redacted]
65+ & *goal seek hospitalisation < ICER £30K (2.79% starting rate)*	[redacted]	[redacted]	[redacted]
65+ and assumed hospitalisation rate 5%	[redacted]	[redacted]	[redacted]

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Starting age 70+	[redacted]	[redacted]	[redacted]
70+ & *goal seek hospitalisation < ICER £30K (2.79% starting rate)*	[redacted]	[redacted]	[redacted]
70+ and assumed hospitalisation rate 8%	[redacted]	[redacted]	[redacted]
Alternative scenarios explored			
Hospitalisation 2.79% & PSSRU administration costs (£33.10)	[redacted]	[redacted]	[redacted]
Hospitalisation 3% & PSSRU administration costs (£33.10)	[redacted]	[redacted]	[redacted]
Hospitalisation 5% & PSSRU administration costs(£33.10)	[redacted]	[redacted]	[redacted]
Starting age for outpatients at 60 years of age	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

#PANORAMIC excluded, DDIs costs for r/n included, reduced admin costs of £41 for molnupiravir, baseline age of 56.6 years)
*Values included in ACD letter response, **BOLD:** values discussed within ACD response

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Appendix 2.3: Disaggregated cost-effectiveness results of exploratory MSD's preferred base-case

Disaggregated results on MSD's preferred base case are reported below for validation purposes. Applying MSD's assumptions results in total discounted costs of £[redacted] and total discounted QALYs of [redacted] for molnupiravir and an overall ICER of £[redacted] for molnupiravir versus SoC. See Table 5 for a breakdown of results.

Table 5: Mean efficacy results for people at high-risk hospitalisation using the Company's preferred base-case

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC▪(£)	NMB compared with SoC▪▪ (£)	Cost per QALY Incremental Analyses (£)
SoC	622	12.90	-	-	-	-
Nirmatrelvir/ritonavir	1,862	13.01	[redacted]	[redacted]	[redacted]	-
Molnupiravir	[redacted]	12.98	[redacted]	[redacted]	[redacted]	Dominated

▪ Assuming a threshold of £20,000 per QALY gained ▪▪ Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care

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Appendix 3: Real-world evidence studies for molnupiravir

Table 6: RWE Comparative Effectiveness Studies With Molnupiravir in Patients With SARS-CoV-2 Infection: Peer-reviewed and Pre-print Manuscripts (Published as of 29-Sep-2022)

Author/ date published	Study Design / Population Enrollment Time Period/ SARS-CoV-2 Variant(s) (if known)	Treatment Groups, N (%)	Main Outcome / Endpoint Results	Reported baseline hospitalisation rate (i.e., untreated arm)
Wong et al, 2022[8] • Published 24-AUG-2022	Territory-wide retrospective cohort study • Adult hospitalized patients with SARS-CoV-2 infection in public hospitals not requiring oxygen therapy on admittance • 26-FEB-2022 to 26-APR-2022 Omicron BA.2	Total N=5492 (after PSM) • MOV: 1856 • NMV+r: 890 • Control for MOV: 1856 • Control for NMV+r: 890	<u>All-cause mortality (primary), n (%):</u> • MOV: 150 (8.1%) • Control for MOV: 295 (15.9%) • NMV+r: 32 (3.6%) • Control for NMV+r: 92 (10.3%) • <u>Comparisons:</u> • MOV vs Control HR=0.48 (95% CI=0.40, 0.59), p<0.0001 • NMV+r vs Control HR=0.34 (95% CI=0.23, 0.50), p<0.0001	<u>Without MOV: 15.9%</u>

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	Bruno et al, 2022[9] • Published 14-NOV-2022	Retrospective study • Individuals with confirmed COVID-19and mild-moderate illness who received an oral antiviral prescription in Taranto and its Province • 11-JAN-2022 to 10-JUL-2022 Conducted during Omicron variant	Total N=719 • MOV: 554 (77%) • NMV-r(NVM) = 165 (23%)	<u>All-cause hospitalization at 30 days, n (%):</u> • MOV+NMV: 43 (5.9%) • MOV: 36 (6.5%) • NMV: 7 (4.24%) • p=0.351 <u>Death at 30 days, n (%):</u> • MOV+NMV: 13 (1.8%) • MOV: 11 (1.99%) • NMV: 2 (1.21%) • P=0.742	<u>N/R</u>
	Flisiak et al, 2022[11] Published 24-AUG-2022	Retrospective analysis of the SARSTer Polish national database • Hospitalized adult patients with COVID-19 • 01-JAN-2022 to 30-APR-2022 Conducted during Omicron variant (not otherwise specified) dominance in Poland	Total N=590 • MOV: 203 (34.4%) No AVT: 387 (65.6%)	<u>Mortality Day 28, n (%):</u> • MOV: 20 (9.9%) • No AVT: 63 (16.3%) • p=0.03 <u>Need mechanical ventilation Day 28, n (%):</u> • MOV: 7 (3.5%) • No AVT: 14 (3.6%) p=0.916	<u>N/R</u>

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	Yip et al, 2022[34] Published 29-AUG-2022	Territory-wide, retrospective cohort study • Non-hospitalized adults with SARS-CoV-2 infection with mild symptoms who attended designated COVID-19 clinics and had not used MOV or NMV+r • 16-FEB-2022 to 31-MAR-2022 Conducted during Omicron outbreak	Total N=14,477 (after PSW) • MOV: 4798 (33.1%) • NMV+r: 4921 (34.0%) • No oral AVT: 4758 (32.9%)	Hospitalized Day 30, n (%): • MOV vs no oral AVT (HR=1.17, p=0.062) • NMV+r vs MOV (HR=0.67, p<0.001)	N/R
	Najjar-Debbiny et al, 2022[10] Published 20-SEP-2022	Retrospective cohort study based on the Clalit Health Services database and the Israeli Ministry of Health COVID-19 database • Adults with SARS-CoV-2 infection with ≥1 comorbidity or condition associated with high risk for severe disease • 01-JAN-2022 to 28-FEB-2022 Conducted when Omicron was the main variant in Israel	Total N=5322 (after PSW) • MOV: 2661 (50%) • Controls: 2661 (50%)	Composite outcome of severe COVID-19 or COVID-19-specific mortality (all patients), n (%): • MOV: 50 (22.8%) • Control: 60 (27.4%) HR (95% CI): 0.83 (0.57, 1.21)	N/R

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	Hashash et al, 2022[35] Published 22-SEP-2022	Retrospective cohort study with propensity score matching • Patients with IBD and COVID-19 who received MOV or NMV+r • Data obtained through 18-AUG-2022 using TriNetX system (start date not identified) Variant not described	Total N=1360 (after PSM) • MOV: 149 (11%) • Control cohort for MOV: 149 (11%) • NMV+r: 531 (39%) • Control cohort for NMV+r: 531 (39%)	Hospitalization, n (%): • MOV: 10 (6.7%) • Control for MOV: 13 (8.7%) • NMV+r: 10 (1.8%) • Control for NMV+r: 27 (5.0%) Comparisons, aOR (95% CI): • MOV vs Control: 0.75 (0.31, 1.77) • NMV+r vs Control: 0.35 (0.17, 0.74)	8.7%
	Wong et al, 2022[7] Pre-print posted 26-MAY-2022 followed by Lancet 08-OCT-2022	Territory wide retrospective cohort study with case-control as sensitivity analysis • Non-hospitalized adult COVID-19 patients • 26-FEB-2022 to 03-MAY-2022 Omicron BA.2.2 wave	Total N=54,217 (after matching) • MOV: 4983 with 49,234 matched controls • NMV+r: 5542 with 54,672 matched controls.	Crude Incidence (per 100,000 person-days) of all- cause mortality: • MOV: 17.9 • Matched Control: 22.1 • HR 0.76 (95% CI 0.61-0.95); p=0.013 Crude Incidence (per 100,000 person-days) of COVID-19-related hospitalization: • MOV: 107.6 • Matched Control: 104.0 • HR 0.98 (95% CI 0.89-1.06); p=0.58	104.0 per 100,000 person days

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				Crude Incidence (per 100,000 person-days) of a composite outcome of in-hospital disease progression: • MOV: 10.2 • Matched Control: 16.8 • HR 0.57 (95% CI 0.43–0.76); p=0.0001	
	Zheng et al, 2022[26] Posted as pre-print 23-SEP-2022	Observational cohort study • Non-hospitalized, high-risk adults with SARS-CoV-2 infection and symptom onset within 5 days in the OpenSAFELY TPP platform • 16-DEC-2021 to 10-FEB-2022 (Period 1) • 16-FEB-2022 to 01-MAY-2022 (Period 2); • Main analyses focused on Period 1; MOV moved to third line after 10-FEB-2022. Omicron BA.2 in Period 2; variant not reported for Period 1	Total N=6020 (Period 1) • MOV: 2689 (44.7%) • Sotrovimab: 3331 (55.3%)	COVID-19 hospitalization Day 28, n (%): • MOV: 55 (2.05%) • Sotrovimab: 32 (0.96%) HR=0.54 (0.33, 0.88)	N/R

Arbel et al, 2022[6] Posted 29-SEP-2022	Retrospective cohort study • Outpatient Clalit Health Services members ≥40 years of age with SARS-CoV-2 infection at high risk for progression to severe disease for whom NMV+r treatment is precluded • 16-JAN-2022 to 31-MAR-2022 Omicron	Total N ≥65 years: 13569 • MOV: 845 (5.9%) • No AVT: 12,724 (94.1%) Total N 40-64 years: 6299 • MOV: 224 (3.4%) • No AVT: 6075 (96.6%)	Hospitalization related to COVID-19, n (%): *Patients ≥65 years of age*: • MOV: 18 (2.1%) • No AVT: 513 (4.0%) • HR (95% CI): 0.55 (0.34, 0.88) *Patients 40 to 64 years of age:* • MOV: 8 (3.6%) • No AVT: 97 (1.6%) • HR (95% CI): 1.80 (0.86, 3.77) Death due to COVID-19, n (%): *Patients ≥65 years of age*: • MOV: 4 (0.5%) • No AVT: 137 (1.1%) • HR (95% CI): 0.26 (0.10, 0.73)	*Patients ≥65 years of age*: 4.0% *Patients 40 to 64 years of age:* 1.6%

NR: Not reported or not possible to estimate based on the data reported.

Table 7: RWE Studies With Molnupiravir in Patients With SARS-CoV-2 Infection: Single Centre Studies and Scientific Abstracts/Posters/Presentations (Available as of 29-Sep-2022

Title (Country) / First Author / Journal / Date Published	Study Design / Population Enrollment Time Period/ SARS-CoV-2 Variant(s) (if known)	Treatment Groups, N (%)	Main Outcome / Endpoint Results
Real-world Experience With Available, Outpatient COVID-19 Therapies in Solid Organ Transplant Recipients during the Omicron surge (US) • Radcliffe et al, 2022 • *American Journal of*	Single center, retrospective review • Outpatient adult solid organ transplant recipients in the Yale-New Haven Health System with SARS-CoV-2 infection with mild to moderate symptoms • 01-JAN-2022 to 16-FEB-2022	Total N=122 • MOV: 49 (40.2%) • Sotrovimab: 24 (19.7%) No COVID-19 Therapy: 48 (39.3%)	Hospitalizations Day 30, n (%): • MOV: 8 (16.3%) • Sotrovimab: 2 (8.3%) • No COVID-19 Therapy: 13 (27.1%) Deaths Day 30, n (%): • MOV: 0

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Transplantation (https://doi.org/10.1111/ajt.17098) Published 18-MAY-2022	Viral sequencing data not available; investigators selected time period to ensure majority of cases were caused by Omicron		• Sotrovimab: 0 • No COVID-19 Therapy: 3 (6.3%)
Preliminary Clinical Experience of Molnupiravir to Prevent Progression of COVID-19 in Kidney Transplant Recipients (Spain) • Villamarin et al, 2022 • *Transplantation* (https://doi.org/10.1097/tp.0000000000004306) Published 02-AUG-2022	Prospective observational cohort single center study • Outpatient adult kidney transplant recipients with SARS-CoV-2 infection and mild symptoms for whom treatment with mAb or RDV (for the MOV group) was precluded • 01-JAN-2022 to 30-APR-2022 MOV patients were reported to be infected with the Omicron variant	Total N=16 • MOV: 9 (52.9%) • RDV: 7 (43.8%)	Progression to SARS-CoV-2 pneumonia, n (%): • MOV: 1 (11%) • RDV: 0 Hospital admission due to SARS-CoV-2 pneumonia, n (%): • MOV: 1 (11%) • RDV: 0
The Role of Molnupiravir in Reducing Risk of Hospitalization in COVID-19 Infection (Serbia) • Ćatović et al, 2022 Poster presented at The First World Conference in Belgrade, Serbia (26- to 28-MAR-2022)	Single center, retrospective review • Non-hospitalized patients with laboratory confirmed SARS-CoV-2, with at least 1 risk factor for developing severe COVID-19 at COVID-19 Clinic at Novi Sad • JAN 2022 Predominant variant not specified	Total N=1011 • MOV: 499 (49.4%) • No AV: 512 (50.6%)	Hospitalization, n (%): • MOV: 11 (2.2%) vs No AV: 26 (5.0%) [p=0.023] Death, n (%): • MOV: 3 (0.6%) vs No AV: 7 (1.4%) [P=not significant] Pneumonia, n (%): • MOV: 47 (9.4%) vs No AV: 86 (16.8%) [P=0.001]
Kidney Transplant Recipients And Omicron: Outcomes, Effect of Vaccines and the Efficacy and Safety of Novel Treatments (UK) • Gleeson et al, 2022	Prospective, single-site study • Kidney transplant recipients with COVID-19 (PCR or lateral flow antigen testing) with symptomatic disease who started therapy (MOV, sotrovimab, or NMV+r)	Total N=122 • MOV: 21 (17.2%) • Sotrovimab: 47 (38.5%) No COVID-19 treatment: 48 (39.3%)	• Hospitalization: MOV, 3 (14.3%); sotrovimab, 1 (2.1%); no treatment, 10 (20.8%), p=0.056 • ICU admission: MOV, 1 (4.8%);

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• Pre-print (https://doi.org/10.1101/2022.05.03.22274524) Posted 03-MAY-2022	within 5 days of testing • 17-DEC-2021 to 30-MAR-2022 Conducted when Omicron was the dominant variant in London		sotrovimab, 0; no treatment, 1 (2.1%) • Deaths: MOV, 1 (4.8%); sotrovimab, 0; no treatment, 2 (4.2%) • Required acute renal support (dialysis or hemofiltration) post-COVID-19 diagnosis: MOV, 2 (9.5%); sotrovimab; 0; no treatment, 4 (8.3%) p=0.035 *P-values are for MOV vs sotrovimab*
Preliminary Experience With Molnupiravir in Immunocompromised Patients With Mild COVID-19 (Spain) • Alvarez et al, 2022 Poster presented at National Congress of the Spanish Society of Infectious Diseases and Clinical Microbiology in Granada, Spain (02- to 05-JUN-2022)	Single-center, retrospective observational study with a non-contemporaneous control group • Immunocompromised patients with mild-to-moderate COVID-19 admitted • MOV: 01-JAN-2022 to 01-APR-2022; Control: 01-JUL-2021 to 01-APR-2022 Predominant variant not specified	Total N=126 • MOV: 62 (49.2%) Non-contemporaneous control group who did not receive MOV: 64 (49.6%)	Absence of symptoms 24 hours after treatment start, n (%): • MOV: 45 (79%) • RMD: 24 (68.6%) • NMV+r:30 (62.4%) Hospitalization at Day 30, n (%): • MOV: 0 • RMD: 0 • NMV+r: 0 Death at Day 30, n (%): • MOV: 0 • RMD: 0 NMV+r: 0
Efficacy of Early Antiviral Therapies Among High-risk Patients With Mild to Moderate COVID-19 (Italy) • Amadasi et al, 2022 Poster presented at the Italian	Retrospective observational study • Non-hospitalized patients with high risk for progressing to severe COVID-19 • 01-JAN-2022 to 15-MAR-2022	Total N=140 • MOV: 57 (40.7%) • RDV: 35 (25.0%) • NMV+r: 48 (34.3%)	Absence of symptoms 24 hours after treatment start, n (%): • MOV: 45 (79%) • RMD: 24 (68.6%) • NMV+r:30 (62.4%)

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Conference on AIDS and Antiviral Research in Bergamo, Italy (12- to 14-JUN-2022)	Predominant variant not specified		Hospitalization at Day 30, n (%): • MOV: 0 • RMD: 0 • NMV+r: 0 Death at Day 30, n (%): • MOV: 0 • RMD: 0 NMV+r: 0
Efficacy of Early Antiviral Therapies Among High-risk Patients With Mild to Moderate COVID-19 (Italy) • Amadasi et al, 2022 Poster presented at the Italian Conference on AIDS and Antiviral Research in Bergamo, Italy (12- to 14-JUN-2022)	Retrospective observational study • Non-hospitalized patients with high risk for progressing to severe COVID-19 • 01-JAN-2022 to 15-MAR-2022 Predominant variant not specified	Total N=140 • MOV: 57 (40.7%) • RDV: 35 (25.0%) • NMV+r: 48 (34.3%)	Absence of symptoms 24 hours after treatment start, n (%): • MOV: 45 (79%) • RMD: 24 (68.6%) • NMV+r:30 (62.4%) Hospitalization at Day 30, n (%): • MOV: 0 • RMD: 0 • NMV+r: 0 Death at Day 30, n (%): • MOV: 0 • RMD: 0 • NMV+r: 0
Oral Antivirals Ritonavir-Nirmatrelvir and Molnupiravir are Highly Effective in Patients with Multiple Myeloma and COVID-19; A Single Center, Prospective Study (Greece) • Spiliopoulou et al, 2022	Prospective study in patients with multiple myeloma • Patients with multiple myeloma and SARS-CoV-2 infection at high risk for severe COVID-19 treated within 5 days of symptom onset	• Total N=64 • MOV: 30 (47%) • NMV+r: 34 (53%)	Hospitalization, RR (95% CI): • NMV+r (2.9%) vs MOV (6.7%) • 0.44 (0.04.4.63) Severe/moderate COVID-19, RR (95% CI): • NMV+r (11.8%) vs MOV (10.0%)

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Poster presented at the International Myeloma Society Annual Meeting in Los Angeles, US (25- to 27- AUG-2022)	Study started in FEB-2022; no end date given		• 1.18 (0.29, 4.84) Mortality, RR (95% CI): • NMV+r (2.9 vs MOV (3.3%) 0.88 (0.06, 13.50)
Nirmatrelvir/Ritonavir and Molnupiravir in the Treatment of Mild/Moderate COVID-19: Results of a Real-life Study (Italy) • Gentile et al, 2022 • Vaccines (https://doi.org/10.3390/vaccines10101731) Pre-print posted 25-AUG-2022 followed by Vaccines 17-OCT-2022	Retrospective single-center study • Adults with SARS-CoV-2 infection treated with oral AVs, no other selection criteria • 18-FEB-2022 to 30-JUN-2022 Not specified, Omicron dominant during the study period	Total N=257 • MOV: 146 (56.8%) • NMV+r: 111 (43.2%)	Hospitalizations through 14-day follow-up, n (%): • MOV: 3 (2.1%) • NMV+r: 1 (0.9%) Death, n: • MOV: 1 • NMV+r: 0 Adverse drug reactions, n (%): • MOV: 13 (8.9%) • NMV+r: 18 (16.2%)

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Appendix 3: Full report & abstract submission of study baseline risk analysis conducted by MSD [CIC].

Attachments shared separately with NICE as CIC

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Appendix 4: Summary of clinical expert feedback collected by MSD during the consultation process

Table 86: Clinical questions and responses provided to MSD during the consultation period

Question	Expert comment
Should the PANORAMIC study have been meta-analysed with Molnupiravir in the NICE MTA, considering it included a different patient population i.e. fully vaccinated, high risk of hospitalisation/death (but highest at risk referred to CMDU instead) and during Omicron?	**Clinical Expert 1:** "The population doesn't include the most at risk (as these were in CMDUs) but there were changes to the virus and the population (with a less pathogenic virus in a multiply vaccinated population). The data are not fully comparable. Omicron is circulating in a well-vaccinated population going forward. But the primary end point (of hospital admission and severe disease) does not include those who are not most likely to have severe disease (in CDMU), which could affect the primary end point." **Clinical Expert 4:** There was no reason to include PANO in the meta-analysis.
If so, in your opinion, should it have been meta-analysed with the 4 RCTs for Molnupiravir when no other drug being assessed was impacted by PANORAMIC?	**Clinical Expert 1:** "Difficult to say as the population that were recruited onto the trial were not being hospitalised at the same rates as previously, due to virus being less pathogenic. Difficult comparison" **Clinical Expert 4:** "They did not include Hetero and other studies with MOV"
What is your expert opinion around the "true population of high risk, progressing to severe disease" that was recruited in the PANORAMIC study?	**Clinical Expert 1:** "What we deem as high risk now with the Omicron variant is different from other variants or the initial "high risk" criteria. Those who were included into the trial were the more vulnerable – to what we thought – so those who we would expect to have severe disease from respiratory infections, and I am sure the inclusion of these would be correct. I think the question is, if the most vulnerable are removed from the trial (to the CMDUs) then those who are left are more of a moderate group so would not be truly high risk." **Clinical Expert 2:** "Patients with Kidney disease (CKD 4/5), end-stage renal disease (ESRD), solid organ transplant patients, those with haematological malignancies, liver disease, heart failure were not included in PANORAMIC". **Clinical Expert 3:** "It was not the MOVe-OUT RCT population. Post-transplant recipients were significantly higher for MOVe-OUT RCT".
The MTA modelled hospitalisation rates ranging from 0.77% (PANORAMIC) to 2.79%. Would you comment on how hospitalisation these rates could change over time, and are you aware of any UK publications with additional hospitalisation rates for high risk patients?	**Clinical Expert 1:** "I do not have specific data on hospitalisation but there was a clear significant drop in admissions, and of those who were admitted it was a few days of oxygen treatment with discharged – it was pretty much only immunocompromised or those who had not had vaccinations who had any significant issues. We did see in primary care that people were still feeling very sick fatigue and tiredness that continued for several weeks including long covid symptoms." **Clinical Expert 2:** "3-5% of high-risk patients need hospitalisation, at the very least double the rate of hospitalisation from PANORAMIC (i.e., 0.77% x 2 = **1.5%**). **If**

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What do to consider as a relevant hospitalisation rate for patients at high risk of progressing to severe disease if left untreated?	**they cannot mount a response to vaccines, up to 7-8% will need hospitalisation."** 28% of CMDU referrals are treated via COVID-19 agents, from these 28% treated, under **20%** fail to mount an immune response and these are patients who are at highest risk of disease progression – these are likely patients who do not respond to vaccines." **Patient group:** Regarding the hospitalisation rate derived from PANORAMIC, they said "*there is no place in this appraisal for this*" i.e., the hospitalisation rate is not reflective since the PANORAMIC patient population did not include those patients highest at risk. **MSD note**: values used in exploratory scenario analyses to ascertain the impact of hospitalisation rates.
Regarding real world evidence, are you aware of any that may be relevant for the ongoing Molnupiravir assessment? -	**Clinical Expert 1:** "The biggest thing in my mind with molnupiravir is its effect on long covid and the cost effectiveness analysis – I do know this is going to be looked at in Panoramic. We have had significant numbers that still have significant time off work and some having prolonged symptoms lasting months. From the trial it was clear symptoms and recovery were improved with Molnupiravir. I think if this translates to reduced long covid symptoms and less time off work etc. this may be significant." **Clinical Expert 2:** "Clalit study from Israel." **Clinical Expert 3:** "Molnupiravir has a potential broad-spectrum antiviral and the need to prepare for future pandemic"
Do you consider the administration costs used currently for oral agents (£410) to be truly reflective of the community setting under the assumption that deployment will be moving outside the CMDUs for most patients?	**Clinical Expert 1:** "This will be difficult to justify. If long COVID shown to be reduced and was cost effective, and it was well tolerated, this would support its use on a larger scale." **Clinical Expert 2:** "Perhaps not fully reflective of those assessed in the community setting alone (vast majority of molnupiravir patients)"
Once community prescribing of COVID-19 antivirals is in place, could you please comment on the % of patients who may require a referral to CMDU or a consultant in the long run due to comorbidities/ poly pharmacy?	**Clinical Expert 1:** "I do not have exact numbers. I would look at this as two groups. High risk – immunocompromised – or moderate risk – with co-morbidities. We do not have many in high risk as a proportion to the moderate risk. The percentage would be low, but the main issue is identifying these patients as not all testing and most feeling not needing to worry about it anymore etc. The significant think in my mind id the long COVID and cost effectiveness of this." **Clinical Expert 2:** **"7-8% or perhaps a 10% would need specialist engagement**, such as CMDU referral due to co-morbidities and DDIs (so this is the group that cannot be managed via GP/pharmacist)". **Patient group:** "If the decision is finalised, there will be no treatment option for highest at-risk patients, that is, those currently classed as high risk (CKD 4 or 5 and on dialysis according to McInnes criteria). Those patients who are aware of this draft guidance are very concerned that they will not have any treatment option. If this decision is finalised, should a patient with

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	the above criteria test positive for COVID-19, they will have to wait until they require oxygen therapy as well as to be hospitalised in order to receive ANY treatment for COVID-19 (they must be on oxygen, not just hospitalised to receive treatment)." **MSD note**: upper value used to adjust the current oral administration costs based on expert feedback.
Do you consider that some patients may still require more extensive review from CMDU equivalent facilities when these treatment are deployed in community setting	**Clinical Expert 1:** "Unclear" **Clinical Expert 2:** "Around 20% of patients cannot be given Paxlovid so alternative choice is needed for these patients".

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Checklist for submitting comments

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

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

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. • The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer
Disclosure **Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.**	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Restriction of the eligible population despite cost-effectiveness in a broader population** Pfizer are disappointed that NICE have chosen to restrict the definition of high risk, effectively removing from consideration a large group of patients who could benefit from treatment (outlined in Appendix 1 Table 2), particularly given the Committee conclusion that this restriction could indirectly discriminate against patients with disability, such as those with severe and profound

	learning disability. This is despite evidence of clinical and cost-effectiveness of Paxlovid in a broader population of patients. In this response we address this issue by discussing the following: • The inappropriateness of using the McInness report definition of highest risk to define a high-risk population • Retained high risk population trends in the era of the Omicron SARS-Cov-2 variant (Comment 2) • The use of age in defining a population at high risk of severe COVID-19 in a robust and equitable way (Comment 3) • Hospitalisation rates adopted in the model by the committee do not align with the considered population, we therefore propose alternative estimate sources (Comment 4) • Perform further cost effectiveness analysis using alternative hospitalisation rates (Comment 9). The appraisal consultation document (ACD) states that subgroups should be considered separately because considering a mixed group of risk definitions disadvantages the highest risk groups. It is unclear why this should be the case, as availability of treatments for all high-risk patients will ensure that the highest risk groups will also receive treatment. Use of the McInnes report to define the eligible population is of particular concern given the stated objectives of this work are not aligned to the objectives of the NICE assessment. The McInnes report sought to define those patients who remain at the very highest risk of severe COVID-19 despite full adherence with community-wide public health measures including vaccination.[1] This is in contrast to defining all those who are at high risk of adverse COVID-19 outcomes that could hence benefit from treatment with Paxlovid®, which should be the remit of this assessment. The very highest risk population as defined by the McInnes report is in effect a subgroup of the population at high risk of severe COVID-19. A clear distinction between high and highest risk needs to be made as was done by in the study by Patel et al., 2022[2] in which they calculated the hospitalisation rate for the for the McInnes report subpopulation. As a result, within the ACD, all references to the “high risk” definition from the McInnes report should more accurately be termed “highest risk”. This conclusion is supported by international guidance,[3] where the definition of “high risk” broadly aligns with the PANORAMIC study,[4] which should be the definition considered in this guidance. The ACD states that the committee was concerned that making a recommendation based on age might cause inequality, given that age is a protected characteristic. While we acknowledge the challenge in defining an age threshold, we disagree that doing so is a source of inequality. The Joint Committee on Vaccination and Immunisation (JCVI) routinely recommends access to vaccinations based on age as an eligibility criterion and this includes access to the COVID-19 vaccine. The JCVI state that for the 2022 autumn booster programme,[5] the primary objective is to augment immunity in those at higher risk from COVID-19 and thereby optimise protection against severe COVID-19, specifically hospitalisation and death, over winter 2022 to 2023. Those at higher risk are defined as: • residents in a care home for older adults and staff working in care homes for older adults • frontline health and social care workers

- all adults aged 50 years and over
- persons aged 5 to 49 years in a clinical risk group, as set out in the Green Book, chapter 14a, tables 3 and 4[6]
- persons aged 5 to 49 years who are household contacts of people with immunosuppression
- persons aged 16 to 49 years who are carers, as set out in the Green Book, chapter 14a, table 3[6]

We agree with NICE that staging recommendations across different subgroups would introduce additional uncertainty. However, restricting the criteria applied in the community setting to only those at the absolute highest risk deprives patient groups at risk of progression to severe disease of effective treatment. We are not aware of any clinical or cost-effectiveness rationale to exclude these patients from receiving treatment and believe this decision goes against the scientific evidence[7] and expert opinions shared in the company submission (CS) and at the appraisal committee meeting (ACM).

Table 1. High- and highest-risk conditions criteria

Highest-risk conditions	High-risk conditions
Down's syndrome	Age ≥70 years
Solid cancer	Long-term respiratory conditions
Haematological disease and stem cell transplant recipients	Chronic heart disease
Advanced renal disease	Chronic kidney disease
Liver disease	Chronic liver disease
IMID	Chronic neurological condition
Immune deficiencies	Diabetes
HIV/AIDS	Weakened immune system caused by medical condition or medication
Solid organ transplant	Obesity (class III)
Rare neurological conditions	Pregnancy
	Severe respiratory conditions
	Rare disease and inborn errors of metabolism

AIDS: acquired immune deficiency syndrome; IMID: immune-mediated inflammatory diseases; HIV: human immunodeficiency virus.
Source: Patel et al. (2022)[2]

2

Evidence to support high risk population in the era of Omicron

The Appraisal Committee has requested additional evidence to support a broader definition of high risk, specifically evidence in a vaccinated population with the Omicron variant. Pfizer has presented this evidence below and on this basis request that the Appraisal Committee re-consider the restriction of the eligible population.

The ACD notes the following: "The committee concluded that more evidence is needed on the impact of age to justify including it as an independent factor that increases risk at similar levels to other comorbidities defined in the McInnes report. This should include evidence, adjusted for comorbidities, from a vaccinated population with the Omicron variant." We are unclear as to why

	this evidence needs to achieve this specific criterion to be considered valid. The McInnes report was published in May 2022 and is predominantly based on evidence published during 2021[1], particularly QCOVID3, which is based on data available to June 2021.[8] As a result, the conclusions from the McInnes report are based on evidence from time periods where the Alpha and Delta variants were dominant in the UK.[9,10] Although it is likely that the conclusions from the McInnes report remain relevant to the "highest risk" population, it is important to note the time period and associated dominant variants contributing to this evidence base. As such, it is unclear why the Committee considered this to be the most robust definition when later evidence is available to support the inclusion of broader patient groups within the high-risk category (see Omicron based evidence in Appendix 2).[11-13] As previously highlighted, the living risk prediction algorithm QCOVID has demonstrated the impact of an increasing age on the risk of COVID-19 death and hospitalisation in England.[14] The algorithm has been externally validated[15] and further validated via real world evidence studies in Wales and Scotland.[16,17] In addition to QCOVID, there is a substantial UK and international evidence base supporting age as an independent risk factor for hospitalisation and mortality,[18-22] detailed in the CS. At the core of the McInnes report is a subset of conditions identified as high risk for severe COVID-19 based on QCOVID3, with additional data from the advisory group evaluating additional data from the ISARIC Coronavirus Clinical Characterisation Consortium (ISIRAC 4C)[13] report. Additional literature and expert opinion were used to provide further granularity allowing for identification of a very highest risk subgroup. In our CS evidence, from an evaluation of QCOVID4 risk algorithm[23] (commissioned by the UK's Department of Health and Social Care), we used data from the Omicron wave, as well as the number of vaccination doses and prior SARS-CoV-2 infection, to identify individuals at highest levels of absolute risk for targeted interventions more accurately than the 'conditions-based' approach adopted by NHS Digital based on relative risk of a list of medical conditions. We also provided evidence from literature showing a clear increased risk of severe COVID-19 for conditions included in the PANORAMIC study, as well as a clear independent correlation between age and risk of severe COVID-19. The independent clinical experts who contributed to the ACM discussion, agreed with this assessment citing similar evidence.[24] In its evidence-based resource for healthcare professionals, the Center for Disease Control and Prevention (CDC) includes age as a risk factor for severe COVID-19 outcomes, going as far to say "Age remains the strongest risk factor".[3] High risk populations included in the PANORAMIC study are also listed by CDC in its summary of conditions with evidence for higher risk for severe COVID-19 outcomes, including asthma, COPD, diabetes, learning disabilities, heart conditions, and obesity (BMI ≥ 30 kg/m^2).[3] The CDC defines higher risk for severe COVID-19 outcomes as an underlying medical condition or risk factor that has a published meta-analysis or systematic review or having completed the CDC systematic review process.[25] The evidence the CDC provide[26] could be used to supplement or as an alternative to the McInnes report for defining high risk populations. Similarly, age is a key criterion in the definition of higher risk applied in the UK for the 2022 autumn booster programme.[5,6] This advice notes that those patients over the age of 65 years have by far the highest risk, and the risk increases with age. As a result, patients are further prioritised for vaccination on the basis of age:

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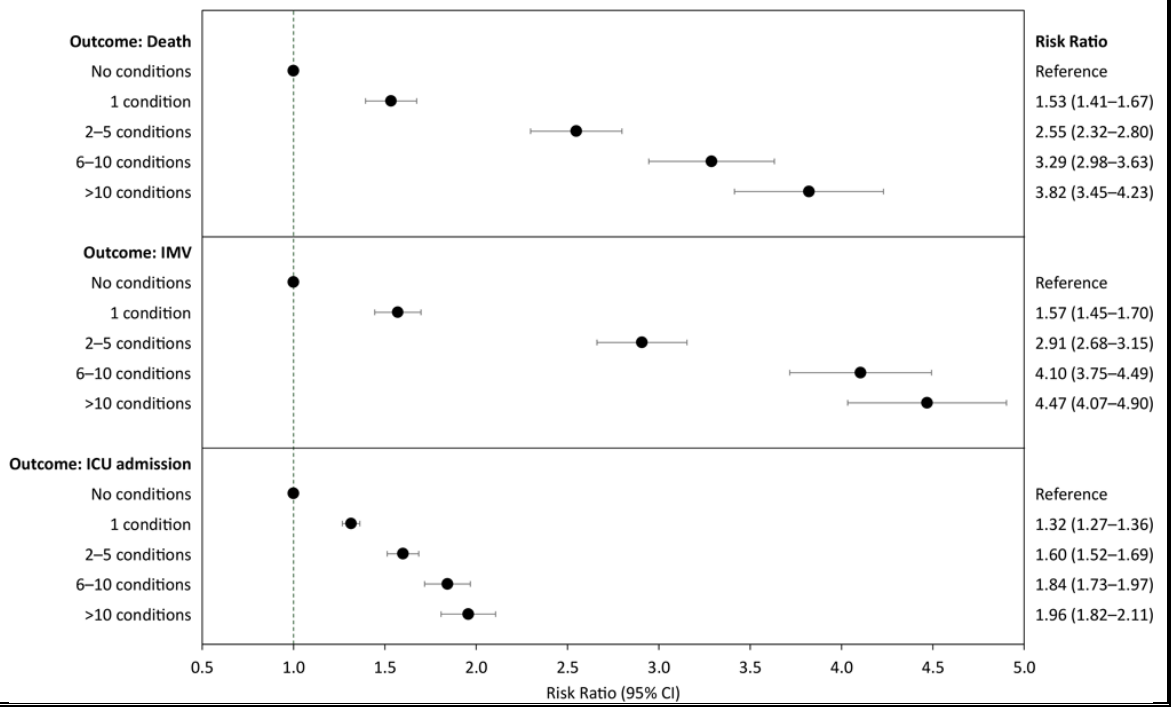
	1. Residents in a care home for older adults or staff working in care homes for older adults 2. Frontline health and social care workers and all those 80 years of age and over 3. All those 75 years of age and over 4. All those 70 years of age and over or individuals aged 16 to 69 in a high-risk group 5. All those 65 years of age and over 6. Adults aged 16 to 65 years in an at-risk group 7. All those 60 years of age and over 8. All those 55 years of age and over 9. All those 50 years of age and over
3	**Age as a robust and equitable definition of high risk** While age is an independent risk factor for severe COVID-19 outcomes,[7,27] pre-existing conditions are also independently correlated to severe COVID-19 outcomes. In addition, the total number of underlying medical conditions (multi-morbidities) was a strong risk factor of severe COVID-19 illness (see Figure 1).[28,29] Even in the Omicron era, older age, frailty and multimorbidity remain significant risk factors for a worse clinical outcome.[11-13,29,30] Guidance from the McInnes report focused on a few specific pre-existing conditions in isolation and did not account for the cumulative absolute risk associated with multiple co-morbidities, age, prior infection, vaccination status or the new variants. 

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Figure 1. Risk ratio (95% CI) of death, invasive mechanical ventilation (IMV), and admission to intensive care unit (ICU), by the number of underlying medical conditions among adults hospitalised with COVID-19 in the Premier Healthcare Database Special COVID-19 Release.

Each panel contains the results of a single generalized linear model with Poisson distribution and log link function, adjusted for age group, sex, race/ethnicity, payer type, hospital urbanicity, US Census region of hospital, admission month, and admission month squared as controls. Patients who died without ICU care or IMV were excluded from the sample when estimating the model with the outcome of ICU care or IMV, respectively.

Source: Kompaniyets et al. (2021)[28]

It is well documented that age is positively correlated with the prevalence of co-morbidities,[31,32] as well as the number of conditions an individual has (multi-morbidities).[32-35] In 2015, it was estimated that over half (54.0%) of the population aged 65+ in England had two or more diseases. When stratified by age, multi-morbidity increases with age: from 45.7% for those aged 65–74 to 68.7% for those aged 85+.[33] Another study looking at British civil servants at Whitehall in London estimated that the prevalence of multi-morbidity (≥2 chronic diseases) was 6.6% (655/9937) at age 55 and 31.7% (2464/7783) at age 70.[33] Multi-morbidity is common, socially patterned, and associated with increased health service utilisation.[35] A Clinical Practice Research Datalink (CPRD) study of adults ages 18+ in England found that greater socioeconomic deprivation was associated with significantly higher levels of multi-morbidity — 30.0% in the quintile with the greatest levels of deprivation versus 25.8% in that with the lowest (see Figure 2 below).[35]

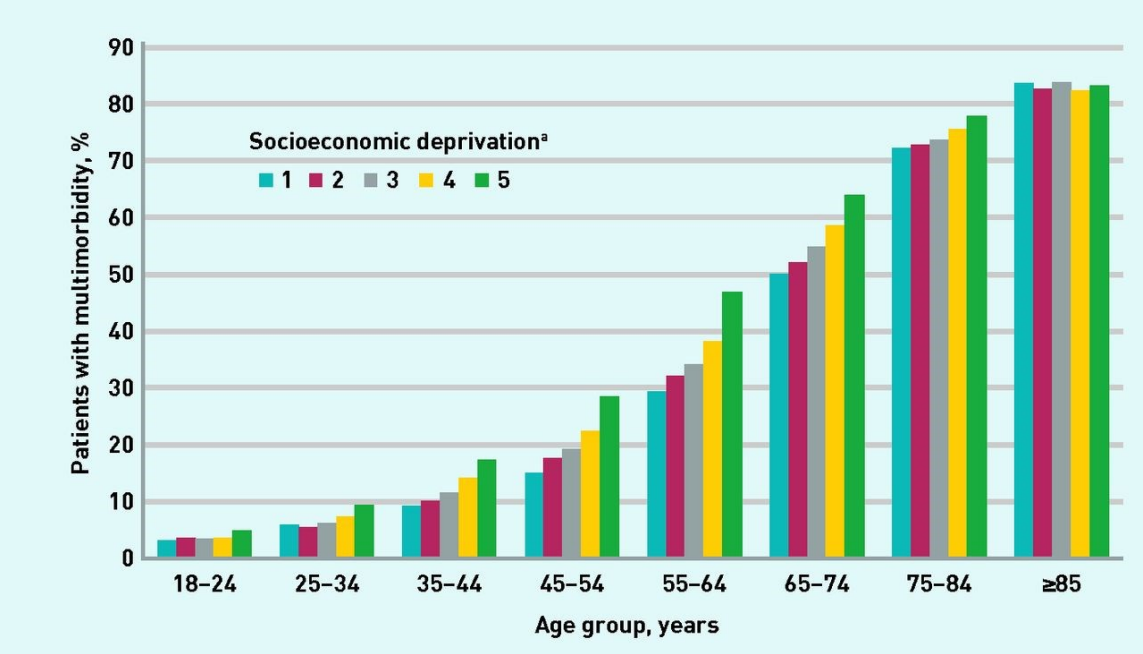

Figure 2. Prevalence of multimorbidity by age and socioeconomic status. A1 is the quintile with the least socioeconomic deprivation, 5 is that with the greatest.

Source: Cassell et al. (2018)[35]

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	An eligibility criterion that includes an age threshold allows for the equitable inclusion of patients with not only individual pre-existing high risk conditions but also those with cumulative absolute risk associated with multiple co-morbidities and age which places them at high risk of severe COVID-19 or COVID-19 related death. In Comment 9, we present results from scenario analysis that in combination with additional data from PANORAMIC would allow the committee to determine an age inclusion criterion using cost-effectiveness analysis. This is similar to the approach taken by the JCVI in their recommendation for the 2022 autumn booster programme,[5] where the primary objective is to augment immunity in those at higher risk from COVID-19 and thereby optimise protection against severe COVID-19, specifically hospitalisation and death, over winter 2022 to 2023.
4	**Hospitalisation rates adopted in the model by the committee do not align with the considered population** We believe that the hospitalisation rates applied in the model (0.77% derived from PANORAMIC) are an underestimate and do not represent all the at-risk population groups, since it excludes the highest risk population. The associated cost-effectiveness results should therefore be considered overly conservative. A retrospective cohort study of non-hospitalised patients who received early treatment for, or were diagnosed with, COVID-19 between 1 December 2021 and 31 May 2022, used data from the Discover dataset in north-west London and included patients who were high risk or highest risk (see Table 1) and treated with sotrovimab, nirmatrelvir/ritonavir or molnupiravir, or were untreated. This study by Patel et al. 2022 which provided the 2.8% hospitalisation rate estimate for the highest risk population also contains data on the hospitalisation rate (2.1%) for a high-risk population treated with Molnupiravir as defined in Table 1. This population was made up of individuals with no highest risk conditions (45.7%), 1 highest risk condition (37.2%) and 2 highest risk conditions (17.0%). Considering these patients were treated, a 2.1% hospitalisation rate would be a conservative estimate for a high-risk population. In light of the limited availability of data to inform the baseline hospitalisation rates, mortality rates and mean age in the community of patients at high risk of progression to severe Covid-19 between the current estimates from the McInness report population (0.8%) and the PANORAMIC trial estimate (2.8%), we propose that NICE obtain these estimates from the PANORAMIC study investigators: stratification of the PANORAMIC population based on their risk criteria or age at study admission would allow NICE and the evidence assessment group (EAG) to explore scenarios aligned to a variety of risk definitions to identify the optimal population in which Paxlovid is cost-effective. We believe this would be the best approach for defining the true patient group for which treatments are cost effective, rather than having to restrict to just the highest risk patients using the McInnes criteria, which excludes patients that would likely benefit from treatment. The PANORAMIC data should be used to explore cost-effectiveness using modified PANORAMIC eligibility criterion, considering all aged 18+ with at least one risk conditions as defined in PANORAMIC study and incrementally one of the following: • all aged 55+ • all aged 60+ • all aged 65+

	• all aged 70+ • all aged 75+ etc • excluding an age threshold While these data would provide additional inputs for the cost-effectiveness model, they would still underestimate the true hospitalisation rates since the population in the PANORAMIC trial excludes the highest risk group.
5	**The administration costs applied in the EAG model are an overestimate compared to real-world costs** The future delivery of treatments will be in a primary care setting and therefore we believe that applying the COVID-19 Medicine Delivery Unit (CMDU) deployment costs (£410) for Paxlovid is an overestimation compared to the likely real-world/business as usual costs once final guidance is implemented. Furthermore, the cost calculation included cost elements not appropriate for a primary care delivery model for antivirals for example clinical consumables, stationery, room hire, office equipment and multiple staff costs. While these might be relevant in accessing the costs of setting up and running a CMDU (which do not have permanent structures), they do not reflect costs associated with routine delivery of an oral treatment in primary care. Based on current systems, the dispensing of Paxlovid may involve an e-consultation or telephone tirage involving a medical clinical review to ensure suitability of treatment and a pharmacy pick up or delivery service. We suggest two alternate costing scenarios based on possible real world administration scenarios: • To model the administration process for Paxlovid for the average patient in primary care, we assume that clinical medical review, prescribing and dispensing will require a maximum of one hour of time (allowing for triage and clinical medical review) from a band 8a pharmacist or prescribing nurse: £75 based on Personal Social Services Research Unit (PSSRU) costs.[36] • An alternative scenario to administration costing representing the more complex medical review required for care home patients should also be considered for a portion of the eligible population. PSSRU review for this scenario found that "the average cost per resident of the multi-professional medication review intervention was £117".[36] This scenario represents the most complex medical review process and is considered as the upper limit for oral antiviral administration cost. This has been applied in the cost effectiveness analysis presented in Comment 9, Figure 4
6	**Manageability of Paxlovid contraindications and interactions** The ACD quotes clinical expert advice that there are many contraindications for Paxlovid (nirmatrelvir plus ritonavir), including severe renal and hepatic impairment, and interactions with many common treatments. However, it is worth noting that the majority of these contraindications align with the profile for ritonavir,[37-39] which is an extremely well-characterised antiviral therapy, first receiving marketing authorisation in the EU in 1996.[40] Although usage has reduced over the following decades, ritonavir remains part of regimens recommended in the 2022 BHIVA guidelines.[41]

	In this context, clinicians are familiar with assessing contraindications and conducting drug interaction assessments for ritonavir-boosted therapies. Further, there are publicly available resources to help support clinicians in assessing the drug interactions,[42,43] reducing the time that will be required during prescribing. As a result, the admin cost we propose in comment 5 would be factoring in the time associated with drug interaction assessment.
7	**Inappropriateness of the low-efficacy scenarios for Paxlovid despite clear evidence of effectiveness in vaccinated individuals and the omicron variant from real-world evidence (RWE)** Recent large RWE studies (see Appendix 2) on the effectiveness of Paxlovid during the omicron period in vaccinated patients,[44-64] is supportive of the efficacy of Paxlovid demonstrated in the EPIC-HR study (this also informs Paxlovid effectiveness estimates in the EAG's model). Paxlovid is effective in a variety of real-world settings with varying standards of care, proportions of people with COVID-19 vaccinations, and varied levels of population immunity derived through natural infection. The numerous RWE studies demonstrate the robust protection offered by Paxlovid in the current setting of Omicron dominance and within a high population seroprevalence. Therefore, we believe the use of the low efficacy scenario in the model for decision making is not supported by clinical evidence. Combining these low efficacy estimates with the hospitalisation rates from PANORAMIC is overly conservative given the available RWE (see Appendix 2) and the evidence included in the CS. We believe this demonstrates that the 'mean efficacy' scenario applied in the model should be considered the lower bound for Paxlovid clinical effectiveness during NICE decision making. The lower efficacy scenario is not supported by any clinical evidence we are aware of and is likely an underestimate of Paxlovid's effectiveness in both vaccinated and unvaccinated populations and during the Omicron period.
8	**Hospitalisation costs used in the EAG model are currently underestimated** While the EAG has taken onboard the need to use an alternative set of HRG codes (DZ11 Lobar, Atypical or Viral Pneumonia) in relation to the COVID-19 hospitalisation costs, an error was made in hospitalisation cost calculation resulting in an underestimation. Hospitalisation costs are crucial in this analysis as hospitalisation costs and hospitalisation rates are coupled on their impact on the incremental cost-effectiveness ratio (ICER). The current approach is underestimating hospitalisation costs. The issues with the current approach are 2-fold: 1. Use of DZ19H - DZ19N (Other Respiratory Disorders) for non-elective (1-2 days) costs is inappropriate since COVID-19 has an average length of admission of 11 days.[65] 2. Non-critical care NHS reference costs were used as cost per day when they are actually costs per finished consultancy episode (FCE). The numbers of FCEs per admission need to be accounted for. COVID-19 specific HRG codes are now available in the NHS reference costs file under HRG code subchapter DX. However, they are not split by level of organ support of severity which limits how they can be mapped to the ordinal scales. Using the Adult HRG codes are DX01A, DX11A and DX21A, the weighted average costs per FCE is £5,027. Accounting for the average number of

	FCEs per admission (2.29 FCEs) and length of stay (11 days) the cost per day admitted to non-critical care ward would be £1,044. This is much higher than the current estimates of £563 and £828 for ordinal scales 4 and 5. Using an alternative set of HRG codes (DZ11) allows for stratification of costs by severity to match the ordinal scales in the EAG model. After accounting for the number of FCEs per admission and length of stay, the estimates of £732.20 and £1124.13 for ordinal scales 4 and 5. We proposed using these estimates (DZ11 based) in the cost-effectiveness analysis. The impact of doing so is presented in our analysis in Comment 9, Figure 4. In Appendix 3, we provide further explanation of issues and solutions on the current approach.
9	**Additional scenario analysis** Using the EAG model, we performed cost-effectiveness analysis of Paxlovid at different baseline hospitalisation rates ranging from 0.77% (Panoramic population estimate) to 2.79% (Patel et al.[2] - McInnes population estimates). This analysis demonstrates that Paxlovid would remain cost effective when broadening the recommended population, the restricted 'highest risk' cohort. Furthermore, an update of the admin costs and hospitalisation costs show that Paxlovid is cost effective across all considered hospitalisation rates when using a mean efficacy for Paxlovid. All model inputs were aligned with that used by the EAG to inform the revised EAG report, with the exception of mortality rate and the average age in the community setting, which was aligned with PANORAMIC. We find that Paxlovid remains cost-effective at £30,000/ quality-adjusted life year (QALY) at baseline hospitalisation rates of 1.45% (low efficacy), 0.89% (mean efficacy), or 0.78% (high efficacy), see Figure 3. As noted above, the low efficacy scenario is inappropriate, particularly in combination with reduced hospitalisation rates. Despite this, Paxlovid remained cost-effective across all scenarios at plausible, conservative hospitalisation rates. When taking into account the updated admin costs and correcting the hospitalisation costs, Paxlovid remains cost-effective at £30,000/QALY at baseline hospitalisation rates of 1.10% (low efficacy), 0.77% (mean efficacy and high efficacy), as shown in Figure 4.

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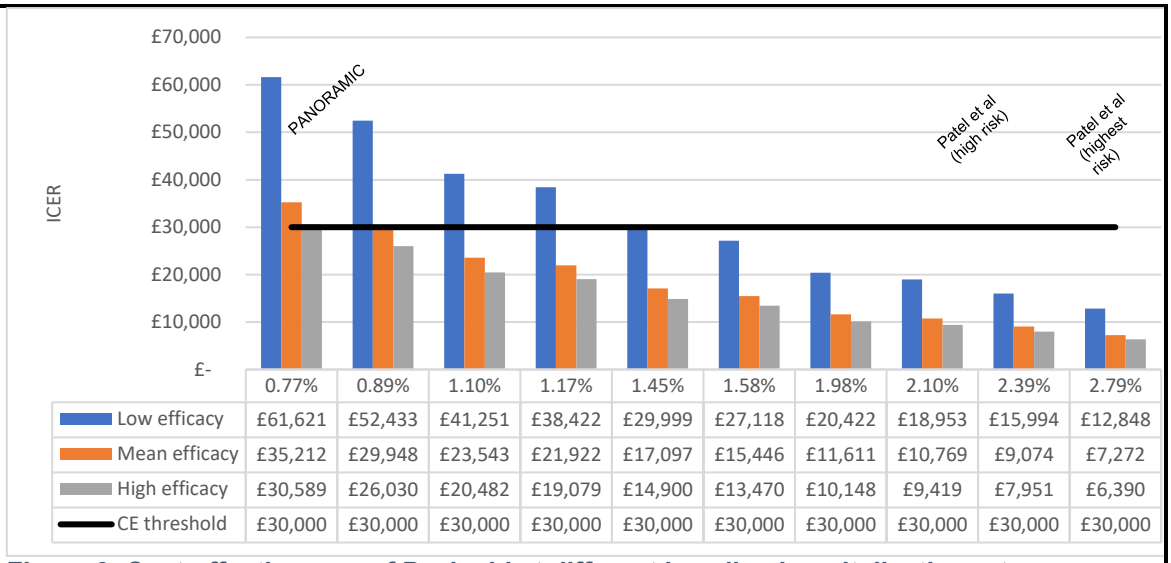
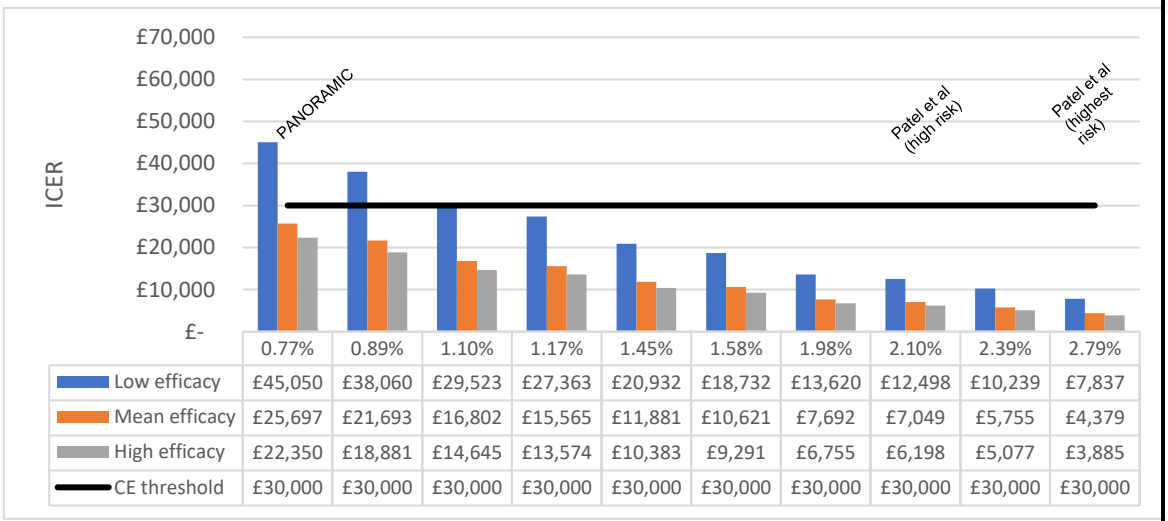


	0.77%	0.89%	1.10%	1.17%	1.45%	1.58%	1.98%	2.10%	2.39%	2.79%
Low efficacy	£61,621	£52,433	£41,251	£38,422	£29,999	£27,118	£20,422	£18,953	£15,994	£12,848
Mean efficacy	£35,212	£29,948	£23,543	£21,922	£17,097	£15,446	£11,611	£10,769	£9,074	£7,272
High efficacy	£30,589	£26,030	£20,482	£19,079	£14,900	£13,470	£10,148	£9,419	£7,951	£6,390
CE threshold	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000

Figure 3. Cost-effectiveness of Paxlovid at different baseline hospitalisation rates



	0.77%	0.89%	1.10%	1.17%	1.45%	1.58%	1.98%	2.10%	2.39%	2.79%
Low efficacy	£45,050	£38,060	£29,523	£27,363	£20,932	£18,732	£13,620	£12,498	£10,239	£7,837
Mean efficacy	£25,697	£21,693	£16,802	£15,565	£11,881	£10,621	£7,692	£7,049	£5,755	£4,379
High efficacy	£22,350	£18,881	£14,645	£13,574	£10,383	£9,291	£6,755	£6,198	£5,077	£3,885
CE threshold	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000	£30,000

Figure 4. Cost-effectiveness of Paxlovid when considering updated admin costs and hospitalisation rates. Updated inputs include and admin cost of £117 and hospitalisation costs from the HRG codes DZ11, of £732.20 and £1124.13 for ordinal scales 4 and 5.

The above analysis demonstrates that even in the pessimistic lower efficacy scenario (which is not aligned with the evidence in comment 7), Paxlovid is cost effective at hospitalisation rates below 2.79%,[2] which is aligned with the highest risk population defined from the McInnes report. Therefore, when broadening the recommended population beyond this 'highest risk' cohort, Paxlovid would still remain cost effective.

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10	**Additional benefits of treatment that have not been captured in the ICER** Clinical experts have stated that the economic model should capture additional clinical benefits beyond hospitalisation and mortality. However, the committee concluded that it had not been presented with strong evidence that the health benefits of Paxlovid had been inadequately captured and therefore that the health utility gained was misrepresented. Pfizer is disappointed with this conclusion and presents herein evidence that describes these additional benefits. In summary: • It is extremely likely that the reduction in SARS-CoV-2 viral load and the acceleration of negative RT-PCR respiratory SARS-CoV-2 conversion observed with Paxlovid treatment will reduce virus transmission in both the community and hospital setting. Reduced transmission will improve quality of life for the population, reduce NHS costs and protect patients at high risk of COVID-19. Impact on viral load is within the scope of this assessment; however, the economic model does not reflect this benefit, overestimating the ICER. • Reduced transmission in the hospital setting has the added benefit of reducing NHS staff absences, supporting them in providing care to non-COVID-19 patients. The economic model does not capture the potential harm associated with additional staffing pressures on the NHS, particularly during winter months. • Early evidence suggests that Paxlovid reduces development of long COVID, improving patient quality of life and reducing NHS costs. While this evidence is not yet definitive, future updates of this guidance should aim to include this value. **Virological outcomes and value of reduced transmission** Virological outcomes are within the scope of the current assessment.[66] Further, these outcomes are a key endpoint for many virologic diseases, with impacts on clinical outcomes and disease transmission for economic models in other indications,[67] particularly for chronic diseases in order to assess impact of treatment on long-term outcomes. Hence, it can be considered well within the scope of the NICE reference case. Paxlovid had a significant impact on viral load in EPIC-HR,[68] and has also demonstrated reduced time to negative RT-PCR test in a real-world cohort study.[45] While the association between virological outcomes and transmission or infectiousness is not fully characterised, published evidence shows that viral load is associated with transmission[69,70] while negative respiratory RT-PCR test is a strong indicator of non-infectiousness.[71] Taken together, this evidence strongly suggests that Paxlovid reduces virus transmission. The Appraisal Committee noted that community treatments may not limit transmission of the virus, because it mostly spreads when people are asymptomatic. However, this is not fully aligned with current evidence. Guidance from the World Health Organisation agrees that infected people appear to be most infectious just before they develop symptoms but notes that infectiousness continues into the early stages of illness and that people who develop severe disease can be infectious for longer.[72] Further, UK evidence up to March 2021 suggests that around 65% of patients continue to shed virus beyond five days following symptom onset and around 24% of patients shed virus beyond seven days.[73] This is supported by recent, non-peer-reviewed evidence assessing populations where the Omicron variant is dominant.[74,75] Given that there is no longer a legal requirement to isolate following a positive COVID-19 test,

	improvements in these virological outcomes may have a significant impact on onward transmission. Taking into consideration the limited timescale of the present assessment and the limited evidence base, a pragmatic approach is suggested, similar to those used in the recent assessment of novel antimicrobials.[76,77] However, full assessment of the impact of viral load and transmission in the economic model would be recommended for future assessments of COVID-19 therapies. **Transmission to healthcare professionals** As noted in the ACD, Paxlovid use is associated with a significant reduction in hospitalisations in patients infected with COVID-19 at high risk of adverse outcomes. A reduction in the number of COVID-19 patients requiring treatment in the hospital setting would be reasonably expected to reduce the risk of virus transmission to healthcare professionals, even in the context of lower rates of transmission in symptomatic patients. This would have beneficial impacts on healthcare professionals individually and also for the NHS more broadly. **Impact on incidence and duration of long COVID** The NICE reference case specifies that all health and cost outcomes should be included in the assessment.[78] Given the cost impact and quality of life decrement experienced by patients with long COVID, the impact of treatment on incidence and duration of long COVID can be considered a vital element of the NICE assessment. Early, non-peer-reviewed real world evidence suggests that use of Paxlovid in line with the licensed indication reduces the risk of long COVID regardless of vaccination status and history of prior infection,[79] indicating that this is a potential benefit not captured in the economic model. The EAG model assumes that 10% of patients in the non-hospital setting would have long COVID, regardless of treatment or subsequent outcomes. While this is a valid simplifying assumption currently, in the context of limited evidence for the Omicron variant, there is likely to be additional data generated in the future that should allow inclusion in the economic model.

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

Draft Guidance comments form

Consultation on the Draft Guidance document – deadline for comments 5pm on Tuesday 6 December 2022. Please submit via NICE Docs.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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Appendix 1: Comparison of 'high risk' definitions

Table 2. Comparison between patient groups included in PANORAMIC, McInnes and JCVI 'high risk' definitions

High-risk population	PANORAMIC	McInnes report	JCVI[6]	Evidence
Down's syndrome and other genetic disorders	✓	✓	✓	[1,23,26]
Solid cancer		✓		[1,26]
Haematological diseases and recipients of haematological stem cell transplant (HSCT)	✓	✓	✓	[1]
Renal disease	✓	✓	✓	[1,23,26]
Liver diseases	✓	✓	✓	[1,23,26]
Solid organ transplant recipients	✓	✓		[1,23,26]
Immune-mediated inflammatory disorders		✓	✓	[1]
Immune deficiencies	✓	✓	✓	[1,23,26]
HIV/AIDS		✓	✓	[1,23,26]
Rare neurological and severe complex life-limiting neuro-disability conditions	✓	✓	✓	[1,23]
Chronic respiratory disease	✓		✓	[23,26]
Chronic heart or vascular disease	✓		✓	[23,26]
Chronic neurological disease	✓		✓	[23,26]
Severe and profound learning disability	✓		✓	[23]
Diabetes mellitus (Type I or Type II)	✓		✓	[23,26,80]
Morbid obesity (BMI > 35)	✓		✓ (≥ 40)	[81], BMI ≥30 kg/m^2,[80] obesity[26,82]
Severe mental illness	✓		✓	[23,26]
Care home resident	✓		✓	[23]
Judged to be clinically vulnerable	✓			
Age ≥ 50 years	✓		✓	[18-22,81,83-85]
Pregnancy			✓	
Carers*			✓	
Household contacts of people with immunosuppression			✓	
Frontline healthcare and social care workers			✓	

*Those who are eligible for a carer's allowance, or those who are the sole or primary carer of an elderly or disabled person who is at increased risk of COVID19 mortality and therefore clinically vulnerable. Further detailed in the Green Book[6]

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Appendix 2: Evidence for Paxlovid efficacy in vaccinated patients and Omicron variant

The committee's conclusion to apply the low efficacy scenario given there is insufficient evidence of efficacy of Paxlovid in vaccinated patients and against Omicron is contrary to the available evidence

Paxlovid has also been demonstrated to be effective in both vaccinated and non-vaccinated patients.[52,54,55,63] Some of this data was presented to the committee in the CS. An updated list of these studies are detailed below.

Table 3. Clinical evidence supporting Paxlovid efficacy in vaccinated patients and the Omicron variant

	Vaccinated patients	Omicron
USA	44,62-64	44,58-62,64
China and Hong Kong	52	45-48,50-53
Israel	54,55	54,55
Greece		49
Italy	56	56,57

Pfizer RWE studies of Paxlovid

We bring to your attention two real world evidence (RWE) studies, currently undergoing peer review, that support evidence of Paxlovid in vaccinated patients where the Omicron variant is dominant. This RWE evidence demonstrates similar efficacy outcomes to the EPIC-HR RCT.

One RWE study was undertaken in a US nationwide, population-based cohort study using electronic health record data from the Optum® de-identified COVID-19 dataset, which included ~12 million US patients as of June 8, 2022.[44] We compared hospitalisation risk between high-risk COVID-19 patients who were prescribed nirmatrelvir/ritonavir and those who were not, regardless of vaccination status, during December 2021–May 2022 (i.e., an Omicron predominant period). An extensive propensity score matching strategy (PSM) was used to balance confounding factors between the two study groups, and the Prescription Time Distribution Method[86] was used to avoid immortal time bias. In the PSM-adjusted analysis, nirmatrelvir/ritonavir prescription was associated with **84% and 89% relative risk reductions** in hospitalisation within 30 and 15 days, respectively, similar to efficacy estimates from EPIC-HR. Subgroup analyses indicated a higher hospitalisation risk among African American versus White patients who were not prescribed nirmatrelvir/ritonavir; this disparity increased among patients prescribed nirmatrelvir/ritonavir despite demonstrated nirmatrelvir/ritonavir effectiveness in both racial subgroups. Furthermore, nirmatrelvir/ritonavir utilisation was lower among African American compared with White patients.

Additionally, a matched, observational cohort study of non-hospitalised individuals with SARS-CoV-2 infection was undertaken to compare outcomes between those who received or did not receive Paxlovid within the Kaiser Permanente Southern California healthcare system.[64] Patients were matched on a range of relevant covariates, including testing date, age, sex, treatment/care setting, symptoms status (including presence or absence of acute COVID-19 symptoms at testing, and time from symptom onset to testing), history of vaccination and SARS-CoV-2 infection, Charlson comorbidity index, and prior-year healthcare utilisation. Patients were eligible for inclusion in the current study if they had a documented positive SARS-CoV-2 polymerase chain reaction (PCR) test result between 31 December 2021 and 29 July 2022 (i.e. a period where Omicron was dominant); no eligibility criteria assessed risk of adverse outcomes. Analyses included 4,329 patients receiving Paxlovid and 20,980 matched non-recipients who were followed ≥30 days after a positive SARS-CoV-2 outpatient test. Overall, 23,603 (93.3%) and 19,564 (78.1%) of 25,039 participants had received ≥2 and ≥3 COVID-19 vaccine doses, respectively,[64] which is reflective of the UK

population.[87] For patients dispensed Paxlovid 0–5 days after symptom onset, effectiveness in preventing all hospital admissions was **88.1% (95% CI: 49.0–97.5%)** over 15 days and 71.9% (95% CI: 25.3–90.0%) over 30 days, respectively.[64] Effectiveness in preventing acute respiratory infection-associated hospital admissions was 88.3% (95% CI: 12.9–98.8%) and 87.3% (95% CI: 18.3–98.5%) over 15 and 30 days, respectively. Subgroup analyses identified similar effectiveness estimates among patients who had received ≥2 COVID-19 vaccine doses.[64]

Our findings collectively demonstrate that nirmatrelvir/ritonavir effectiveness extends beyond the EPIC-HR setting to patients in the real world, including those who are vaccinated and during an era of Omicron predominance, and highlight potential disparities in treatment.

Independent RWE studies of Paxlovid

Omicron era evidence

Independent RWE is available showing consistent the efficacy of Paxlovid during the Omicron dominant period, including studies in China,[45-48] Greece,[49] Hong Kong,[50-53] Israel,[54,55] Italy,[56,57] and the USA.[44,58-62]

Vaccinated population evidence

There have been several RWE studies reporting on the efficacy of Paxlovid on vaccinated populations, including studies in the USA,[62,63] Israel,[54,55] Italy,[56] and Hong Kong.[52]

Together these data demonstrate the robust protection offered by Paxlovid in the current setting of Omicron dominance and high population seroprevalence. Paxlovid is effective in a variety of real-world settings with varying standards of care, proportions of people with COVID-19 vaccinations, and levels of population immunity derived through natural infection. In addition, the risk of future COVID-19 outbreaks and the emergence of new SARS-CoV-2 variants, which may be able to evade vaccine protection or be resistant to available treatments, increases the importance of expanding the toolbox of available antivirals to reduce the risk of severe illness and mitigate the impact of surges in disease activity on NHS capacity.[88]

Appendix 3: Hospitalisation costs
Further explanation of issues and solutions on the current approach:

- Ordinal scale 4 (hospitalised, not requiring supplemental oxygen) is using costs of DZ19H - DZ19N (Other Respiratory Disorders) for non-elective short stay. A COVID-19 admission is on average 11 days or at least > 2 days implying that the use of non-elective short stay is inappropriate.
- The weighted average costs used for Ordinal scales 3-5 were extracted as **costs per FCE** from the NHS reference costs then applied in the model as **costs per day.** Note that cost of critical care stay is recorded per day unlike general ward HRG codes which are per FCE.
- The costs need to be converted first from costs per FCE to cost per admission to account for the fact that an admission can have more than 1 FCE. Cost per admission can then be converted to cost per day by dividing by the length of stay (for the admission).

$$Cost\ per\ day\ = \frac{cost\ per\ FCE\ X\ number\ of\ FCEs\ per\ admission}{Length\ of\ stay}$$

- Length of stay and number of FCEs per admission for COVID-19 admissions are available from NHS digital hospital episodes statistics under the ICD10 codes U07.1 (COVID-19, virus identified) and U07.2 (COVID-19, virus not identified) which are specific for COVID-19:[65]

- General ward number of FCEs per admission:
  - ICD10 code U07.1 = 2.3 FCEs
  - ICD10 code U07.2 = 1.9 FCEs
  - Weighted U07.1 and U07.2 = 2.3 FCEs
- General ward LOS:
  - ICD10 code U07.1 = 11 days
  - ICD10 code U07.2 = 6 days
  - Combined ICD10 codes U07.1 and U07.2 = 11 days

Proposed solutions

Hospitalisation costs for ordinal scales 4 and 5 using HRG codes DX

COVID-19 specific HRG codes are now available in the NHS reference costs file under HRG code subchapter DX.[89] However, they are not split by level of organ support of severity which limits how they can be mapped to the ordinal scales.
There are 6 HRGs within this subchapter, as follows:

- DX01A COVID-19 Infection, with Major Manifestations, 19 years and over
- DX01B COVID-19 Infection, with Major Manifestations, 18 years and under
- DX11A COVID-19 Infection, with Pneumonia, 19 years and over
- DX11B COVID-19 Infection, with Pneumonia, 18 years and under
- DX21A COVID-19 Infection, 19 years and over
- DX21B COVID-19 Infection, 18 years and under

Using the Adult HRG codes are DX01A, DX11A and DX21A. However, they are not split by level of organ support or severity which limits how they can be mapped to the ordinal scales in the model.

- Weighted average costs per FCE is £5,027[90]
- Using the number of FCEs per admission=2.29 FCEs[91] and Length of stay=11 days the cost per day would be £1,044.

Hospitalisation costs for ordinal scales 4 and 5 using HRG codes DZ11

Since the COVID-19 specific HRG codes are not split by level of organ support of severity, this limits how they can be mapped to the ordinal scales. An alternative approach is to use DZ11 HRG codes which cover Lobar, Atypical or Viral Pneumonia as a proxy for COVID-19. DZ11 has been used as a proxy for COVID-19 as was previously done by UKHSA.[92] DZ11 is stratified by complexity of care including number of interventions used making it easier to map to the ordinal scales. Table 4 below summarises the mapping and associated hospitalisation costs.

Table 4. Derivation of hospitalisation costs

HRG codes DZ11	Ordinal scale	General ward Unit Cost (note cost per FCE)[90]	Number of FCEs per admission[91]	Duration of stay in General ward[91]	General ward Cost per day
Q-N (Lobar, Atypical or Viral Pneumonia,	**5 (**hospitalised, requiring any	£5,410.55	2.3 FCEs	11 days	£1,124.13

with Single Intervention)	supplemental oxygen such as LFO)				
V-R (Lobar, Atypical or Viral Pneumonia, without Interventions)	**4 (**hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions))	£3,524.16	2.3 FCEs	11 days	£732.20
FCE: finished consultancy episode; LFO: low-flow oxygen					

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Therapeutics for people with COVID-19 [ID4038]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roche
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Name of commentator person completing form:	[redacted]
Comment number	**Comments**
1	We appreciate the Committee's efforts in producing this complex guidance and would like the NICE to consider two points: 1. Clarifying further within the document the reasons behind the negative recommendation for casirivimab/imdevimab, as currently it seems contradictory *"Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?"* We ask to review the statement on page 5 **Why the committee made these recommendations**, it is written: *"Casirivimab plus imdevimab (...) are not recommended because the likely cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources."* This is in contrast with section *3.22 pg. 31* **Cost-effectiveness estimates Hospital settings with supplemental oxygen**: *"For the low efficacy scenario, casirivimab plus imdevimab was cheaper and less effective than standard care. In the mean-efficacy scenario, the ICER for casirivimab plus imdevimab compared with standard care was below £20,000 per QALY gained."* We understand that the effectiveness of neutralising monoclonal antibodies is variant dependent and agree with the generalisability concerns of this analysis, expressed in section 3.10, pg. 18 **Generalisability to the Omicron variant**: *"The committee recognised that the neutralising monoclonal antibodies had shown effectiveness against previous variants. However, it considered that the generalisability concerns in relation to Omicron were too substantial to ignore".* This sentiment is also reflected elsewhere in the document, including in Sections 3.11 and 3.12, pages 19-22 **Relative treatment effect**, where the results for casirivimab/imdevimab based on the studies underpinning the current marketing authorisation are not discussed. Given the above, we believe the reason behind a negative recommendation is the generalisability concerns of this analysis due to the lack of / uncertainty of effectiveness in the current omicron variant, not the cost-effectiveness estimates. This interpretation is also in line with NICE's press release (1). It would be pertinent for this to be clarified and the statement on page 5 removed for the recommendation rational to be clear.

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	(1) https://www.nice.org.uk/news/article/nice-recommends-3-treatments-for-covid-19-in-draft-guidance
2	2. How to rapidly review this recommendation, should monoclonal antibodies be needed by patients in the future, with evolving COVID-19 variants, evidence and label updates *"Are the provisional recommendations sound and a suitable basis for guidance to the NHS? "* Given the evolving nature of the virus, the evidence and the linked marketing authorisations, we believe that the production of this guidance document has to go hand in hand with a clear plan on how to review it in future. The German G-BA decided to address this by giving separate recommendations for variants against which casirivimab/Imdevimab did not have enough efficacy, versus variants where it is proven effective, where it is recommended (2). Alternatively, we welcome the publication of a clear and simple process to update this guidance at the same time as the guidance becomes effective and invite the Committee to highlight this potentially time sensitive need within this draft guidance. Should the need for these treatments emerge, the lack of a clear and fast process for reviewing the guidance could put UK patients, the health system and all the stakeholders involved at a disadvantage. (2) https://www.g-ba.de/downloads/39-261-5649/2022-10-06_AM-RL-XII_Casirivimab-Imdevimab_D-810_BAnz.pdf

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

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- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Action for Pulmonary Fibrosis
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	[redacted]

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1	**Relevant evidence** Although evidence has been provided in the Draft Guidance for each drug, the impact of removing them on the 500,000 immune compromised people in UK does not seem to have been fully considered. Many people, including solid organ transplant patients, will no longer have access to any anti-virals or antibody treatments, if the recommendations go ahead. The only one left on the list (Nirmatrelvir plus ritonavir - Paxlovid), cannot be taken by most transplant patients because it interferes negatively with the immune-suppressant drugs we take. This would mean increased costs of hospitalisation for some of these patients, using up both stretched and precious NHS resources. We suggest that the committee re-examines its recommendations and assesses the implications for all the different categories of people who are immune suppressed and ensures that each category of immune suppressed patient will have access to at least one effective anti-covid therapy. So, in our view, the question that should have been asked was: • what is the most cost-effective COVID-19 treatment that can be provided for each of the different categories of immune suppressed patient? **not** • What is the most cost-effective therapy for the NHS to use, given limited resources? We notice that there was no patient representative on the Evaluation Committee. This issue might have been considered earlier, if there had been.
2	**Clinical and cost effectiveness** We think the committee's cost effectiveness analysis should have taken account of the money the NHS has invested to date in the 500,000 immune compromised people. A lung transplant patient, for example, has probably cost the NHS £150-200K. As considerable public money, time and expertise has already been invested, it seems short-sighted to deny immune suppressed people COVID-19 therapies. In our view, providing the drugs would be a cost-effective way of protecting the NHS's overall investment in the nation's health, though there are ethical considerations. A broader benefit-cost analysis is needed.
3	**Impact of shielding on mental health**

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	We are surprised that the document makes no mention of the fact that many immune suppressed people are still shielding with serious impacts on mental health. These social costs should have been included in the analysis. For example, I am immune suppressed following a lung transplant. Since March 2020, I have only once been into a building other than my house and the hospital. When Covid therapies became available in December 2021, I felt I had a 'safety net' and was happy for friends to visit after taking a lateral flow test first. But, if these guidelines are approved, I would have to revert to full shielding since Paxlovid is contra-indicated for me and no other COVID-19 therapy will be available to me. **These guidelines, if implemented, would put tens of thousands of people, like me, back into full lock-down, with significant impacts on mental health.** In the draft section, there is a section on 'Equality Issues' but you seem to play down the fact that the 500,000 immune suppressed people are a minority who need special attention. In our view, your recommendations do not adequately address our needs. Please reconsider.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Blood Cancer UK Lymphoma Action Anthony Nolan Myeloma UK Leukaemia Care CLL Support

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Blood Cancer UK - None Lymphoma Action - None Anthony Nolan - None Myeloma UK- None Leukaemia Care - None CLL Support - None
Name of commentator person completing form:	[redacted] - Blood Cancer UK - Lymphoma Action [redacted] - Anthony Nolan - Leukaemia Care [redacted] - Myeloma UK [redacted] - CLL Support

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that by limiting options for treatment, the current NICE decision does not allow for patient choice; multiple options are always preferred. This decision is removing access to treatments that patients value.
2	We disagree with the application of the PANORAMIC trial to calculate baseline hospitalisation risk. Omicron may have a lower hospitalisation rate, but the PANORAMIC trial did not include those with the highest risk of hospitalisation and death due to COVID-19, like blood cancer patients and recent stem cell transplant recipients. Patients with blood cancers were given access to treatments through rapid commissioning agreement outside of the PANORAMIC trial. Many people at the highest risk of COVID-19 do not mount a sufficient response to vaccination and should be considered unvaccinated. There were no unvaccinated people in the PANORAMIC trial. Therefore we believe the hospitalisation rates in the PANORAMIC trial do not accurately reflect the hospitalisation rates that would be observed in people with high risk of COVID-19.
3	We welcome the approval of Paxlovid, but are concerned about contraindications. Paxlovid on its own is not a sufficient option for blood cancer patients. Many of the contraindications and drug interactions will limit access to the treatment within the high risk group. We consider a failure to account for this group of patients to be both unfair and unreasonable. The contraindication due to renal failure could limit myeloma patient access. Myeloma and its treatments can damage the kidneys, and reduced kidney function is common in myeloma. Half of myeloma patients experience serious kidney problems. They are more common at diagnosis and

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	relapse when the level of immunosuppression is highest because patients have active myeloma and are starting treatment. 10% of these myeloma patients develop chronic dialysis-dependent kidney disease. Relevant drug interactions for Paxlovid for people with blood cancer: <u>Contraindicated:</u> ● Venetoclax - used for active treatment in Chronic Lymphocytic Leukaemia, Small Lymphocytic Lymphoma and Acute Myeloid Leukaemia. <u>'May not mix':</u> Haematology should be contacted for patients on the following treatments, in regards to rationalising treatments and considering COVID-19 risk. ● Dasatinib – active treatment for Chronic Myeloid Leukaemia. ● Nilotinib - active treatment for Chronic Myeloid Leukaemia. ● Vincristine – active treatment for Acute Lymphoblastic Leukaemia and Hodgkins disease. ● Vinblastine – active treatment for Acute Lymphoblastic Leukaemia, Non Hodgkins Lymphoma and Hodgkins disease. ● Ibrutinib – active treatment for Chronic Lymphocytic Leukaemia and other B-cells disorders. ● Ivosidenib – new active treatment for Acute Myeloid Leukaemia. ● Anticoagulants – as a whole are often used as patients with haematological malignancies can be predisposed to clots due to Central Venous Lines commonly used and deranged bloods at diagnosis (particularly Acute Leukaemia patients)and treatment with immunomodulatory drugs (e.g. lenalidomide). ● Anti-fungal treatments and prevention – Itraconazole and Voriconazole, particularly prescribed to those having intensive chemotherapy, stem sell transplants and CAR-T cell therapy. ● Steroids – dexamethasone and prednisolone are commonly used in anti-myeloma combination treatments
4	NICE considered the significant number of treatments contraindicated by Paxlovid, yet failed to provide an alternative treatment option for this patient group. They justified this decision by claiming that no other treatment was cost-effective in the whole high risk population. However, it is both unfair and unreasonable for NICE to come to this conclusion without separately modelling which treatments would be cost-effective in the subgroup of patients who would be ineligible for Paxlovid. This blood cancer patient subgroup will likely have a higher risk from COVID-19, and higher hospitalisation rate, because they are likely to be on active cancer treatment and/or other immunosuppressive therapies. NICE must therefore calculate the cost-effectiveness of community treatments solely for this smaller, higher-risk patient group, in order to conclude whether alternative treatments for these patients are cost-effective.
5	As well as clinical contraindications, there may be other reasons why patients cannot have particular treatments. These include socio-economic reasons and personal circumstances, such as whether they have access to transport or practical support for potential side effects. It is unfair and unreasonable that NICE has not explained how its decision making impacts on those people who cannot have treatments for non-medical reasons and what their options would be.
6	The decision to recommend only Paxlovid in the community setting has resulted in only one mode of administration for COVID-19 community treatments. The Living with Leukaemia survey (2017) by Leukaemia Care shows how patients often have a preference on delivery of treatment, but the preference depends on their circumstances and is therefore not universal. As such it is important that options and choices are made available for all patients.

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7	It is unfair and unreasonable not to consider the impact of fewer treatment options on the mental wellbeing, quality of life and economic activity of those who are affected by this decision. Our submission and further conversations with patients show that this will impact people's quality of life. Some blood cancer patients are still shielding and we have heard from patients that this decision will lead to some deciding to further reduce their contact with others.
8	Drug interactions need to be carefully monitored and managed. This has the potential to impact patients, their families and clinical practice. Patients and their families have the added anxiety of looking for and noticing any change in side effects due to increased toxicity from drug interactions or choosing between COVID-19 treatment and disease-related treatments. For example, patients recovering after a stem cell transplant and on preventative anti-fungal treatments would be forced to choose between either stopping that treatment or foregoing the one COVID-19 treatment available in the community. Monitoring and managing drug interactions impacts clinical and pharmacy capacity. It takes longer to prescribe treatments with multiple interactions, and more clinical staff need to be notified and consulted on treatment decisions. This complexity could also cause service delays and lead to patients missing out on treatment due to the narrow window for treatment after testing positive for COVID-19.
9	It is unreasonable not to consider the serious clinical and cost impacts caused by pausing the above active cancer treatments in order to take Paxlovid, and the benefits in this area that other treatments offer.
10	Removing existing options for immunocompromised individuals will add to existing anxiety and concerns around COVID-19. It is unreasonable to expect patients who are on treatments that are contraindicated by Paxlovid to choose between returning to isolation, or waiting for their COVID-19 infection to progress to such severity that they are hospitalised. As a CLL patient explained to Blood Cancer UK: “Due to my cancer drug regime I cannot have Paxlovid. I considered the two treatments I could have as a safety net in case I caught Covid; by offering only Paxlovid that net has been removed completely. I cannot contemplate stopping my cancer treatment so the only option for me is to completely isolate myself again…As I am a self-employed contractor I will no longer be able to fulfil the requirements of my contract and so will lose my income. It is unfair and unacceptable that I am being asked to risk catching Covid with no treatment option or to give up my livelihood and subject me to the high levels of anxiety due to loss of income, no available treatments, and the mental effects on me and my family from reentering complete isolation.”
11	NICE must take the uncertain and evolving nature of the virus’s epidemiology into consideration, and place more weight in its model on higher hospitalisation rates. We feel the current interpretation is unreasonable in light of the available evidence. In doing so, treatments may prove to be more cost-effective.
12	It is unreasonable for NICE to acknowledge uncertainty, but use hospitalisation rates based off of the Omicron variant, when hospitalisations rates would vary with different SARS-CoV-2 variants. Future variants may be more pathological and lead to more severe disease, therefore potentially leading to higher rates of hospitalisation. The current cost-effectiveness analysis is based on hospitalisations rates of variants which are mild.
13	It is unfair and unreasonable for NICE not to explain why it favours the advice of WHO and FDA over other clinical advice for sotrovimab.
14	We welcome the McInnes report definition of high risk as covering most people with blood cancers, but NICE guidance must ensure those who have been previously left out are included, such as those not undergoing active treatment for T cell blood cancers and chronic lymphocytic leukaemia.
15	It is unfair and unreasonable that NICE has not set out the specific reasons why it has approved Paxlovid over the other treatments. If NICE is accepting “significant uncertainty” in some circumstances, regarding data, efficacy and changing variants, it should be clearer why it hasn’t

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	in others. It appears that NICE has accepted uncertainty of data where it reduces cost-effectiveness, but not where it doesn't, however the rationale behind this is not given.
16	NICE has acknowledged that antivirals and anti-inflammatories are least likely to be impacted by evolving variants.Clinical experts consulted by Leukaemia Care have also seen improvement in symptom severity when using remedesivir, so we urge NICE to re-evaluate the usage of this treatment, as well as all others in this context.
17	Having only one treatment available risks leaving these vulnerable blood cancer patients subject to supply issues, leaving even those eligible for Paxlovid with no options at all. We urge NICE to consider the impact of their decision on this.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Cardiothoracic Transplant Patient Group (Under the governance of the Organ Donation and Transplantation Directorate at NHS Blood and Transplant) Response formally approved at Cardiothoracic Transplant Patient Group Meeting on 7 December 2022
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The Cardiothoracic Transplant Patient Group is concerned that the preliminary recommendations could have an adverse impact on those individuals whose life is sustained with a donor heart and / or lung. That the preliminary recommendations will discriminate against this group. In section 3.24 the committee noted that nirmatrelvir plus ritonavir would not be a viable option for some patient groups due to the contraindication for concomitant use. This would apply to all heart and / or lung transplant recipients due to their immunosuppressant drug regimes. The Cardiothoracic Transplant Patient Group recognise that the committee acknowledged this issue and considered alternative treatments (such as Sotrovimab) but concluded that they "had substantially higher Incremental Cost Effectiveness Ratios and were not considered a cost-effective use of NHS resources". The Cardiothoracic Transplant Patient Group would like to formally raise concerns that the Incremental Cost Effectiveness Ratios have been calculated for the McInnes defined high risk patient group and suggest these figures should be calculated for the subgroups of heart and lung transplant. During such an exercise the following considerations should be taken into account; • The lack of viability of nirmatrelvir plus ritonavir for this patient group • The very high Covid severe disease risk with heart and lung transplant patients. This is exemplified by the latest Covid 19 mortality figures published by NHS Blood and Transplant (monthly-report-on-covid-19-nhsbt-16-march-2022.pdf (windows.net)), which shows mortality rates of 15.5% and 7.5% for lung and heart transplant respectively. The Cardiothoracic Transplant Patient Group was pleased to note that in 3.25 the committee stated that "in theory it would be willing to accept an Incremental Cost Effectiveness Ratios slightly more than what is usually acceptable if it addressed such health inequalities (people with protected characteristics disproportionately)". In summary, the Cardiothoracic Transplant Patient Group appreciate that the committee has considered the potential for the guidance to discriminate against people with certain disabilities. However, it does not believe that the committee has specifically analysed the impact of the draft guidance on heart and / or lung transplant patients to be confident that this patient group is not being discriminated against.

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2	The Cardiothoracic Transplant Group would like to raise concerns that the hospitalisation rates used for calculating the Incremental Cost Effectiveness Ratios, are a likely significant underestimate of actual rates experienced by heart and / or lung recipients. The maximum rate used for calculating the ICERs was 2.79% (DISCOVER-NOW). However, Shields et al. 2022 report 18.4% for people with primary or secondary immunodeficiency and known Covid mortality rates for lung and heart transplant recipients are 15.5% and 7.5% respectively (monthly-report-on-covid-19-nhsbt-16-march-2022.pdf (windows.net)). The Cardiothoracic Transplant Patient Group acknowledge that the committee recognised the uncertainty around hospitalisation rates for some patient groups, citing transplant recipients as an example. However, the Cardiothoracic Patient Transplant Group do not consider that the committee have investigated the available evidence in sufficient detail to assure itself that the draft guidance would not cause discrimination to people with a protected characteristic. It is difficult to conclude that 2.79% is a sufficient hospitalisation rate ceiling for a patient group with known publicly available mortality figures of 15.5% and 7.5% (monthly-report-on-covid-19-nhsbt-16-march-2022.pdf (windows.net)) In summary the Cardiothoracic Transplant Patient Group consider that the hospitalisation rates selected for the Incremental Cost Effectiveness Ratios will almost certainly have discriminated against those individuals whose life is sustained with a donated heart and / or lung.
3	The Cardiothoracic Transplant Patient Group is concerned that the committee may have not received all relevant evidence relevant to cardiothoracic transplant recipients due to the lack of stakeholder inclusion and engagement from the cardiothoracic transplant patient and clinical communities. The extensive list of patient carer groups included most disease types within the Independent Advisory Group defined list of highest risk patients. However, apart from Pulmonary Fibrosis no other patient carer group relating to cardiothoracic transplant was involved.
4	The Cardiothoracic Transplant Patient Group are concerned that the time allocated to the External Advisory Group was insufficient for them to consider the impacts on individuals with certain protected characteristics such as those whose life is sustained by a donor heart and / or lung. The External Advisory Group Assessment report specifically highlights this issue in 1.4.5 stating, “Due to time constraints, the only subgrouping considered was related to whether oxygen was required upon admission to hospital entry… The External Advisory Group is aware that other possible criteria for selecting subgroups includes but are not limited to age; immune system competence; comorbidities; seroprevalence; vaccination status; and the predominant SAR-CoV-2 variant but did not have time to explore the impact of these characteristics.” The consequence has been that the preliminary recommendations are only based on hospitalisation rate data from PANORAMIC or DISCOVER-NOW which the Cardiothoracic Transplant Patient Group believe is a significant underestimate of the actual rates for their patient population. The preliminary recommendations will have an adverse impact on people with a donor heart and / or lung.
5	The Cardiothoracic Transplant Patient Group believe that the preliminary recommendations are not sound and suitable guidance to the NHS as they remove many treatment options for heart and lung transplant recipients. The primary recommendation of nirmatrelvir plus ritonavir is known to be clinically unsuitable for this patient group.
6	The Cardiothoracic Transplant Patient Group would like to highlight new evidence to the Appraisal Committee. An observational study published in the BMJ (BMJ 2022;379:e071932) comparing the effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community suggested, “sotrovimab was associated with a lower risk of severe covid-19 outcomes than molnupiravir, including in those patients who were fully vaccinated”.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Kidney Care UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

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1	We are very concerned that implementation of this draft guidance would result in the highest risk kidney patients in the community having no available treatment options to prevent them from developing severe Covid. As the guidance notes, Paxlovid (the only treatment option recommended in the draft guidance for non-hospitalised patients) is contraindicated in severe kidney disease and for most people taking widely used immunosuppressant medications. Kidney patients have been among those at highest risk from Covid (Williamson et al, 2020) and OpenSafely data confirms that they remain at much higher risk. Amongst those on dialysis compared to people not on dialysis, the risk of death increased from 8 times greater in wave 1 (March 2020 to May 2020) to 12 times greater in wave 3 (May 2021 to Dec 2021). In people with a kidney transplant, the relative risk increased from 7 times higher compared to people without a kidney transplant in wave 1, to 26 times in wave 3. (Nab et al, 2022). A decision to remove all community treatment options from such a high-risk group cannot be justified given the issues within the appraisal which we outline below.
2	A recommendation by NICE to remove all community treatment options for high-risk kidney patients would cause considerable anxiety and distress among this group of patients and their families, particularly immunosuppressed people who are less likely to be protected by the vaccine. Kidney Care UK hear from many patients that are struggling to take their first steps to come out of shielding and implementation of this guidance is likely to discourage people from ending their isolation. The mental health impact is considerable and it is hard to access support from overstretched mental health services. The heavy burden on shielders' mental health has been underscored by research from the University of Bath. Poor mental health increases the likelihood of poorer health outcomes among kidney patients (Tsai, Y., Chiu, Y., Hung, C., Hwang, S., Tsai, J., Wang, S., Lin, M., & Chen. H. (2012). Association of symptoms of depression with progression of CKD. American Journal of Kidney Diseases, 60(1), 54-61. https://doi.org/10.1053/j.ajkd.2012.02.325) The reports we received from kidney patients in response to this draft guidance highlight their concern: • *I have been a transplant patient for 26 years with my second one in 2010. I thought the idea of transplants was to give a person and their family a life. I have worked and lived a full life up until 3 years ago… However, if covid treatments are withdrawn then transplants are going to be pointless! What is the point in being alive but not being able to see family, socialise, go out, enjoy holidays etc.* • *I have basically shielded with my wife now for 3 years. I cannot continue to live like this and if the few treatments which are available in most other countries are withdrawn then please bring in voluntary euthanasia for the most vulnerable in society who just cannot continue to live in a country that will not protect or help them.*

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	• *Please add our voice in expressing concern over the NICE recommendations. The very idea that an immuno-suppressed/compromised group already at a higher risk of severe illness and death from Covid-19 should be forced into hospitalisation in order to get treatment when appropriate GP prescribed medication is denied to them is utterly abhorrent. Making an alternate drug available to those for whom Paxlovid is not an option is the only right, proper and morally defensible choice. Not only would this, by early intervention, have the potential to reduce the severity of any illness but it also reduces the burden on the NHS by not tying up a bed, always a good option where possible.*
3	The draft guidance acknowledges that the studies were carried out in different stages of the pandemic with an ever-changing context. It is not clear how well the data accurately reflects the clinical and cost effectiveness of the drug treatments in the high-risk group (as defined by the McInnes report) which informs current commissioning policy for the community treatments. The appraisal has used different scenarios to reflect uncertainty. However, we do not think NICE have achieved fairness. The Panoramic data is used for the lower estimate of hospitalisation rates despite the Panoramic population being different to those at highest risk. People at highest risk would have had access to the treatments via CMDUs and would not therefore have entered Panoramic and indeed would be unlikely to choose to do so, given there would be a 50/50 chance of receiving a placebo. Hospitalisation rates within the McInnes group are likely to be higher found in the Panoramic study. And Shields et al. 2022 highlights that hospitalisation rates for people who are immunosuppressed are particularly high (18.4% for people with primary or secondary immunodeficiency). It is unfair to use lower estimates from Panoramic, particularly as hospitalisation rates are a key driver of cost effectiveness. The clinical efficacy data is unlikely to reflect the clinical efficacy for kidney patients in the McInnes group. For example, the COMET-ICE trial (included within the COVID-NMA review) included people with CKD 3 and 4 (inclusion criteria was at least one risk factor for Covid, which included CKD defined as eGFR less than 60). This group of people would not be eligible for treatment under current commissioning policy. We recognise that it may not have been possible to use only data that reflects clinical and cost effectiveness for high-risk kidney patients, but given that: • limitations are likely to lead to underestimating the cost effectiveness of the treatments (particularly due to hospitalisation rates) • the current recommendations remove all treatment options for kidney patients who remain at highest risk from Covid • the cost per QALY for sotrivomab is close to £30k when using high hospitalisation and mean efficacy We believe it is unreasonable for NICE not to have used its flexibility in accepting an ICER slightly higher than usual, for those in the highest risk group who are currently left with no treatment options in the community.
4	We consider it unfair not to take into consideration the reduced protection provided to immunosuppressed people by the Covid vaccine (discussed in para 3.4). A single definition of high risk is used, because of model limitations. However, the much higher hospitalisation rates identified in the Shields study highlights the impact of immunosuppression on risk from Covid. The treatments can therefore provide an important lifeline for people who are immunosuppressed.

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	The higher estimate of hospitalisation rate (2.79%) is very likely to be an underestimation for the immunosuppressed group. We believe it would be unreasonable not to do a subgroup analysis for the immunosuppressed group or adopt greater flexibility in ICER accepted for this vulnerable group.
4	The Committee acknowledged the contraindications of nirmatrelvir plus ritonavir and tocilizumab means the draft guidance could affect some people with protected characteristics disproportionately which would contribute to health inequality. We believe it would be appropriate to assess the cost and clinical effectiveness of the Covid treatments in the subgroup of people who will be left without a treatment option. If this could not be done, we believe it would be unreasonable for the Committee not to apply flexibility in the ICER it would accept in order to address such health inequalities, particularly given the level of uncertainty on the clinical and cost effectiveness of the drug treatments in this specific group.
5	Implementing the draft guidance would also risk increasing inequality based on race. As noted in the draft guidance, CKD is more common in BAME groups, who also experienced a substantially higher risk of COVID-19-related death than white people. Removing treatment options from this group would exacerbate this inequality and it is unfair not to be flexible in the level ICER accepted, particularly given the level of uncertainty on the clinical and cost effectiveness of the drug treatments in this specific group.
6	We believe NICE was unreasonable to have accepted the WHO's recommendations against Sotrovimab when there is ongoing debate in the academic literature. In particular, NICE have not properly explained how they took into consideration the observational evidence from OpenSafely which found continued efficacy of Sotrovimab against the Omicron BA.2 subvariant. New OpenSafely data (currently in pre-print) supports the ongoing efficacy of Sotrovimab in patients on kidney replacement therapy (dialysis and kidney transplantation). Given that implementation of the draft guidance would remove all treatment options from this group we believe NICE have a duty to consider all available data and err on the side of supporting access to treatment for highest risk kidney patients while uncertainty continues.
7	We note the 1st December alert to state that Sotrovimab should only be used by exception only and that Paxlovid is the first line treatment from now on. We very much regret this statement, which pre-empts a NICE decision. It creates a barrier to kidney patients receiving prompt treatment while approval is sought. It also means that specialists will have to spend valuable time justifying the use of a therapy which kidney doctors believe is efficacious to kidney patients. It is important that kidney patients can still access Sotrovimab, but if this is something that NICE might consider, we would urge them to recommend a process that avoided the additional hurdle of seeking approval for exceptional use.

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Example 1	We are concerned that this recommendation may imply that ……..
1	The draft guidance would leave many kidney patients with no effective treatment outside of hospital, despite being in a high-risk group for COVID-19. This does not present a sound and suitable case for guidance to the NHS. Kidney patients are less likely to have adequate responses to vaccinations and are more vulnerable to infection. To remove all potential treatments from this group of patients is grossly unfair. Paxlovid is not appropriate for this patient population, as it cannot be used alongside anti-rejection drugs or in patients with reduced kidney function. The committee agreed in their summary that the risk of hospitalisation and death, and other longer-term impacts of COVID-19, can result in severe physical and mental health burden. This is without a greater consideration of the impact of long COVID, which can have significant impacts on other comorbidities, such as cardiovascular health, and wider societal economic impacts. NICE should allow additional flexibility to QALY thresholds given the severity of risk for this patient population through the newly implemented severity modifier. This is particularly pertinent for consideration of sotrovimab. Sotrovimab has no significant interactions reported with other medicines. Extensive laboratory data, including the OPENSAFELY study, and recent analysis by the Francis Crick Institute, has demonstrated continued efficacy of sotrovimab against newer COVID-19 variants.
2	We do not believe that relevant evidence has been appropriately considered with regards to the risk of hospitalisation for high-risk kidney patients. Evidence used to analyse hospitalisation risk focused primarily on the PANORAMIC study. This study did not include higher risk patients, who would have been treated via CMDU, which makes it less relevant for consideration of these treatments for this group of patients. Other studies, such as OPENSAFELY and the DISCOVER NOW study of the cohort in the McInnes report have indicated higher hospitalisation risks than the data used in this analysis. The OPENSAFELY study found COVID-19-related hospital admissions for those with kidney transplants, dialysis, and chronic kidney disease: 76.08 (95% CI 71.03–81.49), 70.73 (95% CI 63.34–78.99), and 49.49 (95% CI 45.33–54.02), respectively. We believe that it would be fair and reasonable to conduct sub-group analyses of high-risk patient populations. A recent analysis of data from the Scottish Renal Registry looked at hospitalisation rates for patients on kidney replacement therapy (dialysis and transplant) from 17 Dec 2021 to 27 March 2022 (during the Omicron wave). Hospitalisation rates in triple-vaccinated individuals were 22%. Clearly this is significantly higher than the generic 2.79% used in the committee's calculations.

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	Without this sub-analysis, we do not reasonably believe that the potential impact for high-risk renal patients, including either loss of transplantation or progression to dialysis, has been fully costed and considered.
3	We do not believe that this process has been approached in a way that will enable the timely consideration of evidence in relation to a rapidly evolving virus. We appreciate that COVID is an on-going challenge for the health-system, and this is no different for those responsible for reimbursement and regulatory decisions. However, new variants and mutations demand the need for greater flexibility and the acceptance of greater uncertainty. Most of the clinical evidence presented for this assessment is analysed from studies completed before the Omicron variant was dominant, for example. We believe that it would be reasonable therefore to allow greater acceptance of present data uncertainty. This is particularly important when considering a potential recommendation which will leave kidney patients unprotected without the only treatment currently available to them, sotrovimab. It is reasonable to accept that there will be continued uncertainty and rolling updates to evidence on the efficacy of these treatments against new variants and mutations, but it is unjust to remove access based on narrow cost-effectiveness assessments on already out-of-date data. As noted by the committee, 'observational evidence (OPENSAFELY) suggests continued efficacy of sotrovimab against the Omicron BA.2 subvariant' and the Francis Crick Institute's COVID surveillance unit suggests that 'neutralising monoclonal antibodies have only a reduced effect (against the BA.2 subvariant) that may be mitigated by an increased dose'. This evidence further emphasises the need to maintain this treatment options for high-risk patients.
4	The summary makes clear that the committee did not consider that family background can have a significant impact upon access to a treatment, while at the same time agreeing that the prevalence of kidney disease is higher in people from ethnic minority backgrounds. Merely noting that nirmatrelvir plus ritonavir was contraindicated in people with renal impairment, is not an acceptable consideration of health inequalities for a body which has reducing health inequalities as one of its core principles. As such, we do not believe that the recommendation is a sound and suitable basis for recommendation to the NHS.
5	
6	

Insert extra rows as needed

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Therapeutics for people with COVID-19 [ID4038]

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Long Covid Kids**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[no links to disclose]
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	The definition of 'high risk' is flawed and does not include Long Covid as an outcome, it only considers those at the "highest risk of an adverse COVID-19 outcome, namely hospitalisation and death". Yet there are currently over 1.6million people in the UK whose symptoms adversely affect their day to day lives. Children and adults of all ages are disabled by Long COVID. With it occurring for a period of months and years for significant numbers. It should therefore be classified as disability. Ignoring a population with a disability could be seen as discrimination against those with Long COVID as the impact of an acute Covid-19 infection on this group is not considered or detailed in the published document. There is increasing evidence that there's an increased risk of Blood clots, Pulmonary emboli, strokes, heart attacks etc in the 12 months after a confirmed Covid-19 infection. This is not mentioned or considered in the guidance. Long COVID should be considered as both an outcome to prevent, and as a high-risk group because repeated infections can increase symptoms, and those with Long Covid are already proved beyond any doubt to have come to lasting and potentially lifelong as well as life changing harm. The WHO says, ""we need all countries in the WHO European Region to recognize that Long COVID is a serious problem with serious consequences and that it requires a serious response to stop the lives of those affected from getting any worse – and not just on a physical health level," said Dr Kluge. "We are hearing stories of so many individual tragedies, of people in financial crisis, facing relationship problems, losing their jobs, and falling into depression. Many health workers who risked their lives on the front lines of the pandemic now have this chronic and debilitating condition as a result of an infection acquired in the workplace. They, and millions of others, need our support. The consequences of long COVID are clearly severe and multifaceted." " In Children this is affecting their ability to attend school, socially interact with other children and to live and have a "normal" childhood, affecting their future life opportunities and experiences significantly.
2	Children with Long COVID and those who have Long COVID and other conditions which also increase their risk should be considered. Using a definition of "high risk" which omits children under 12, is discriminating on their age, as is excluding PIMS as a cause of death and morbidity caused by SARS-CoV-2. From the draft guidance, which references the Department of Health and Social cares advisory group guidance on "high risk" definition. The "DHSC asked the independent advisory group to identify a set of patient conditions based on who is at the highest risk of an adverse COVID-19 outcome, particularly hospitalisation and death" according to the guidance this group did not include the main ways SARS-CoV-2 affects children, they defined COVID-19 as "Disease caused by SARS-CoV-2 infection, disambiguated from long COVID, paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) and multisystem inflammatory syndrome in children (MIS-C)". To create a definition of high risk from Covid-19, but exclude Paediatric multisystem inflammatory syndrome, which is a cause of death in children and significant morbidity is excluding them from any potential assessment of benefit. This should be corrected, and "high risk" should consider other SARS-CoV-2 driven diseases, and all ages.
3	The severity and impact of Long COVID needs to be appreciated or at least acknowledged in the guidance. The paragraph Impact of COVID-19 3.1 defines Long COVID as "These are health problems that can last several months ". That is incorrect. The ONS data shows that at least "half

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	(55%) reported experiencing long COVID symptoms for at least one year. Around a quarter (27%) reported experiencing symptoms for at least two years." It should read instead Post COVID-19 symptoms (Long COVID) can last months, years and potentially life long, there significant numbers infected in the first wave in 2020 who are yet to recover. The condition fluctuates and is complex as new issues can present with repeated infection and over time. It can cause over 200 different symptoms. (the NHS website lists 20 main ones https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-effects-of-coronavirus-long-covid/) The evidence is that Long COVID lasts at least 2.5 years, and counting, by the time this is published some with have had it for 3 years.
4	There is increasing evidence that viral infections and long term consequences, the long term consequences of a COVID-19 infection are currently unknown. Human papilloma virus (HPV) has been identified as the cause of most cervical cancers as an example. The risk of infections with viruses must not be downplayed. It is important that research happens into preventing both long and short term sequala. Long COVID should therefore be assessed as both an outcome to determine effectiveness and as a condition to be treated, especially as we do not know if there is viral persistence in Long COVID.
5	The Impact of COVID-19 3.1 paragraph states; Long Covid can ", potentially affect their ability to work or do their usual activities." This should be corrected to read "affects their ability to work and for over 75% of people their usual activities are adversely affected , the fluctuating nature of Long Covid, with relapses, along with the wide variety of body systems affected make it difficult to manage and predict and causes significant impact on people ability to continue to or return to work or carry out their activities of daily living. (from ONS data "Symptoms adversely affected the day-to-day activities of 1.6 million people, or 75% of those with self-reported long COVID."). In Children this is affecting their ability to attend school, socially interact with other children and to live and have a "normal" childhood, affecting their future life opportunities and experiences significantly.
6	Re the statement "PUBLISHED Draft guidance consultation – Therapeutics for people with COVID-19 Page 23 of 37 Issue date: November 2022 © NICE [2022]. All rights reserved. Subject to Notice of rights. distributions to long COVID data from the Office of National Statistics (ONS) and estimated the mean duration of long COVID to be 108.6 weeks. The AG assumed that 100% of people in the hospital setting and 10% in the non-hospital setting would have long COVID." Our question is where did the average 108.6 weeks come from? To fully understand the modelling, need to know how many we are predicting to be lifelong/last years. The recent Long Covid Kids study https://www.futuremedicine.com/doi/10.2217/fmb-2021-0285#F1 showed a mean length of 249 days with significant numbers, having it for over 12 months. The data also showed at their initial COVID-19 infection, only 4.3% children were hospitalized; 62 were asymptomatic, 74% were managed at home and 9.4% went to hospital but were not admitted. 80.6% children had no pre-COVID mental health concern or diagnosis, which means they were left with significant life changing symptoms after their infection.
7	The cost calculated for Long COVID are using incorrect modelling "Costs Long COVID costs 3.17 The AG assumed the annual per person management costs of long COVID to be comparable with chronic fatigue syndrome (£1,013)." Long COVID- cannot be equated to chronic fatigue syndrome. The NICE definition of long covid is Post-COVID-19 syndrome is"Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed."

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	Therefore, when modelling it is clear by NICE's own definition that Chronic fatigue syndrome is not an ideal option for modelling costs, and morbidity. Because; 1) as stated alternative underlying disease needs to be assessed and ruled out, 2) the fatigue element is only one of many symptoms, which as stated can affect any system in the body, from cardiovascular, to immune system, to respiratory to haematological and many more, only a small amount of the costs and impact on life and function are considered if fatigue is taken as the only symptom. Over 200 symptoms have been identified. 3)Each individual should be investigated thoroughly, initial diagnostic costs should be included. The long-term prognosis is unknown and with repeated infections causing worsening symptoms it is likely symptoms for many will worsening and require review/input. If paediatric multisystem inflammatory syndrome is not considered then the costs of the virus on children have not been included in the modelling.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Long Covid SOS Registered Charity no 1199120
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to declare

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Example 1	We are concerned that this recommendation may imply that ……..
1	We believe that whilst it is unknown what causes the development of Long Covid, anyone with current or history of Long Covid should be treated as a high-risk population. Emerging evidence suggests that repeat infections with Sars-Cov-2 can lead to increased risk of hospitalisation as well as development of Long Covid. Bowe, B., Xie, Y. & Al-Aly, Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med* 28, 2398–2405 (2022). https://doi.org/10.1038/s41591-022-02051-3
2	We agree with the recommendation of nirmatrelvir plus ritonavir (an oral dose antiviral combination) to be used in the community setting. As stated above, we request that this is available to those with (a history of) Long Covid on a subsequent Sars-Cov-2 infection.
3	With the emerging evidence of common infections potentially leading to future disease burden (Human Papilloma Virus (HPV), cervical cancer and Epstein Barr Virus (EBV), Multiple Sclerosis), we would encourage caution with rushing to an endemic setting with Covid-19 in the absence of long-term surveillance studies and investigation of factors within the acute phase of Covid that lead to the causation of Long Covid within the community. Scientifically we don't believe it is demonstrated that the interface between acute and Long Covid meets the current definitions used. What is it about the acute phase that leads a proportion to develop Long Covid? At what stage can potential biomarkers be seen, can potential risk be identified in the acute period? Do protocols defining test dates adequately capture the causation of any relapses as it is not a steady state or worsening condition? It may be a new methodology of research and evidence gathering is required for the emerging evidence of the chronic burden of infectious disease
4	We feel that the concept that severity of COVID is denoted by acute hospitalisation or need for oxygen therapy is narrow, and has skewed research, clinical practice and practice. In reality, severe impact of COVID has occurred since March 2020 in non-hospitalised individuals who develop Long Covid, and this continues to have a major impact on individuals, populations, health systems and the economy. Treatment trials are urgently required.
5	Any modelling of Long Covid effects or potential impact on people with Long Covid must properly account for impact on morbidity, loss of function and quality of life, as well as the impact of time off work and lost earnings. These aspects are currently neglected in the economic models.
6	The language used in section 3.1 'COVID-19 may cause long-term symptoms that continue or develop after acute infection called 'long COVID'. These are health problems that can last several months which severely impact a person's physical or mental health, or both, and potentially affect their ability to work or do their usual activities.' minimises the impact of Long Covid for the significant proportion that still have chronic health impacts from 2020 Covid infections.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Long Covid Support
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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1	**The utility impact of Long Covid (-0.13) used by the AG in the economic model is too low, leading to an underestimation of the cost-effectiveness of the various drugs.** The AG has underestimated the severity of Long Covid (section 3.3.5.3). The evidence for this estimation is problematic as it is from the PHOSP study (Evans 2021). This study is of hospitalised patients that show a different phenotype and prognosis to those with Long Covid, the majority who are not hospitalised. The evidence that has not been taken into account, that demonstrates that Long Covid has a greater impact on health-related quality of life, includes: **1. Evidence from Long Covid** i) Dec 22 ONS survey - 370,000 (17%) said their ability to undertake their day-to-day activities had been limited a lot. The Oct 22 ONS Survey 70% percent of people with Long Covid in England (1.4 million people) say that their ability to do things in their day to day live is adversely affected and a fifth say this has been limited “a lot” (398,000 or 20% of people). The EQ-5D takes into account the mobility, self-care and usual activities – these are significantly affected in Long Covid so the disutility scale should be higher. ii) [redacted] iii) ‘Characterising Long Covid in an international cohort – 7 months of symptoms and their impact’ (Davis et al 2021) - PEM (post exertional malaise) affects 89% of people with Long Covid; fatigue, pain, orthostatic intolerance, sleep disturbance, cognitive impairment other common Long Covid symptoms lead to low functionality and quality of life. iv) Long Covid Support Reinfection Study We asked respondents to rate their health now compared with before Covid on a scale of 0-100. The average score was 48. “I still have symptoms which are having a MAJOR impact on my life” 42.62% -” I am SEVERELY DISABLED by Long Covid” 11.58% **2. Evidence from MECFS** NICE are using the data from a CFS study for the cost effectiveness so we feel that data from ME/CFS should be considered for the utility decrement calculation. This is also supported by the evidence that 50% of people with Long Covid meet ME//CFS Criteria; 46 %(Mancini et al., 2021); 50% (Kedor et al., 2021); 50% (Haffke et al., 2022) and 58.7% (Twomey et al. 2022). i) ‘The Health-Related Quality of Life for Patients with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)’ (Hvidberg et al 2015) **-** ME/CFS has an unadjusted disutility scale 0.47 -

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	OLS regression estimated disultility scale 0.29 for ME/CFS, compared to 20 other conditions – ME/CFS had the lowest quality of life compared to all 20 conditions. ii) 'What is known about severe and very severe chronic fatigue syndrome? A scoping review' (Strassheim 2017) - - 25% of ME patients are severe Long Covid severity is being underestimated because 50% of people with Long Covid meet ME/CFS criteria which means a significant amount are severely incapacitated and disabled. iii) 'The functional status and w**ell-being** of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers' (Nacul et al 2011) **-** ME/CFS is as disabling and has a greater impact on functional status and well-being than other chronic diseases. People with ME/CFS experience on average greater disability than those with type 2 diabetes, congestive heart failure, back pain/sciatica, lung disease, osteoarthritis, multiple sclerosis and even most cancers (Buchwald *et al* 1996) (Hvidberg *et al* 2015) (Komaroff *et al* 1996) (Schweitzer *et al* 1995) (Winger *et al* 2015) – also confirm that the scale of impairment across a range of physical and mental activities can be just as great or greater than in many other chronic medical conditions. iv) ME Association review 2017 **-** ME/CFS has been compared to MS in a range of studies – people with ME/CFS are significantly more disabled in functional ability compared to MS. Yet MS disultility score 0.66 - 0.63 'A Scoring Algorithm for Deriving Utility Values from the Neuro-QoL for Patients with Multiple Sclerosis' (Matza et al 2020) If 50% of people with Long Covid have ME/**C**FS and ME/**C**FS is functionally worse than MS with a disultility score of 0.66- 0.63 surely the 0.13 figure is far too low? **3. Other Evidence** i) For context other disutility scales for other conditions are: moderate migraine- 0.186; Flu like symptoms - 0.2;, Mild rash - 0.13; Severe migraine - 0.493; Depression - 0.47; Mild anaemia - 0.12. Noting the vast array of symptoms (up to 200) that can affect people with Long Covid a rating of 0.13 the same as a mild rash is not sufficient. The EQ-5D measure includes 5 dimensions: mobility, self-care, usual activities, pain or discomfort, anxiety, or depression the NICE evidence does not sufficiently take into account these for Long Covid.
2	**The use in the model of £1013 for the annual cost of Long Covid is too low, leading to an underestimation of the cost-effectiveness of the various drugs. The reasons for this include:** • Underestimation of the Severity of Long Covid • Underestimation of consultant specialisms ie Cardiology, Respiratory, GI, ENT (BMJ Long Covid - an update in primary care) • Underestimation of tests needed • Underestimation of the type and continuous extent of care needed for Long Covid • Underestimation of Occupational Health needed • Underestimation of the NHS financial support needed for severe patients especially in Social Care Many Long Covid services are not fit for purpose and patients are dissatisfied and feel they are not receiving adequate care. Evidence not taken into account:

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	1. Evidence from Long Covid i) Even with the investment made into clinics, patient satisfaction with services is poor. A survey undertaken by Healthwatch (n=858) 'What people told us about Long Covid (Healthwatch, 2022) ii) The initial plan, The NHSE Long Term Plan for Long Covid was an underestimate and a misjudgement on the nature on the need for the clinics. The plan in 2020 set out plans for £10m for services. This assumed that 68k people would need services. This was based on the false assumption that services would predominantly be needed by those who had been hospitalised. Therefore, the extent of the investment needed and the numbers needing long term care has been historically underestimated. iii) [redacted] iv) 'Experiences of living with long COVID and of accessing healthcare services: a qualitative systematic review' (Macpherson et al 2022) - A qualitative systematic review which included three surveys from the UK in addition to two international surveys examined patient experience of healthcare and found a lack of information, knowledge and understanding of Long Covid amongst health professionals which contributed to patients sometimes receiving patchy, inconsistent information and support which could generate anxiety and confusion at the point where patients were specifically seeking clarity. **2. Evidence from ME/CFS** The evidence from other ME/CFS sources is not considered, we feel that because evidence for the duration of Long Covid is derived from ME/CFS evidence it should be considered for other clinical and cost-effective calculations. The evidence from ME/CFS states that the nature and the costs for the NHS services for ME/CFS are underestimated especially when considering nonspecialised treatment which is significantly higher. So, there is the possibility the NHS is running a false economy on Long Covid and ME/CFS. i) ME Association Counting the Cost Report 2017 2016 -" Based on financial data obtained from 35 specialised CFS/ME services in the UK, service running costs average at just under £1,000 per referral, with 75% of those referred receiving a CFSME diagnosis. A number of services reported an average of 8–10 clinical contacts (quoted range of 1 – 24 contacts) during the course of a year. Eight services reported running costs at less than £100,000 per annum" "Health boards, CCGs and trusts that have not invested in CFS/ME expertise may be running false economies. Our economic analysis revealed NHS spending on people with CFS/ME to be in the region of £542 million. Drawing on matched sample findings by Lin et al. (2011), this amounts to well over £300 million more than a 'non-fatigued' population. Just 3% of the £542 million applies to the running of joined up, specialised services. Clinicians with CFS/ME specialism are not of course exclusive to such services, but it is highly probable that the NHS is spending substantial amounts of money on the non-specialised treatment of CFS/ME."
3	**The estimated mean duration of Long COVID of 108.6 weeks is too low, leading to an underestimation of the cost-effectiveness of the various drugs.** The research that has not been taken into account to lengthen the prognosis of Long Covid is:

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	1. Evidence from Long Covid i)ONS December 2022 27% duration of LC over 2 yrs. ii) Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort (Tran et al 2022)- At 12 months, the probability of symptom persistence (including patients in remission who relapsed) was 84.9%. iii) Outcomes among confirmed cases and a matched comparison group in the Long-COVID in Scotland study (Hastie et al 2022) Up to 18 month follow up, 6% don't recover, 42% partially recover. **2. Other SARS Post-Acute Viral Illness** i) **Is 'Long Covid' similar to 'Long SARS'?(** Patcai 2022) -A report of a 7 year follow up on 50 healthcare workers who had severe SARS1 from the 2022/3 Toronto outbreak showed that **none of them** regained their former state of health. **3. Evidence from ME/CFS** **i**)' A systematic review describing the prognosis of chronic fatigue syndrome' (Cairns et al 2005) – a systematic review of 14 studies of ME/CFS found a median full recovery rate during the follow-up periods of 5%, and the median proportion of patients who improved during follow-up was 39.5%. ii) Report to the CMO ME/CFS Independent Working Group – "Prognosis is extremely variable. Although many patients have a fluctuating course with some setbacks, most will improve to some degree. However, health and functioning rarely return completely to the individual's previous healthy levels; most of those who feel recovered stabilise at a lower level of functioning than before the illness…." "Overall, there is wide variation in the duration of illness with some people recovering in less than two years while others remain ill after several decades. Those who have been affected for several years seem less likely to recover; full recovery after symptoms persist for more than five years is rare." **iii)** 'Factor analysis of symptoms among subjects with unexplained chronic fatigue: What can we learn about chronic fatigue syndrome?' (Nisenbaum et al) estimated a duration of 6yrs.
4	**We are concerned that the evidence that people with Long Covid are immunocompromised, have a maladaptive immune response and T cell exhaustion is not being taken into account.** This evidence that hasn't been taken into account demonstrating the need that people with Long Covid should be considered at risk and eligible for antivirals: i)'Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms' (Peluso et al 2021) ii)'Neuro-COVID long-haulers exhibit broad dysfunction in T cell memory generation and responses to vaccination' (Visvabharathy et al 2021) iii)'Long-term perturbation of the peripheral immune system months after SARS-CoV-2 infection' Ryan et al 2022

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	iv)'SARS-CoV-2-specific T cells associate with inflammation and reduced lung function in pulmonary post-acute sequalae of SARS-CoV-2' Palmer et al 2022 v)'Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection' Patterson et al 2022 vi)'Distinguishing features of Long COVID identified through immune profiling' Klein et al 2022 vii) 'Immune signatures underlying post-acute COVID-19 lung sequelae' Cheon et al 2021
5	**The clinical and cost effectiveness summaries fail to take adequate account of the considerable evidence of excess mortality and morbidity following acute Covid infection, that is not classified as Long Covid. This evidence includes cardiovascular events (eg heart attacks and strokes), endocrine disorders (diabetes) as well as neurological consequences. Taking account of these will further improve the ICERs associated with the various drugs.** **1 Evidence for Excess Mortality** i) Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality' (Lancet 2022) ii) "Coronavirus Pandemic (COVID-19)". (Mathieu et al 2020-22) iii) '. Excess deaths associated with covid-19 pandemic in 2020: age and sex disaggregated time series analysis in 29 high income countries' (Shkolnikov et al 2021) iv) WHO Global excess deaths associated with COVID-19, January 2020 - December 2021 **2. Evidence for Negative Cardiovascular Outcomes** i) 'Long-term cardiovascular outcomes of COVID-19.'(Al-Aly et al 2020) ii) https://www.science.org/doi/10.1126/science.abe2813#body-ref-R7 Covid can damage the heart iii) 'Risk of Cardiovascular Events after Covid-19: a double-cohort study' (Tereshchenko et al 2021) iv) 'Cardiovascular disease and mortality sequelae of COVID-19 in the UK Biobank' (Raisi-Estabragh et al 2022) **3. Evidence for the increase of Diabetes risk:** i) 'The Incidence of Diabetes Among 2,777,768 Veterans With and Without Recent SARS-CoV-2 Infection.' (Wander et al 2022) **4. Evidence for the increase of Neurological complications:** i) 'Long-term neurologic outcomes of COVID-19' (Al-Aly et al 2022)
6	**We are concerned that the evidence for deterioration in people with Long Covid on reinfection is not being taken into account:**

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	1 Long Covid Support Reinfection Survey 80% worsened with reinfection. Of those who had recovered or were in remission from Long Covid, reinfection caused a recurrence in 60%. 2. 'Acute and postacute sequelae associated with SARS-CoV-2 reinfection. (Al-Aly et al 2022) – "evidence shows that reinfection further increases risks of death, hospitalization and sequelae in multiple organ systems in the acute and post-acute phase".
7	**The AG report and the draft guidance fail to take account of the considerable psychological and social costs associated with fear of infection or of reinfection. A key benefit associated with treatments for acute covid is the reduction in fear and social isolation for immunocompromised people and people with Long Covid. Taking account of this benefit would greatly improve the cost-effectiveness of the various drugs.** The evidence of personal testimony on the potential harmful impact of reinfection is not being taken into account. Many are self-imposing restrictions, limitations and/or shielding, to reduce their risk of reinfection which would mean the risk of their Long Covid and/or pre-existing health condition worsening. This is having an unnecessary adverse effect on those with a pre-existing disability. In the work place this contradicts making reasonable adjustments under the Equality Act (2010) and health and safety law as people or their families are not able to safely access work without significant risk of reinfection and with no precautionary antiviral or MAB treatment. The availability of treatments for acute covid will reduce those fears and increase health related quality of life (HRQoL). This means that the model will greatly underestimate the HRQoL benefits of treatment.
8	**We are concerned that the evidence for reducing the risk of Long Covid through the treatment of acute Covid with Paxlovid is not being taken into account:** 'Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19' (Al-Aly et al 2022) – which shows that people given Paxlovid in the first five days of their infection were 26% less likely to come down with Long Covid. Paxlovid significantly reduced 10 of the 12 sequelae assessed, including cardiovascular disease, coagulation disorders, kidney problems, etc. as well as fatigue, musculoskeletal pain, and cognitive problems.
9	**We are concerned that not all the evidence has been taken into account to justify the removal of many of the acute Covid treatments:** i) Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe COVID-19 outcomes in non-hospitalised patients: an observational cohort study using the OpenSAFELY platform (Zeng et al 2022) – shows that the Cilgavimab component still displays neutralising activity against BA 5 needs to be considered to reinstate Evushield Crick News. "Our data strongly suggest that we should be more aggressive in getting monoclonal antibodies into the clinic to treat COVID-19." David LV Bauer, Group Leader of the Crick's RNA Virus Replication Laboratory and member of the G2P-UK National Virology Consortium.

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	ii) WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed - Sotrovimab also shows that it still retains active ability against current variants. iii) 'Early Remdesvir to prevent progression to severe Covid 19 in outpatients' (Gottlieb et al 2022)- shows remdesivir still works when given at early stage to reduce hospitalisation so should be reinstated. Especially as it can be used in paediatrics. iv) PANORAMIC – was the lower performing ability of Molnupiravir considered in the light that the recent patient cohort was recently vaccinated?
10	We are concerned that the provisional guidelines as a provisional basis for the NHS lack the flexibility and the adaptability needed for mutations and waves of Covid. The possibility of the dangers of resistance are not being taken into account.
11	We are concerned that provisional recommendations are not a suitable basis for guidance to the NHS because without mitigations in place and then the removal of another layer of defence through a wide arsenal of therapeutics it's seriously questionable if the most vulnerable are being considered as worthy to be given a chance of a normal life.
12	We are concerned that provisional recommendations are not a suitable basis for guidance to the NHS because the 5 treatments no longer recommended will have an unacceptable impact on patients at highest risk i.e. immunocompromised, elderly, those with co-morbidities.
13	We are concerned that provisional recommendations are not a suitable basis for guidance to the NHS because by taking away a wide spectrum of medicine this takes away the safety net and leaves more people at risk from Covid – from death & disability from long covid & long-term cardiovascular complications.
14	We are concerned that the removal of Evushield has a significant negative psychological and physical effect on the immunocompromised. Leading to more people shielding, being left behind, being forced to work in unsafe conditions at risk to their morbidity and mortality.
15	We are concerned that provisional recommendations are not a suitable basis for guidance to the NHS because by not considering combinations of direct antivirals/monoclonals which improve activity and longevity against Covid.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	LUPUS UK
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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the lack of treatment options in the community setting within the preliminary recommendation will disproportionately impact people with medical conditions or existing treatment(s) that are contraindicated for nirmatrelvir plus ritonavir (Paxlovid). Without other treatment options in the community setting, these people will be unable to access therapeutics to reduce the risk of COVID-19 progressing to severe disease. Paxlovid is the only recommended treatment for the community setting but it has wide-ranging contraindications (**HERE**). In their systematic review, Dessie & Zewotir (**HERE**) found that diabetes, CVDs, COPD, hypertension, and acute kidney injury were the most significant risk for COVID-19 mortality. For most of these patient cohorts Paxlovid will be contraindicated due to their disease and/or medications. Without other treatments to prevent the progression of COVID-19 to severe disease in the community setting, many people will be exposed to increased risk; they will either need to recover from COVID-19 by themselves or become sufficiently severe as to require hospitalisation and access to therapies. *"The availability of sotrovimab made it possible to enjoy some ordinary close contact with my school and university-aged children after 18+ miserable, damaging months. When I got covid from my son last June, prompt treatment with sotrovimab was both reassuring and successful despite lupus-related lung and heart disease, immunosuppression, and weak antibody/vaccine protection. Paxlovid is totally contraindicated if you take colchicine- so I will be back to square one without the sotrovimab option. It feels like a hard choice between increased social disability/inequality, even in my own home, or increased medical disability since I'm tempted to stop the colchicine if this goes ahead; so that Paxlovid would be an option (although with active lupus pericarditis that's not a good idea)."* The withdrawal of viable COVID-19 treatments in the community setting will incentivise some people to maintain or return to shielding in order to minimise exposure to Cov-SARS-2 and reduce risk of contracting COVID-19. This can have a significant detrimental impact on an individual and their household. *"Shielding has had a negative impact on all aspects of my life - apart from the fact that I've succeeded so far in avoiding catching Covid"*

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	Sloan et al. (Jan 2021) found shielding has a negative influence on mental health. The changes included: ○ **Increased isolation** - feeling isolated and depressed from reduced social interaction; especially severe among those fully following shielding guidance and living alone. • *"I was so, so lonely. I haven't been shielding for months now but I still haven't mentally recovered from the isolation. I felt like the people shielding were often an afterthought for the government and it made me feel like I wasn't valuable compared to others. I am so scared of needing to shield again in the future."* ○ **Fear** – many estimated their mortality risk from COVID-19 as very high and expressed great anxiety. Additional risk factors, such as being from a Black, Asian and minority ethnic group, also increase anxiety. • *"As time has gone on it is much more stressful. I am still being very cautious, no planes, holidays, restaurants, cinemas etc. only meeting others outside. I feel isolated in winter. I have missed funerals, weddings, and milestone birthdays. It has caused friction with some family members and friends who act like covid is over and no longer a risk (as per government spin). I now have issues with my employer who thinks as some 'clinically vulnerable' people have returned, we all should."* ○ **Identity** - for many, the shielding classification provided medical and societal acknowledgement, and validation of the severity of their disease. However, the term 'clinically extremely vulnerable' was sometimes reported to have negative impacts on social and self-identity, with some perceiving their disease to have greater control over their lives than before the pandemic. • *"I was lucky enough to have a husband to support me in shielding, but I was unable to work as a nurse. This was very distressing, watching the circumstances that my colleagues and friends were working in. Because I was unable to work for about 2 years my registration has lapsed, and I am now not able to work as a nurse after almost 40 years. I am still grieving this loss."* The availability of viable COVID-19 treatments in the community setting provides important reassurance to people from our community. Knowing that treatments are available to help reduce the risk of severe illness from COVID-19 has enabled some people to live a better quality of life and be less isolated than that otherwise might have been. • *"I am grateful for the treatment I received. I had remained shielding and concerned for 28 months until I caught COVID-19 from my son, but knowing I can access treatment and recover if I get it again has made me a bit less concerned and I am shielding less (but still not socialising in crowded indoor settings/other's homes)."* • *"As clinically vulnerable and immunosuppressed, knowing that I will be given priority for treatments should I get COVID has allowed me to stop shielding and return to the office but I still do avoid busy places."* • *"The availability of treatments greatly puts my mind at ease. I feel less scared about contracting COVID knowing that treatments are now available. This means I'm happier going out and about in my daily life."* • *"Knowing that the antiviral medication would be available to me, should I contract COVID again, means that I have become more confident to leave the house and start living my life, carefully again."*

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	Due to the widespread use of immunosuppressants, corticosteroids and biologic treatments in the management of lupus, many people in our community do not have as much reassurance of protection from the vaccines. As such, the availability of viable post-exposure treatments is essential.
2	We are concerned that the preliminary recommendations are based on an incomplete review of evidence. Within the Committee's report, they assert that, *"…it is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (all neutralising monoclonal antibodies) are effective against the Omicron variant"*. We recommend that the committee includes these published studies within their review: • Wu et al. (**HERE**) advises an urgent reassessment of WHOs recommendation against using sotrovimab or casirivimab–imdevimab. Their study indicated that sotrovimab, imdebvimab and cilgavimab neutralised Omicron BA.2, BA.2.12.1, BA.4 and BA.5. • Zheng et al. (**HERE**) examined clinical data from patients on kidney replacement therapy in England between 16th December 2021 and 1st August 2022. During the 28 days of follow-up after COVID-19 treatment initiation, 1.1% in the sotrovimab group had COVID-19 related hospitalisations/deaths compared to 3.3% in the molnupiravir group. Those who received sotrovimab had substantially lower risk of severe COVID-19 outcomes than those receiving molnupiravir. • Zheng et al. (**HERE**) examined the comparative effectiveness of sotrovimab and molnupiravir between 16th February and 1st May 2022 when the Omicron BA.2 was the predominant variant in England. They demonstrated a reduced risk of hospitalisation or death from all causes within 28 days in the sotrovimab group compared to the placebo group. They also found risk of hospitalisation or death within 28 days was lower in the molnupiravir group compared to the placebo group, although this was a weaker effect. This supports the persistent protective role of sotrovimab and, to a lesser degree, molnupiravir.
3	We are concerned that the preliminary recommendations are over-reliant on in-vitro evidence of the neutralising effect of mAbs such as casirivimab plus imdevimab, sotrovimab, and tixagevimab plus cilgavimab. This approach makes significant assumptions regarding tissue penetration and mechanism of action of mAbs. Research has indicated that in-vitro studies analysing the neutralising effect of mAbs on different variants of SARS-Cov-2 do not accurately demonstrate the real-world, clinical efficacy of the treatment. In some cases a mAb developed for a historic variant could regain activity against the spike protein of a future variant. As such, the recommendations should not be reliant on in-vitro analyses. Uraki et al. (**HERE**) demonstrated that molnupiravir and sotrovimab can restrict viral replication in the lungs of hamsters infected with Omicron BA.2 in an in-vivo experiment, despite in-vitro experiments suggesting that Omicron BA.2 had resistance to sotrovimab. It is also important to assess the trial population of the evidence for COVID-19 treatments. Some trials only recruited non-vaccinated populations which may not capture some mechanisms of action that could provide additional protection for vaccinated populations. The threshold of evidence to enter a COVID-19 treatment into clinical practice is unrealistically high, especially due to the rapid changes in circulating variants and lower hospitalisation rate impacting recruitment of trial participants. On the other hand, the threshold to withhold or withdraw

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	the same treatment is much lower when based on in-vitro neutralising evidence alone. This disproportionately affects people at higher risk of COVID-19 whose medications or comorbidities exclude COVID-19 therapeutics other than a neutralising mAb (i.e. Paxlovid).

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Infection Association**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None to Declare**]
Name of commentator person completing form:	[redacted]

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Example 1	As an organisation, BIA (British Infection Association) serves as voice of Infection specialists all over UK. This consultation was sent around for comments to all our members; and as Guidelines Secretariat, we have compiled here the response comments as representing views from experts within BIA. The comments are separated out as individual response in separate rows as there are diverse aspects covered. We are concerned that these recommendations carry many implication that will affect standard of care in NHS as reflected by comments here below. ……..
1	**1.2 Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who:** **• are having systemic corticosteroids and** **• need supplemental oxygen or mechanical ventilation.** *This recommendation suggests that everyone with COVID-19 might be eligible for tocilizumab which is neither evidence-based nor safe. At present there is a very small subgroup of patients hospitalised with COVID-19 who warrant COVID-specific treatment, but often a low threshold for Emergency/Acute medicine doctors to give steroids (who on reflection do not have a covid pneumonitis but other reasons for their oxygen need), and this risks overtreating. The recommendation should narrow down the recommendation to meet RECOVERY and REMAPCAP criteria… evidence of covid pneumonitis plus CRP >75 or within short timeframe of respiratory support.* **1.5 Molnupiravir is not recommended, within its marketing authorisation, for treating mild to moderate confirmed COVID-19 in adults who have at least 1 risk factor for developing severe COVID-19.** *This is poorly worded. It might be read as suggesting that it is recommended in patients who do not have at least 1 risk factor.* *Also – the data to support use of molnupiravir is from the PANORAMIC study which showed no benefit in terms of hard outcomes (hospitalisation/death) and only in terms of symptom duration in a non-blinded study. If the recommendations evolve after consultation and revert to the current system of availability of alternatives to Paxlovid where contraindicated, it is quite unclear why this has translated into an ongoing recommendation ahead of sotrovimab for those with much higher risk factors (eg CEV),*

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	despite OPENSAFELY data suggesting a clear benefit of sotro over molnu for both BA1 and BA2. **1.6 Remdesivir is not recommended, within its marketing authorisation, for treating COVID-19 in:** **• people aged at least 4 weeks and weighing at least 3 kg with pneumonia who need supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation) at start of treatment** **• young people weighing at least 40 kg and adults who do not need supplemental oxygen and have an increased risk for progression to severe COVID-19.** *This is poorly worded. It suggests that remdesivir might be recommended in those aged less than 4 weeks or weighing less than 3kg or in young people weighing less than 40kg or in people who do not have an increased risk of progression etc….* *This removes the only antiviral other than Paxlovid (often contraindicated due to co-morbidities/drugs) for a severely immunocompromised patient hospitalised with COVID and not requiring oxygen, despite often a significant impact of ongoing viral replication on their health, and an obvious benefit in such a sick patient in bringing viral replication under control among the other elements of their care. A patient with a haematological malignancy would be a typical example.* *Given the statement about remdesivir, If the recommendations evolve after consultation and revert to the current system of availability of alternatives to Paxlovid where contraindicated, it is quite unclear why this has translated into an ongoing recommendation ahead of sotrovimab for those with much higher risk factors (eg CEV), despite much published data demonstrating the high rate of relapse in severely antibody deficient states.* Eg Treatment of chronic or relapsing COVID-19 in immunodeficiency - PubMed (nih.gov) and Shields AM, Burns SO, Savic S, Richter AG; UK PIN COVID-19 Consortium. COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. J Allergy Clin Immunol. 2021 Mar;147(3):870-875.e1. doi: 10.1016/j.jaci.2020.12.620. Epub 2020 Dec 15. And comment in Persistent SARS-CoV-2 infection: the urgent need for access to treatment and trials - PubMed (nih.gov) **1.7 Sotrovimab is not recommended, within its marketing authorisation, for treating symptomatic acute COVID-19 in people aged 12 years and over and weighing at least 40 kg who:** **• do not need oxygen supplementation and** **• have an increased risk for progression to severe COVID-19.**

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	*We have previously expressed in publications (Lancet letter, emails, OPENSAFELY preprint) [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01938-9/fulltext; **https://doi.org/10.1101/2022.05.22.22275417**] the arguments in favour of maintaining sotro for CEV patients who cannot have Pax, arguing that the in vitro data DOES support ongoing efficacy against BA.2 and that (in OPENSAFELY supplementary table) the benefit of sotro over molnu is maintained in BA2 era.* **1.9 People may be offered treatment from supplies already purchased by the Department of Health and Social Care before this guidance was published under the existing interim clinical commissioning policies, if clinicians consider it an appropriate option for people with COVID-19.** *This is confusing – either NICE think these are appropriate medications or they do not. How might clinicians consider them appropriate options if NICE believe that they are not? If the decision is purely and simply a cost-effectiveness decision, then this should be made clear but would require a great deal more health economic analysis for example to determine the cost effectiveness of 2nd line treatment in a very high risk patient (eg someone on rituximab) for whom Paxlovid is contraindicated.* *There is a significant risk of inequity of access here to say that someone on certain drugs and without renal impairment do deserve treatment whereas others who have renal impairment and/or happen to be on other contra-indicating drugs (cardiovascular drugs, transplant drugs, anticoagulation, etc) do not.* **3.4 The clinical experts gave examples of additional considerations around how high-risk groups are affected differently: •** **They cited the OPENSAFELY cohort analysis study that assessed the risk of severe COVID-19 in people with immune-mediated inflammatory diseases. This showed that people with inflammatory diseases who are having systemic therapies had similar rates of hospitalisation and death as people having targeted therapies, except for rituximab. The committee considered the different risk of progressing to severe COVID-19 may be related to which immunosuppressant drugs are taken, but the relationship may be complex and differ in other disease areas.** *Unfortunately this distinction wrt rituximab does not seem to have translated to a recognition of the significant risk associated with COVID in patients on this drug (or with other reasons for severe antibody deficiency such as primary or secondary IgG deficiency) and so with no access to drugs other than Paxlovid despite a significant proportion potentially having contraindications to Paxlovid.* **3.7 Current clinical management of COVID-19 in people who have a high risk for progressing to severe COVID-19 includes treatments available through an NHS**

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	interim commissioning policy (see section 3.3). As of June 2022, the policy recommendations are as follows: **• first-line treatment: nirmatrelvir plus ritonavir (antiviral) or sotrovimab (a neutralising monoclonal antibody)** **• second-line treatment: remdesivir (antiviral)** **• third-line treatment: molnupiravir (antiviral)** **• combination treatment with a neutralising monoclonal antibody and an antiviral is not routinely recommended.** *This is actually not correct. See https://www.england.nhs.uk/coronavirus/interim-clinical-commissioning-policy-antivirals-or-neutralising-monoclonal-antibodies-in-the-treatment-of-hospital-onset-covid which does not include molnupiravir.* **3.8** **…..The clinical experts considered that antivirals may have a limited role for people in hospital with COVID-19 because their mechanism of action focuses on blocking viral replication rather than controlling inflammation.** *Of course this may be a reasonable view from the perspective of biological plausibility, however RECOVERY clearly demonstrated a benefit of anti-SARSCOV2 nMAB (Ronapreve) in a subgroup of patients hospitalised with COVID-19 who were seronegative… and meta-analyses have demonstrated a benefit of remdesivir. So the biological plausibility is not enough to stand alone in a statement in a NICE guideline; Moreover if there is an argument to be made about biological plausibility it should by definition tgake account of the fact that a significant patient subgroup (those who are immunocompromised) have a biologically plausible reason why stopping viral replication may contribute to a better outcome from the downstream effects. This statement risks inequity of recognition of this subgroup as a population deserving clinical management that takes account of their different host response* **3.10** **• Anti-inflammatories (baricitinib, tocilizumab): Most evidence on these was generated during the earliest waves of the pandemic. Although later circulating variants have substantially lower mortality than earlier variants, the committee considered the relative benefit of treatments largely generalisable to later waves. This is because the mechanism of action regulates hyperinflammation, which it did not consider specific to a particular variant.**

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	What is the basis for this view? It is entirely without an evidence base. There is every reason to consider that the hyperinflammation may be less pronounced and less responsive to anti-inflammatories with a less virulent variant or in a vaccinated host. If such views are considered worthy of justification for use of anti-inflammatories in omicron era (ie not subject to NICE cost-effectiveness calculations done for omicron outcomes) then non-cost-effectiveness arguments should be used to provide access to antivirals. • **• Antivirals (molnupiravir, nirmatrelvir plus ritonavir, remdesivir): Most evidence on these was generated before later circulating variants. This is except for evidence on molnupiravir from PANORAMIC that recruited participants while the Omicron variant was circulating. The committee noted that some observational data supported efficacy of antivirals against later variants, but noted that these were not considered in a systematic approach.** *There is a systematic approach which is the use of data linkage cohorts such as OPENSAFELY to explore outcomes of patients receiving current antiviral therapy. While this is not an RCT it is unfair to say that it is not systematic. The capacity for RCTs to answer this question is minimal given current hospitalisation rates and changing variants so systematic observational data carefully analysed and reviewed should be considered a better determinant than committee consensus.* **• Neutralising monoclonal antibodies (casirivimab plus imdevimab, sotrovimab, tixagevimab plus cilgavimab): The committee recognised that these treatments bind to spike proteins that may change with each new variant. Therefore, neutralising monoclonal antibodies may lose the ability to neutralise the virus over time. This could create uncertainty in any assessment of generalisability of response from previous clinical trials and clinical efficacy estimates… etc etc** *We have argued in this article* WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed - The Lancet why the existing data does NOT support the argument that sotro is ineffective against BA2 (nor in fact does the Crick data make a specific argument for a higher dose), and if anything emerging evidence suggests better efficacy against even newer variants. **3.12 Remdesivir** **"…..The committee considered that remdesivir's mechanism of action may not fit the stated treatment aims. This is because antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation…"**

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	See comments above – while this was an early hypothesis, and no doubt applies to a majority of patients, this should not be allowed as a statement in an evidence-based policy document given that (a) meta-analysis has shown an overall benefit of remdesivir in hospitalised patients (b) RECOVERY showed a mortality benefit of REGNCOV in a subgroup with negative serology (c) controlling viral replication in heavily immunocompromised patients is a key part of management and follows as plausible a biological process as one arguing that in immunocompetent patients antiviral therapy is ineffective. Remsdesivir is currently the ONLY antiviral that can be used in hospital settings for immunosuppressed patients hospitalised FOR Covid, and the idea that for example a BMT or CarT or rituximab-treated patient with no antibodies (and contraindications to Paxlovid or ineligible as being hospitalised FOR Covid) with ongoing symptomatic viral replication should not be able to access antivirals is rather perverse in taking a key part of management of infection out of the armamentarium. **3.13 economic model** *In general it is unclear how cost effectiveness models take account of the consequences of SARSCOV2 infection in heavily immunocompromised patients* **3.20 non-hospital treatments** *I also have concerns as to whether the specifics around eg 3 hospital visits with associated transport costs (for remdesivir), as well as the high chance of relapse in antibody deficient patients warranting repeat treatment as they would have a high rate of relapse, been adequately costed* **3.24 Equality issues** *Inequity due to "pushy" articulate patients demanding a local solution vs others accepting NHSE policy decision.* *It seems completely inequitable that, for example, a patient meeting CMDU criteria for Paxlovid and falling into a very high risk group, would have it explained to him/her that they would qualify for treatment in terms of reduction in poor outcomes, but then in the course of the telephone consult be told that they cannot have it (and therefore any other treatment) because they happen to be on eg clopidogrel, or carbamazepine, or tacrolimus, or have an eGFR <30. How can that be equitable? There is also a risk that, in the absence of alternatives, the prescriber gives the medication anyway and risks serious adverse events due to the interaction*
2	Overall general point- I am surprised Remdesivir is not authorised within the hospital setting only. I agree it's not cost effective to bring outpatients in for it but our antivirals in hospital are very limited in the first 10 days of disease and I would imagine it may have a cost effective role then- as it was only considered across the whole time frame of disease this may have been missed- I would think it should be for particular subgroups though such as those who are immunosuppressed and unable to take paxlovid- I appreciate some of them also would be unable to take Remdesivir

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	Otherwise the recommendations make sense and align with current practice and other guidelines- except that we currently give steroids and baricitinib together and then only tocilizumab if the CRP is high- there is no mention of such stratification here. Section 1.1 p3 the link is to • as defined in the independent advisory group report commissioned by the Department of Health and Social Care. However- this is a cumbersome link and not a simple table- there should be a user friendly table e.g. in the appendices and it should be clear that this evidence basis was in unvaccinated populations so may overestimate the benefit to an individual vaccinated patient with a normal immune system 1.4 • Casirivimab plus imdevimab is not recommended, within its marketing authorisation, for treating acute COVID-19 in adults. • Worth adding except in the extremely rare scenario of proven delta infection? People with COVID-19 who have a high risk for progression to severe COVID-19 are offered treatments to stop their symptoms worsening. P4 “Usually, people would be offered nirmatrelvir plus ritonavir, sotrovimab, remdesivir or molnupiravir.” Should read People with COVID-19 who have a high risk for progression to severe COVID-19 and are not currently requiring oxygen are offered treatments to stop their symptoms worsening. P20 • **Molnupiravir:** The committee noted that published PANORAMIC results (Butler et al. 2022) Isn’t this still a pre-print? For all ‘publications’ cited this should be made clear P23 • The AG assumed that 100% of people in the hospital setting and 10% in the non-hospital setting would have long COVID • This is simply incorrect- 100% of people in the hospital setting definitely do not develop long COVID. Why did the committee not model this on a more realistic estimate such as 25% or similar? P25 • recurrent Clostridium difficile infection - needs italics

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3	Decision not to recommend sotrovimab – whilst understandable in economic terms – leaves a major problem with all solid organ transplant patients due to issues of drug interaction +/- stage 4/5 CKD with Paxlovid. Hence unless there is some change in guidance around potentially stopping/reducing calcineurin inhibitors or reducing Paxlovid dose further in severe CKD – nothing will be available for this group who are currently at highest risk of severe COVID (as per Agrawal U, et al. Lancet 400. October 15, 2022: DOI:https://doi.org/10.1016/S0140-6736(22)01656-7) – 10 -20 times risk, whereas most other groups in McInnes list were no more than 5x increased risk.
4	Thanks you for asking me to provide comments on this draft NICE guidance, which is now out for consultation. I have read the document in its entirely and my comments would be as follows: <u>GENERAL</u> · It is welcome that NICE is now reviewing the use of drugs for the treatment of COVID-19 in the systematic manner used of other drugs, adopting a cost-effectiveness approach. During the early stages of the pandemic there was a very understandable rush to try to get new drugs to clinicians in the NHS as quickly as possible. Whilst this was in many ways welcome, it has also led to a lot of debate and confusion– particularly given the fact that the original trials for these drugs were largely performed in the pre-Omicron era. · It is also welcome that the NICE guidance, when published, will hopefully result in a significantly simplified approach to therapeutics for COVID-19. I think most of our clinical colleagues (including some in ID and Micro!) are simply lost in the complexity of the multiple CAS alerts/ UK Interim Clinical Commissioning Policy (UK-ICCP) documents etc etc. that have been pinged out over the last couple of years. Despite laudable attempts to summarise guidance within some simplified UK-ICCP 'Clinical Guide' flow diagrams, it all remains far too complicated for busy front of hospital staff to follow and adherence to the guidance is therefore poor. Simplified guidance, with a more limited range of therapies that we all have some confidence actually work(!), is very desirable. · Publication of the NICE guidance MUST go hand in hand with withdrawal of the UK-ICCP guidance and flow diagrams, so as not to just cause further confusion · In my view he summary Recommendations (Section 1) are sensible and sound, and would tie in with what I would see as an appropriate way forward based on my own knowledge of the literature along with my own clinical experience of managing COVID-19 <u>SPECIFIC</u> · At times I found it difficult to follow whether the discussion in the document (e.g in the ICER discussions) relates to ALL patients, or just to 'highest risk' patients. This could/ should be clarified as far as possible

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	· The Table in the Conclusion section (page 35) is over-simplified and, because of that, actually misleading/ confusing. Specifically, it does not really tie in with the guidance in the Recommendations section (Section 1), and completely fails to address the question of ALL patients vs highest risk patients. Thus surely we will still be recommending Paxlovid (nirmatrelvir plus ritonavir) to symptomatic 'highest risk' patients who are in hospital but who do not have a requirement for supplemental oxygen? Why would this not happen if this is something that would be getting offered if they were still in a non-hospital setting?? · Remdesivir: I think it is appropriate to see the role of this drug demoted, for the reasons described in the document. There should however probably be a clearer separation between the 2 different indications and treatment protocols that are currently in place for Remdesivir: § 5-day course for unwell patients on oxygen and dexamethasone: I have never been in any way convinced that Remdesivir confers any therapeutic benefit in this situation. Indeed, locally we took it out of our local prescribing guideline, only to reluctantly add it back in so as not to cause confusion following the roll-out of the UK-ICCP 'clinical guide' flow diagrams. So glad to see it go – which is a view shared by my ID Consultant colleagues § 3-day course, on an outpatient basis, for 'highest risk' patients with mild/ mod symps, to prevent deterioration and hospital admission: There is better (but not great) data to support use in this scenario. However, the data is pre-Omicron, Remdesivir is expensive and attending daily for an IV infusion is very challenging (esp when you need to consider weekend provision of IV infusions). In practice, we have not used Remdesivir in this fashion at all, due to all the logistical challenges posed. So again – glad to see it dropped from the guidance § I have no doubt that Gilead will challenge the position taken by NICE on Remdesivir use. This challenge should be resisted with the cost-effectiveness data and what I believe is a strong clinical consensus opinion · Sotrovimab (+ other nMABs): The in vitro data does not support use. I really do not understand why we are still advocating the use of Sotrovimab at present – we wouldn't use any other antimicrobial drug that in vitro testing shows is ineffective Locally, we have just agreed to drop the use of Sotrovimab, based on the Sept 2022 WHO updated guidance. So in my view it is appropriate to see it dropped by NICE as well. However, again I suspect we may well see a drug company challenge here – as well as possibly from patient groups.
5	It must be acknowledged that the shifting standards of care, vaccination status of the population, and differing circulating variants have made any assessments and

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	conclusions difficult for the committee, and they should be congratulated for their work to date. Though many of the conclusions and assumptions are reasonable and correct, there are some areas of internal disagreement within the consultation document and some vital data that has not been fully accounted for. In terms of the general background, it is important to point out that future variants of concern could well be more virulent (in terms of causing hospitalisation and death) than the current omicron variant. Though a pathogen over time is likely to decrease in pathogenicity, this is often over decades or longer and the next major variant of concern is perhaps as likely to be more rather than less virulent. Also the evolutionary pressure resulting in new variants is based on immune responses to the spike protein, which is not the target of the antivirals being assessed. There is no evidence that current variants have any significantly altered sensitivity to these antivirals (in fact some evidence to the contrary (e.g. Vangeel L et al. *bioRxiv* 2021. DOI: 10.1101/2021.12.27.474275), and it would not be expected that future variants are likely to have altered susceptibility. I therefore disagree that '…the evidence of antivirals is uncertain for newer variants. It therefore considered a broader range of efficacy estimates to account for the uncertainty…' (section 3.10). For tocilizumab use in those requiring oxygen who are hospitalised, the RECOVERY trial - a major contributor to the evidence – only utilised this therapy in those with a C-reactive protein level exceeding 75. It is puzzling that this has not been significantly commented on, and that conclusions utilising this data have been extrapolated to those with lower C-reactive protein levels. It is disappointing that marketing authorisation seems to be required for an assessment (for example with baricitinib). The data is available, and the decision and timing of seeking authorisation have many other contributing factors. Such a decision (i.e. not providing a judgement) may be a policy of NICE but could well deny individuals access to an efficacious therapy, and therefore should be reconsidered. Similar could be expressed for the use of altered dosing of neutralising monoclonal antibody therapy, e.g. for tixagevimab/cilgavimab – for which there is currently data on efficacy against several prevalent omicron strains e.g. BA.4/5 (see https://covdb.stanford.edu/page/susceptibility-data) and there is therefore a risk in taking the position that '…the committee considered it reasonable to extend the likelihood of reduced efficacy to tixagevimab and cilgavimab.' (section 3.10) – each neutralising antibody differs from others and a broad generalisation has been shown to be invalid against earlier variants (as shown by data used to establish the Stanford algorithms: https://covdb.stanford.edu/page/susceptibility-data). The most fundamental areas where the committee should reconsider are based on the judgements on remdesivir therapy. There seems to be an assumption accepted by the

	panel that antivirals have limited efficacy and a limited role in those hospitalised requiring oxygen (as stated in section 3.8, and in section 3.12 – 'Remdesivir's mechanism of action may not fit the stated treatment aims.'). Though it is true that the pathogenetic mechanisms shift during COVID-19 from being predominately virus-mediated to being predominately inflammation-based there is significant overlap with both processes being responsible for disease in a large proportion of individuals. It is important to note that many of those hospitalised have on-going active viral replication (as demonstrated by cytopathic effects), and such active viral infection may persist for a significant period (e.g reference: Folgueria MD, *et al. Clin Microbiol Infect* 2021; 27:886–891) and, more importantly, there is a significant amount of efficacy data demonstrated for this product in this hospitalised setting (for example ACTT-1, final SOLIDARITY results, and significant real-World data (such as Olender SA et al. CROI. 2021; Olender SA et al. *Clin Infect Dis*. 2021;73:e4166–e4174; Garibaldi BT et al. *JAMA Netw Open*. 2021;4:e213071; Go A et al. ASM. 2021; Arch B et al. *MedRxiv*. 2021. DOI: 10.1101/2021.06.18.21259072; Joo EJ et al. *J Korean Med Sci.* 2021;36:e83; Chokkalingam AP et al. ASM. 2021; Mozaffari E et al. ASM. 2021; Mozaffari E et al. CROI. 2021; Garcia-Vidal C et al. *Lancet Reg Health Eur*. 2021;3:100041; Garcia-Vidal C et al. *Rev Esp Quimioter*. 2021;34:136–40; Mozaffari E et al. EFIM. 2021; Wong CKH et al. *Clin Infect Dis.* 2021. DOI: 10.1093/cid/ciab728; Mehta RM et al. *Int J Infect Dis.* 2021;106:71–7.). Other points in more detail: • It is unclear why Nirmatrelvir/ritonavir in the community is judged by its ability to reduce progression, whilst Remdesivir is seemingly judged by survival benefit (section 3.11), when the primary endpoint was similarly prevention of hospitalisation and all-cause mortality at 1 month. • Section 3.12 states that the use of Remdesivir '…is not as clearly defined' in the hospital setting – but it is quite clear from ACTT-1, the final SOLIDARITY results and a wealth of real-World data that a consistent mortality benefit is seen in those requiring oxygen support. • It is unclear why the large randomised SOLIDARITY trial's final results are not fully considered but rather '…the value of including this information is uncertain' (Section 3.12) - when data on the other products were similarly impacted (as acknowledged by the report on page 5) by trials performed prior to the emergence of omicron and largely in unvaccinated populations. Consistency in assessment is required from the panel. • There is also a contradiction where there is acknowledgement earlier in the report that '… clinical experts said a hierarchical flow of treatments is followed in the hospital and recommending one treatment over another is challenging' (section 3.8), but then section 3.22 states that '… Remdesivir was dominated by cheaper and more clinically effective treatments'. These other treatments being cited have a completely different mechanism of action, and there is data on the additive

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	benefit of Remdesivir therapy in combination with immune modulation (e.g. RECOVERY Collaborative Group et al. *MedRxiv*. 2022. DOI: 10.1101/2022.03.02.22271623). As a minor point, it is worth re-phrasing that not all the antivirals are oral (as specified in section 3.7) – as Remdesivir is intra-venous.
6	A. Has all of the relevant evidence been taken into account? This Consultation has not given enough weightage to clinical effectiveness evidence as much as it has laid emphasis on cost rather than even cost effectiveness as the evidence on cost-effectiveness too is quite skewed and confounded by looking at data across the entire pandemic timeline where the different variants that evolved have been so different from each other, and also from the original strain. If cost effectiveness is studied as a distinct time period for the current omicron post-origin era, that will instruct more accurately the ICERs of antivirals including Remdesivir quite early on in the presentation and especially in unvaccinated and/or immunosuppressed patients. However, there is a lot of data on clinical effectiveness of remdesivir in low oxygen requirement conditions; and even in those not needing oxygen which needs to be considered and I am not sure that this current appraisal document has. **Real-World Effectiveness of Remdesivir in Adults Hospitalized With Coronavirus Disease 2019 (COVID-19): A Retrospective, Multicenter Comparative Effectiveness Study** *Clinical Infectious Diseases*, Volume 75, Issue 1, 1 July 2022, Pages e516–e524, https://doi.org/10.1093/cid/ciab1035 A recent metanalysis: **Remdesivir for the treatment of patients hospitalized with COVID-19 receiving supplemental oxygen: a targeted literature review and meta-analysis** ***Scientific Reports*** **volume 12, Article number: 9622 (2022)** **https://www.nature.com/articles/s41598-022-13680-6** B. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The cost effectiveness analysis is skewed on the grounds that most of the data is drawn across different covid variants cycles, and more often than not the 'time-to-initiation' of therapy with some antiviral agents (esp remdesivir) has been broad with therapy instituted too late. The narrowing down to low flow oxygen indication happened quite late in the pandemic cycle in terms of mortality rates time line graphs. The committee had made the argument that in this omicron era, the recommendation cannot be generalised,

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	which could in fact suggest that the QALYs/ICER may be better in the Omicron/post-Omicron era if remdesivir is started early. Furthermore, there are 3 important practical points to consider: 1) What is the antiviral option when paxlovid is ruled out due to its myriad of drug-drug interactions? 2) Have the committee considered data or would it ask for data / literature need on how cost effectiveness [ICER/QALYs] and clinical effectiveness for the Remdesivir, sotrovimab, evusheld would be distinctly improved for those with failed immune function [immunosuppressed] and/or failed to take any SARS-CoV-2 vaccines or have been ineligible for it. 3) Has the committee looked at readmission rates in those immunosuppressed if not given adjuvant monoclonal antibodies [sotrovimab or evusheld]; or can there be a recommendation to look for evidence of that? C. Are the recommendations sound and a suitable basis for guidance to the NHS? The recommendation prevaricate mainly towards the cost of medications and it has not been a proper cost effectiveness analysis. As such, these recommendations will lead to poorer outcomes and standard of care for covid-19 in NHS. D. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? There is no perceived discrimination against individuals with protected characteristics. However, as highlighted above, the options for immunosuppressed individuals will be sub-optimal if depending on the SARS-CoV-2 variant in circulation, monoclonal antibodies such as sotrovimab or evusheld are withheld from being available.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Paediatric Allergy Infection and Immunity Group (BPAIIG)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

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Therapeutics for people with COVID-19 [ID4038]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**General comment:** This document recommends against use of any specific treatments in the context of acute COVID for those under 18 years of age without adequate discussion of the available data in this age range or acknowledgement of the impact this may have in the rare instances when severe disease may occur in this age group. There appears to be very limited consideration of the needs of individuals under 18 years in this guidance. Notable exclusions from the stakeholder list include RCPCH and BPAIIG, two organisations which have provided rapid, inclusive, multidisciplinary, evidence-based guidance on the management of COVID in children throughout the pandemic. There are significant differences in the frequency of severe disease, in disease phenotype and in risk factors for severity between adult and paediatric COVID, although there is clearly a spectrum of disease manifestations between birth and young adult. Despite the rarity of severe disease in children, significant efforts have been made to provide robust observational data and to include children and young people in studies relating to treatment safety, pK and efficacy. This does not appear to have been taken in to account in this guidance. We request that the needs of those under 18 years of age are specifically taken in to account and discussed more thoroughly for each agent listed in this guideline taking in to account the well recognised differences between adult and paediatric disease and the comparative availability of licensed agents.
2	1.1 Nirmatrelvir plus ritonavir is recommended as an option for treating COVID-19 in adults, only if they: - do not need supplemental oxygen for COVID-19 and - have an increased risk for progression to severe COVID-19, as defined in the independent advisory group report commissioned by the Department of Health and Social Care. Comment – no additional considerations for children as not licensed in this age group although it should be noted that any recommendation for use of this agent in adults but not in those under 18 years of age automatically discriminates against those individuals. Adolescent (>40kg >12 years) COVID disease phenotype (especially in those with obesity and risk factors associated with severe disease in adult populations) is very similar to that of young adults and by extrapolation agents with proven efficacy could be recommended in those age groups if/when licensed. PK and safety studies for children >6yrs of age are underway and this drug has received emergency authorisation in the USA, where observational data will shortly be published.
3	1.2 Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who: - are having systemic corticosteroids and

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	- need supplemental oxygen or mechanical ventilation. Tocilizumab is only recommended if the company provides it according to the commercial arrangement (see section 2). Comment – Patients under 18 years of age were included in the RECOVERY trial which demonstrated efficacy of tocilizumab. Although rare it is reasonable to extrapolate that CYP experiencing the hyperinflammatory phase of COVID may benefit from tocilizimab as has been demonstrated in adult studies. Consideration should be made for inclusion of individuals under 18 years in this recommendation. There is extensive safety and dosing data for use of tocilizumab for other indications in children.
4	1.3 Baricitinib is recommended as an option for treating COVID-19 in adults, subject to it receiving a marketing authorisation in Great Britain for this indication. Comment – Patients under 18 years of age were included in the RECOVERY trial which demonstrated efficacy of baricitinib. Although rare it is reasonable to extrapolate that CYP with COVID may benefit from baricitinib as has been demonstrated in adult studies. Consideration should be made for inclusion of individuals under 18 years, >40kg in this recommendation. Safety and dosing data for use of baricitinib for other indications in children are available.
5	1.4 Casirivimab plus imdevimab is not recommended, within its marketing authorisation, for treating acute COVID-19 in adults Comments – There is no mention of those under 18 years of age in this recommendation. This product is licensed for use in the treatment of COVID in adolescents and therefore a consideration of whether this agent should or should not be used in the adolescent age range (in which oral antiviral agents are not licensed) is warranted.
6	1.5 Molnupiravir is not recommended, within its marketing authorisation, for treating mild to moderate confirmed COVID-19 in adults who have at least 1 risk factor for developing severe COVID-19. Comment – no additional considerations for children as not licensed in this age group although it should be noted that any recommendation for use of this agent in adults but not in those under 18 years of age automatically discriminates against those individuals. Adolescent (>40kg >12 years) COVID disease phenotype (especially in those with obesity and risk factors associated with severe disease in adult populations) is very similar to that of young adults and by extrapolation agents with proven efficacy could be recommended in those age groups if/when licensed.
7	1.6 Remdesivir (RDV) is not recommended, within its marketing authorisation, for treating COVID-19 in: - people aged at least 4 weeks and weighing at least 3 kg with pneumonia who need supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation) at start of treatment - young people weighing at least 40 kg and adults who do not need supplemental oxygen and have an increased risk for progression to severe COVID-19. Comment – Reassuring safety and pK data is available from well designed clinical trials for remdesivir in those under 18 years of age. In addition, carefully reported observational data is also available. It is licensed for pre-hospital treatment in the adolescent age range and for hospitalised patients down to very young ages. In the under 12 age range this is the only licensed treatment available. Furthermore the disease phenotype in younger children is more of an acute viral syndrome (similar to other acute viral respiratory infections) rather than the hyperinflammatory process observed in older age groups. Efficacious antiviral agents are therefore likely to play more

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	of a role than anti-inflammatory agents in this age range. In addition RDV is licensed for outpatient treatment of high risk individuals with symptomatic COVID, based on trial data which included adolescents. In the absence of a license for oral antivirals this is the only antiviral option for non-hospitalised children and young people with COVID as well as those with hospital onset early disease in those hospitalised for different reasons. These considerations do not appear to have been adequately discussed or taken in to account when making this recommendation which could be considered discriminatory against this age group.
8	1.7 Sotrovimab is not recommended, within its marketing authorisation, for treating symptomatic acute COVID-19 in people aged 12 years and over and weighing at least 40 kg who: - do not need oxygen supplementation and - have an increased risk for progression to severe COVID-19. Comment – in the absence of a license for the oral antiviral therapies licensed for adults, sotrovimab is one of only 2 options available for treatment of non-hospitalised individuals under the age of 18 years with symptomatic COVID at risk of hospitalisation (the other being remdesivir which requires 3 daily doses of IV administration). Sotrovimab requires only 1 infusion and there are well established processes for providing this to those eligible (along with accumulating safety and tolerability data). Although there is some doubt about efficacy of sotrovimab for newer variants or in the context of natural or vaccine induced immunity, there is still evidence available that would support its use, especially if oral antiviral agents are not an option. The limited options available to those 18 years does not appear to have been taken in to account in this recommendation.
9	1.8 COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The role of tixagevimab and cilgavimab for pre-exposure prophylaxis in CYP peri-transplant/ or significant immunosuppression (eg induction chemotherapy) should be considered. PK, Safety and efficacy studies are underway in the UK for children and young people between the ages of 28 days and 18 years. It is noteworthy that the trials that these recommendations are based on predominantly included unvaccinated adults, the majority of whom were not immunocompromised. The current population who is at risk/ vulnerable to severe disease and death, for whom these recommendations are key, are largely immunocompromised through underlying disease and treatments, and are often unable to respond effectively to vaccinations for the same reasons. Emerging data specific to these cohorts is crucial for informing NICE guidance. In particular, monoclonals, including tixagevimab plus cilgavimab, are likely to play a greater role in those unable to mount an appropriate antibody response. The children who are unwell with COVID, or at risk of severe disease are either those with significant immunocompromise, for whom even small benefits from monoclonals may be relevant, or are susceptible to viraemic pneumonitis and have limited reserve (those with complex neurodisability), for whom anti-virals are likely to be play a crucial role. These considerations should be part of this document.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Thoracic Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
Name of commentator person completing form:	[redacted]

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1	We are concerned that this guideline provides for 1x antiviral preparation (Paxlovid) only, in non-hospitalised patients at high risk of progression. This is a drug with several CIs including liver and renal disease, and numerous drug interactions – including with several 'essential' or high risk medications which may be challenging to stop or replace during the treatment period. We would expect to see some analysis of the % of immunocompromised patients who would be ineligible for treatment with Paxlovid – this would seem key to a decision about providing this single antiviral treatment only.
2	We are concerned that this guideline will provide anti-inflammatory therapy only, with tocilizumab or baricitinib, for hospitalised patients requiring oxygen, with no antiviral or neutralising mAb provision. - Thresholds for admission vary, and we are increasingly seeing patients with early disease but a high comorbidity burden (particularly the elderly) being admitted to hospital +/- oxygen requirements. One would hypothesise a role for antivirals in this patient group - There is likely a transition period, even in those with more severe disease, who have both ongoing viral replication and a growing inflammatory response. There is likely a role for both antiviral and anti-inflammatory treatment in this patient group. - This approach makes no provision for immunocompromised patients / those with persistent viral PCR positivity who are admitted to hospital unwell, with failure to clear the virus – this is a growing proportion of our (extended) hospital admissions in whom antiviral treatment is essential.
3	There is repeated concern expressed that there is limited data for the efficacy of remdesivir – perhaps in relation to limited data about use in vaccinated groups / Omicron (p21/22). We wonder if this has led to inappropriate under weighting of data from the SOLIDARITY study. Whilst we understand the concern about efficacy across strains, it is not clear why remdesivir would be less effective in a vaccinated cohort – hospitalisation with evidence of PCR positivity presumably reflects viral replication +/- host inflammatory response, irrespective of vaccination status. It would be helpful if this concern could be justified / supported by some data.
4	We have some questions about the assumptions made within the model re. long Covid – - The analysis seems to conflate complications of an ITU admission amongst hospitalised patients, with the experience of long-Covid. I believe these are two distinct sequalae of Covid disease, with different types of care required, different duration of illness, and affecting

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	different Covid patient groups. I'm not sure one set of utility values can be applied across these conditions. - Perhaps related to this - the assumptions made on p23 re. the proportion of hospitalised / non-hospitalised patients experiencing long-covid do not feel quite right. Is there data to support this? Clinical experience suggests that there is a poor correlation between disease severity and the incidence / severity of long-Covid with a high burden of disease seen amongst non-hospitalised individuals who had relatively 'mild' initial disease.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Transplantation Society (BTS)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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1	The British Transplantation Society is concerned that the recommendation, as currently phrased, may imply that solid organ transplant patients do not benefit from treatment with sotrovimab in the community (data not available to support this position).
2	The consultation does not include a recent publication of factors associated with severe infection in the UK following an extended vaccine course, including an additional booster[1]. The study found that solid organ transplant recipients remained at highest relative risk of severe infection, which is an important consideration as the key driver in the economic models was the baseline rate of hospitalisation. Data is now also available showing a significant proportion of kidney transplant recipients fail to have detectable serological or cellular responses, even after 4-doses of COVID-19 vaccines[2]. The OCTAVE data, referenced in the consultation, contains minimal immunogenicity data on solid organ transplant recipients[3]. Solid organ transplant (SOT) recipients have been able to receive community treatment for COVID-19 following infection. This treatment option will be removed, if this guidance is ratified, and the alternative Paxlovid is not recommended for people with severe renal or hepatic impairment and is contraindicated with concurrent use of immunosuppression medications (CYP3A metabolic pathway). Therefore, both patients on the transplant wait list and transplant recipients, will not have access to antiviral treatment, despite being the population at highest risk. The consultation references data by the Crick Institute and OpenSAFFELY group, which supports continued access to sotrovimab for transplant recipients, until evidence suggests the agent no longer has clinical effectiveness[4,5]. The data from the OpenSAFELY group, also supports the benefit of sotrovimab over molnupiravir[6](pre-print). It should be noted that the PANORAMIC Study only reported outcome data on 127 SOT recipients, of whom all were eligible for concurrent monoclonal antibody therapy, and therefore will not be readily applicable to inform ongoing management in this population[7]. Access to community treatment has provided an additional layer of protection for SOT recipients, who are aware that vaccination may not provide as much protection as in the general population. Our patient representatives have already raised concerns and removal of access to community treatment will increase anxiety still further within this population- exacerbating health inequalities. The higher prevalence of lower socio-economic status and ethnic minorities in both the organ failure and SOT recipient populations has been well described, and this guidance will exacerbate those differences. **References:** 1. Agrawal U, Bedston S, McCowan C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30

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	million individuals in England, Northern Ireland, Scotland, and Wales. Lancet (London, England) 2022; 400(10360): 1305-20. 2. Thomson T, Prendecki M, Gleeson S, et al. Immune responses following 3rd and 4th doses of heterologous and homologous COVID-19 vaccines in kidney transplant recipients. EClinicalMedicine 2022; 53: 101642. 3. Kearns, P, Siebert, S et al. Examining the Immunological Effects of COVID-19 Vaccination in Patients with Conditions Potentially Leading to Diminished Immune Response Capacity – The OCTAVE Trial. http://dx.doi.org/10.2139/ssrn.3910058. 4. Wu MY, Carr EJ, Harvey R, et al. WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed. Lancet (London, England) 2022. 5. Zheng B, Green ACA, Tazare J, et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform. BMJ (Clinical research ed) 2022; 379: e071932. 6. The OpenSAFELY Collaborative, Bang Zheng, Jacqueline Campbell, Edward J Carr, et al. The LH&W NCS (or CONVALESCENCE) Collaborative. Comparative effectiveness of sotrovimab and molnupiravir for preventing severe COVID-19 outcomes in non-hospitalised patients on kidney replacement therapy: observational cohort study using the OpenSAFELY-UKRR linked platform and SRR databas. doi: https://doi.org/10.1101/2022.12.02.22283049 7. Butler, C, Hobbs, FD et al. Molnupiravir Plus Usual Care Versus Usual Care Alone as Early Treatment for Adults with COVID-19 at Increased Risk of Adverse Outcomes (PANORAMIC): Preliminary Analysis from the United Kingdom Randomised, Controlled Open-Label, Platform Adaptive Trial (October 4, 2022). http://dx.doi.org/10.2139/ssrn.4237902.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Faculty of Pharmaceutical Medicine
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	This draft guidance, if implemented, would result in the majority of the population of the UK being unable to access treatment for symptomatic COVID illness. This will particularly impact vulnerable individuals, who have been targeted by JCVI for receipt of vaccination boosters by virtue of their disease susceptibility and risk of more severe outcomes. In addition, this guidance stands in contrast to similar recommendations for the use of antiviral treatment for influenza, which provides access to treatment for the identical same group of patients that are recommended for free influenza vaccination (https://www.nice.org.uk/guidance/ta168). The committee might wish to consider whether the differences in recommendations for the management of two, now quite similar, respiratory viral diseases is justifiable and explicable to prescribing healthcare professionals. Many of the general population are at risk of more severe outcomes from both COVID and influenza based on age (>65) or comorbidities (chronic cardiac disease, diabetes, chronic respiratory disease, chronic renal disease, chronic neurological conditions), which are conditions in addition to those cited in the current NHS commissioning guidance. An explanation for use of treatment in these groups, who are regularly documented to be at high risk of more severe outcomes if covid infected, might be offered. For example, an overweight woman of 68 with no other risk factors has a 1:734 chance of dying from COVID according to the QCovid risk calculator, while an overweight male of 65 with chronic respiratory disease has a 1:475 chance of dying, The calculator does not list the risk of hospitalisation: if this could be added perhaps use of the risk calculator and a defined risk of hospitalisation/death is proposed then this would enable doctors to advise patients.
2	It is observed that NICE guidance is applicable only to access in the NHS. At what point will members of the public able to pay for therapy be able to access these treatments?
3	The expert panel that provided an independent view of patient groups eligible for treatment was restricted to the identification of patient groups *deemed to be at the very highest risk of an adverse COVID-19 outcome, namely hospitalisation and death.* The committee then restricted use primarily to immunocompromised patients as these individuals cannot respond adequately to vaccination. However, such groups include a high proportion of patients with poor T cell immunity and an inability to adequately clear virus, which has been reported in the past to contribute to the emergence of resistant viral variants in patients with influenza (van der Vries E et al), prolonged influenza virus shedding and emergence of antiviral resistance in immunocompromised patients and ferrets (PLoS Pathog. 2013;9(5):e1003343. pmid:23717200). Resistance to nirmatrelvir readily emerges in non-clinical experiments (Moghadasi SA et al). Transmissible SARS-CoV-2 variants with resistance to clinical protease inhibitors have emerged (bioRxiv [Preprint]. 2022 Aug 8:2022.08.07.503099. doi: 10.1101/2022.08.07.503099. PMID: 35982678; PMCID: PMC9387136.) suggesting that the current monotherapy strategy is inadvisable and may, if used widely among an immune compromised population, eventually result in the emergence of a transmissible, protease inhibitor resistant variant which would then threaten the general community. In immunocompromised patients, combination antiviral chemotherapy is preferable to monotherapy. This should be a subject for further research and also for additional cost benefit analysis.
4	While many monoclonal antibodies that were highly effective in the initial covid waves have now lost efficacy against omicron variants, researchers continue to explore new antibody treatments which

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	may enable reconsideration of the use of these agents, not only for treatment but also for primary prevention of covid in patients unable to respond to vaccination. Progress in this field should be kept under review and consideration given to reinstituting use, should newer antibodies become available.
5	Given the significant shift in pattern of disease accompanying emergence of the Omicron variants and the considerable strain on the economy of workforce shortages to which covid may have contributed and continues to contribute, the decision not to model the cost impact of expanded use of antiviral treatments seems inappropriate. It is appreciated that the model was not designed to explore this but a model can nonetheless be derived from the outcomes of PANORAMIC and prior work with influenza treatments with which to explore the value to industry and the NHS of preserving workforce effectiveness by earlier alleviation of illness and return to work. In addition, nirmaltrelvir-ritonavir has been suggested to reduce the frequency of sequelae post covid (Yan Xie, Taeyoung Choi, Ziyad Al-Aly Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19 medRxiv 2022.11.03.22281783; doi: https://doi.org/10.1101/2022.11.03.22281783). Although data are not yet available for molnupiravir, the results of the PANORAMIC study are compatible with similar outcomes being likely to be observed in longer term follow up of that population.
6	It appears that the cost of Long Covid may have been considerably underestimated. For patients with residual lung injury, post infection new onset diabetes, cardiovascular events or kidney disease, which are observed in patients following both community based and hospitalised disease, the costs are likely to be substantively higher than the costs of care for patients with Chronic Fatigue Syndrome. Several long covid clinics have been established and it would be appropriate to ask these centres for their own estimates of costs of care (https://www.england.nhs.uk/2020/12/long-covid-patients-to-get-help-at-more-than-60-clinics/) in their centre. Recent work investigating long term outcomes of patients with covid has documented a considerable increase in cardiovascular disease and stroke which is highest immediately following a disease episode in patients managed in the community and in hospital, and then persists, particularly in older persons for up to 12 months after infection (Knight R, Walker V, Ip S et al. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales. Circulation. 2022 Sep 20;146(12):892-906. doi: 10.1161/CIRCULATIONAHA.122.060785. Epub 2022 Sep 19. PMID: 36121907; PMCID: PMC9484653). The authors recommend consideration of post covid anticoagulation for vulnerable high risk adults and this should be further considered in treatment guidance, while investigating whether antiviral treatment might reduce the incidence of these complications, which has been observed in the past with influenza antivirals (Dutkowski R, Thakrar B, Froehlich E, Suter P, Oo C, Ward P. Safety and pharmacology of oseltamivir in clinical use. Drug Saf. 2003;26(11):787-801. doi: 10.2165/00002018-200326110-00004. PMID: 12908848.) and may also be an appropriate topic for further research.
7	No explanation is given for the continued recommendation of nirmatrelvir-ritonavir but the omission of molnupiravir for community use. The Panoramic study has yet to report the outcomes of the nirmatrelvir -ritonavir arm, but it is possible that the very low incidence of severe outcomes may also preclude convincing evidence of reduction of severe outcomes with this agent, as it did for molnupiravir, given the very low risk of hospitalisation/death in general, even in higher risk patients, during the Omicron era. Nirmatrelvir-ritonavir has not been shown to specifically reduce the overall duration of illness in affected patients – indeed in a study investigating this outcome in low risk patients (EPIC-SR) no difference in duration of illness, calculated as time to alleviation of all symptoms for at least 4 days, was observed (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-reports-additional-data-paxlovidtm-supporting). In addition, the required use of ritonavir in this agent is a problem, as mentioned at the meeting, for patients post-transplant taking anti-rejection therapy for which concomitant administration with ritonavir is contraindicated. It is recommended the panel consider whether molnupiravir might be

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	offered as an alternative in this group, or indeed for other patients for whom use of ritonavir could cause serious adverse drug-drug interactions, as is recommended by the WHO.
8	Examination of the AG model used to assess cost effectiveness is unclear as to the incidence of hospitalisations and deaths assumed to follow covid infections in the UK. Page 1 provides data from the ONS dated May 2022 suggesting a hospitalisation rate of >4% in the population overall, although the risk increases very steeply reaching very high levels in older individuals (aged >65). This observation makes the decision not to evaluate cost effectiveness according to age inexplicable, particularly as it is the older, frailer population that may be disproportionately admitted to hospital from which it may be difficult, due the present difficulties with the social care sector, to move recovered patients back to community based care. This is not discussed at all in the guideline other than to comment on potential for discrimination if recommendations were to be made based on age. It is suggested that it is discriminatory NOT to permit appropriate use of antiviral treatment in the community for a broader population of older patients with other conditions increasing risk of more severe disease following COVID infection. In the decision-tree page the presumed hospitalisation/death rate in SOCi (i.e. untreated) patients is 2.7%, which does not match the apparent community data based on the May UK analysis. In addition, neither of these percentages matches the incidence of hospitalisation/death reported in the PANORAMIC trial (0.8%) and these discrepancies should be discussed as to which are the appropriate presumptions to use in the analysis. FPM has commented previously that the publication of results from PANORAMIC suggest a potential reduction in the rate of hospitalisation/deaths among molnupiravir treated subjects aged 65 and over but insufficient details are provided in the publication and should be sought from the trial centre. It is suggested that the discrepancies in the basic assumption for hospitalisation/death from covid is further discussed and if appropriate the model adjusted to accommodate more accurate and up to date information relevant to current practice.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**UK Renal Pharmacy Group (UK RPG) leading on behalf of UK Kidney Association (UKKA)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	Extremely concerned that the recommendation for use of Paxlovid only in non-hospitalised, higher risk patients will exclude solid organ transplant recipients or patients on immunosuppression for renal autoimmune diseases due to complex, high clinical risk drug interactions with Paxlovid involving tacrolimus, ciclosporin or sirolimus. The latter drugs have a narrow therapeutic index whereby high levels can lead to nephrotoxicity which in extreme cases can lead to a patient requiring dialysis support due to acute kidney injury. Ritonavir (pharmacokinetic enhancer for nirmatrelvir in Paxlovid) is a potent liver enzyme inhibitor so co-administration will increase tacrolimus drug levels (up to ten-fold higher). But on stopping ritonavir there is then a time period of usually 7 days (but can be much longer in some) before liver enzyme activity normalises. Patients during this period are then at risk of under exposure of tacrolimus which can lead to graft organ rejection which if severe can lead to transplant graft loss. This draft guidance is inequitable - it excludes from pre hospital treatment, the group of patients consistently shown to be at the highest risk of developing severe COVID-19 infections (OPENSAFELY study). A key reason for this is the high proportion of transplant patients who are vaccine non responders or poor responders as evidenced by the OCTAVE study amongst others.
2	There is some real-world experience in Canada of using Paxlovid in solid organ transplant recipients (personal communication). However, managing this interaction is extremely labour intensive (estimated 4-6 hours extra senior MDT staff time per patient to follow up individual patients and ensure safe dosing) and there are high risk stakes if drug levels are not forthcoming, timely or patient misunderstands dosing advice especially as this advice will be given verbally over the phone. Patients would need to be advised to stop tacrolimus based immunosuppression for 7 days on starting Paxlovid and then tacrolimus would be reintroduced at reduced dose with blood levels every 2-4 days to guide tacrolimus dose up titration. Levels would need to be taken in hospital (but patients likely still covid positive) so logistics here would be extremely challenging. Tacrolimus levels need to be measured by the same laboratory to ensure consistency, as there is some intra-laboratory variation. The degree and duration of ritonavir liver enzyme inhibition is patient specific and variable. For some patients' enzyme inhibition can be extremely prolonged, with tacrolimus drug levels not normalising for some weeks and therefore extended intensive monitoring would be required, which adds further logistical challenges and significant clinical risk. Co-administration of these medicines would carry a high risk of toxicity (nephrotoxicity which in extreme may require dialysis support for acute kidney injury or graft organ rejection). This interaction would similarly apply to ciclosporin or sirolimus based immunosuppression. Furthermore, transplant patients are on many different medications including blood pressure medication. For example, Paxlovid can elevate the drug levels of calcium channel blockers commonly used for hypertension, rendering patients hypotensive, which may lead to acute kidney injury, and necessitate further medication changes and further confusion for the patient.

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3	Similarly, extremely concerned that there is no UK licensed dose or proven safe dose for use of Paxlovid in patients with severe renal impairment, eGFR <30ml/min (Chronic Kidney Disease: CKD stage 4-5) or patients on renal replacement therapy (haemodialysis/peritoneal dialysis), therefore excluding these patients, known to be at high risk of developing severe COVID-19 infections (OPENSAFELY study) from pre hospital treatment with Paxlovid. A trial protocol was accepted by the company to address this safe dosing question, but they chose to follow this up in Canada and to link it to trialling a paediatric, non-solid dose formulation. A published Canadian case series of 15 haemodialysis patients reported safe use of a reduced dose regimen – published 17/08/2022 CJASN Aug 2022, 17 (8): 1247–1250. Hiremath S, McGuinty M, Argyropoulos K et al. Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD Any use of Paxlovid in this cohort is outside of UK product license as an appropriate dose has not been determined. This exclusion of patients with advanced kidney disease therefore makes the draft guidance inequitable as this group are at higher risk of developing severe covid disease.
4	There is a significant medicine safety risk of incorrect dosing/medication error when any dose other than 300mg nirmatrelvir /100mg ritonavir is used in the UK due to how the drug is packaged.
5	New evidence for consideration: A recently published paper in British Medical Journal on 16/11/2022 (*BMJ* 2022;379:e071932) – reported real world observational data on use of sotrovimab and molnupiravir in community according to NHSE national policy. This paper demonstrated that patients who received sotrovimab were at lower risk of severe outcomes of covid-19 than those treated with molnupiravir.
6	Further evidence for consideration: published on line 6/10/2022 in The Lancet, the Crick group reported that sotrovimab neutralised Omicron variants BA.2, BA.4 and BA.5 in vitro to similar extents and suggesting that sotrovimab would remain effective against BA.5.
7	Recently published new evidence for consideration - preprint online in MedRxiv (www.medrxiv.org), posted on 04.12.2022. Comparative effectiveness of sotrovimab and molnupiravir for preventing severe COVID-19 outcomes in non-hospitalised patients on kidney replacement therapy: observational cohort study using OpenSAFELY-UKRR linked platform and SRR database. The OpenSAFELY Collaborative; Zheng B, Campbell J, Carr EJ et al https://medrxiv.org/cgi/content/short/2022.12.02.22283049v1 In summary this paper concluded in the routine care of non-hospitalised patients with COVID-19 on kidney replacement therapy, those who received sotrovimab had substantially lower risk of severe COVID-19 outcomes than those receiving molnupiravir.
8	Considering all above points, we believe it is imperative to retain the use of sotrovimab in these patient groups, where Paxlovid cannot be used safely or effectively. This is especially so for patients on concomitant tacrolimus, ciclosporin or sirolimus as detailed in points 1 and 2.
9	If Paxlovid is recommended in the final guidance, then allowing the off-license use of Paxlovid in patients with CKD stage 4-5 and on dialysis should be included with unlicensed dose recommendation specified and corresponding revision of the blueteq form. The medication safety risks identified in point 4 require further consideration. Reduced dosing has been trialled in a small number of patients with advanced CKD as discussed in point 3. Liverpool COVID-19 drug interactions group/website has produced a Paxlovid in Renal disease dosing guide, accessed 2.12.22 www.covid19-druginteractions.org/prescribing_resources/paxlovid-renal-dosing This same reduced dosing regimen is also referenced in the Renal Drug Database, accessed 2.12.22 https://renaldrugdatabase.com

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Physicians (RCP)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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General	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with the British Thoracic Society (BTS), The UK Kidney Association (UKKA), the Faculty of Pharmaceutical Medicine (FPM), the British Geriatric Society, and the British Society for Rheumatology (BSR) to inform our response. We have also created an RCP working group of clinical experts and would like to comment as follows.
1	Our experts are concerned that this recommendation restricts access to treatment for COVID to a small group of non-hospitalised patients with a single antiviral agent. This group of patients are defined according to the criteria identified by an independent advisory group formed early in 2022 and targets those at increased risk of progression to severe COVID-19. This restriction will particularly impact vulnerable individuals, who have been identified by the JCVI for receipt of vaccination boosters by virtue of their disease susceptibility, and risk of more severe outcomes, but who have not been included by the independent advisory group criteria to be included for anti-viral treatments. In addition, this guidance stands in contrast to similar recommendations for the use of antiviral treatment for influenza, which provide access to treatment for the identical same group of patients that are recommended for free influenza vaccination (https://www.nice.org.uk/guidance/ta168).
2	Our experts are concerned that although it is noted that vaccinated patients may be less likely to have severe pneumonitis and a reduced need for ventilation, the assumption that the finding of longer hospital stays for those with COVID-19 is due to infection control restrictions is simplistic. Clinical feedback suggests that older hospitalised COVID patients are more likely to have non-specific symptoms such as delirium which lengthens their hospitalisation. Wider NHS benefits from reducing viral load and shortening illness for patients should be considered in health economic analysis. Reducing hospital stay will be critical for managing recovery from the COVID pandemic in NHS hospitals.
3	Our experts want to highlight the group of patients who are very immunosuppressed e.g., those receiving antiCD20 treatment with rituximab and those with primary immune deficiencies who have no/reduced antibody production. These patients are less likely to mount a good response to COVID-19 vaccines and remain extremely vulnerable to serious consequences from COVID-19 infection. Those who are not eligible for nirmatrelvir/ritonavir (Paxlovid) require an effective alternative. We support the continuing use of sotrovimab for these patients.
4	Our experts are concerned that there is no analysis of the % of immunocompromised patients who would be ineligible for treatment with Paxlovid because of this drug combination's contraindications including renal and liver disease. It was also noted that Paxolvid is associated with numerous drug interactions which may be difficult to stop or replace during any COVID-19 treatment period. Renal colleagues highlighted particularly the vulnerable post –transplant group and we would expect that this MTA would consider other options for such immunocompromised patients, ineligible for Paxlovid. Key to any decision about providing a single antiviral option is the alternative options if the drug is unsafe or not tolerated. Renal colleagues have specifically highlighted a lack of therapeutic options for patients with low GFR (< 30mls/min) with Paxlovid and Remdesivir requiring further urgent clarification of safety in these patients.

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	Recently published new evidence for consideration: Preprint online in MedRxiv (www.medrxiv.org), posted on 04.12.2022. Comparative effectiveness of sotrovimab and molnupiravir for preventing severe COVID-19 outcomes in non-hospitalised patients on kidney replacement therapy: observational cohort study using OpenSAFELY-UKRR linked platform and SRR database. The OpenSAFELY Collaborative; Zheng B, Campbell J, Carr EJ et al https://medrxiv.org/cgi/content/short/2022.12.02.22283049v1 This paper concludes that in the routine care of non-hospitalised patients with COVID-19 on kidney replacement therapy, those who received sotrovimab had a substantially lower risk of severe COVID-19 outcomes than those receiving molnupiravir raising concerns that molnupiravir may not be optimal treatment for this group. Whilst acknowledging recent concerns about the efficacy of sotrovimab against newer COVID-19 variants, our experts remain concerned that specific consideration needs to be given to patients with renal disease who currently remain exceptionally vulnerable with limited therapeutic options.
5	We are concerned that this guideline will provide anti-inflammatory therapy only, with tocilizumab or baricitinib, for hospitalised patients requiring oxygen, with no antiviral or neutralising mAb provision. • Thresholds for admission vary, and we are increasingly seeing patients with early disease but a high comorbidity burden (particularly the elderly) being admitted to hospital +/- oxygen requirements. One would hypothesise a role for antivirals in this patient group • There is likely a transition period, even in those with more severe disease, who have both ongoing viral replication and a growing inflammatory response. There is likely a role for both antiviral and anti-inflammatory treatment in this patient group. • This approach makes no provision for immunocompromised patients / those with persistent viral PCR positivity who are admitted to hospital unwell, with failure to clear the virus – this is a growing proportion of our (extended) hospital admissions in whom antiviral treatment is essential.
6	No explanation is given for the continued recommendation of nirmatrelvir-ritonavir but the omission of molnupiravir for community use. It is recommended the panel consider whether molnupiravir might be offered as an alternative in this group and for other patients for whom use of ritonavir could cause serious adverse drug-drug interactions, as is recommended by the WHO.
7	Our experts are concerned about the modelling of long Covid. We have some questions about the assumptions made within the model re. long Covid: • The analysis seems to conflate complications of an ITU admission amongst hospitalised patients, with the experience of long-Covid. These are two distinct sequelae of Covid disease, with different types of care required, different duration of illness, and affecting different Covid patient groups. We have concerns that one set of utility values may not be appropriate across these conditions.

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	• Similarly, the assumptions made on p23 re. the proportion of hospitalised/non-hospitalised patients experiencing long-covid seem inaccurate. Our experts question whether there is data to support this. Clinical experience suggests that there is a poor correlation between disease severity and the incidence / severity of long-Covid with a high burden of disease seen amongst non-hospitalised individuals who had relatively 'mild' initial disease.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**UKCPA Pharmacy Infection Network**]
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Example 1	We are concerned that this recommendation may imply that ……..
1	The revised guideline provides no viable treatment option for patients in which Paxlovid is contra-indicated. This is a significant proportion of high-risk patients treated currently through the CMDUs and acute hospitals at present. Based on local performance, we may expect one in three patients to be excluded from future CMDU treatments based on Paxlovid contra-indications including organ dysfunction and or concurrent interacting medications. This will result in a) patients being deprived any treatment options due to their concurrent medications or renal / hepatic dysfunction or b) clinicians using this Paxlovid therapy outside of the product license for patients with known interacting drugs or renal / hepatic impairment. The latter is expected based on patient pressure for treatment and the lack of viable alternative options. If this does occur, we may see some significant drug related toxicities due to unexpected interactions and / or Paxlovid toxicities in renal/hepatic dysfunction. Thus the current treatment recommendations with lack of alternative will make for non-equitable delivery of treatment for patients and increase pressures on prescribers.
2	The loss of remdesivir as a treatment option for CMDU patients appears inconsistent with other recommendations made within the guidelines. The primary study findings of EPIC-HR (Paxlovid) and PINETREE (Remdesivir) are similar in the study design and timing (pre-vaccination population predominantly) and their results and conclusions also overlap with similar relative risk reductions seen in the primary outcomes. Whilst accepting a lower mortality burden within the Remdesivir study (both control and treatment) compared to the EPIC-HR study, we cannot draw firm conclusions on mortality differences between the two therapies yet the recommendations appear to differ based on this finding. Independent of costing of the therapies, there is little published data to demonstrate any differences in efficacy between these two therapies. We would welcome further clarification therefore on the contrasting recommendations made for these two therapies in the setting of CMDU.
3	The guidelines for management of acutely unwell patients with COVID-19 requiring O2 supplementation recommend against the use of remdesivir based on the assumption that antiviral therapy will be too late to benefit the patients. There is little published evidence to support this assumption and the ACTT-1 NIHR study showed some modest clinical benefits in this studied population. This assumption about lack of antiviral activity in this group of patients may not reflect patients with immunodeficiencies where viral clearance can be significantly impaired. Delaying or avoiding antivirals may have infection prevention and control implications (increased onward spread of disease) and result in delayed time to clearance of active infection. This assumption of lack of remdesivir in moderate – severe COVID-19 needs further scrutiny and transparency as well as some options for high-risk patient groups. We may suggest that routine use is recommended against but treatment may be considered in patients were viral clearance may be impaired due to host immune deficiencies. This would enable the most vulnerable patients to have some available antiviral options.
4	The removal of all neutralising monoclonal antibody therapies (nMAB) therapies poses a major change in clinical practice. Will the OpenSafely database and scrutiny of the CMDU patient clinical

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	outcomes for treated patients over the summer 2022 (predominantly exposed to the Omicron variants) be used to inform this recommendation? Comparison to first-line (Paxlovid) should be possible and provide a more objective analysis in the absence of timely prospective studies in Omicron infected patients.
5	Will the Panoramic study data be available for Paxlovid outcomes prior to the publication of these guidelines?
6	The committee welcomes the recommendations for tocilizumab and baricitinib for deteriorating patients with COVID19 infection. The current advice and recommendations do not provide explicit data on when these therapies need to be introduced and the when combination therapy can be considered. This has resulted in some variation in implementation across the country with these agents used at same time as dexamethasone introduction for some practices or reserved for patients who are not responding to dexamethasone treatment after 1-3 days. The study design of RECOVERY had early steroid introduction before randomisation (on to the study). Some clarification on when to introduce these therapies relative to dexamethasone in patients not on high-flow O2 / intensive care would be useful. Furthermore, advice on when to combine the JAKi and IL-6i would be useful for standardised implementation nationally.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England
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1	We broadly agree that the relevant evidence has been taken into account. [redacted]. It is not clear if this has yet been made available to NICE as part of the appraisal process
2	We note that the draft refers to the SOLIDARITY trial for remdesivir, and that not all results from this study were included in the AG's evidence synthesis, which the AG commented 'would likely have likely impacted the final conclusions for remdesivir'. We understand that GSK may be making further data available to NICE as part of its consultation response.
3	The draft includes a comment on the use of remdesivir in people hospitalised due to COVID-19, that '…antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation'. This appears to be the view of the committee based on the therapy's potential mechanism of action; we feel that it is important to consider the evidence for effectiveness of remdesivir in people hospitalised with COVID-19 rather than base recommendations on a mechanistic hypothesis
4	Based on the two points above, we would encourage NICE to assure itself that all of the relevant SOLIDARITY results have been considered
5	We would be grateful to receive confirmation that evidence of improvements in time to recovery have been considered alongside evidence of reductions in the risk of hospitalisation or death
6	We know there is significant clinical interest in the potential to use therapies in combination (and the World Health Organization (WHO) specifically recommends the consideration of combination use of dexamethasone, baricitinib and an IL-6 inhibitor in patients admitted due to COVID). Is NICE intending to comment on combination use of licensed COVID-19 therapies?
7	Testing of patients will be an integral part of the patient treatment pathway and an additional deployment cost to the NHS specific to the treatment of eligible non-hospitalised cohorts. It is not clear if the additional cost of testing (which will involve the provision of multiple tests to be available to eligible patients should they experience COVID-type symptoms) has been included in the cost-effectiveness analysis
8	We note that an estimated average CMDU deployment cost for the administration of oral antivirals has been used (£410) in the analysis; please note that future delivery models are likely to change, for example, access through GPs and community pharmacies; so the associated cost of delivery/administration may change
9	It is noted that the AG assumed the annual per person management costs of long COVID to be comparable with chronic fatigue syndrome; we agree with the need to consider evidence on long COVID costs as they become available
10	We note that the draft states 'Baricitinib is recommended as an option for treating COVID-19 in adults, subject to it receiving a marketing authorisation in Great Britain for this indication'. There is a concern that a clinically- and cost-effective therapy may be available, but not recommended if the marketing authorisation for GB is not granted in time for the final MTA recommendations. This risks continuity of provision of a clinically and cost-effective medicine and does not seem to be a suitable basis for guidance to the NHS
11	The recommendation for nirmatrelvir plus ritonavir suggests use only in people who have an increased risk for progression to severe COVID-19 as defined by the Independent Advisory Group

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	report. It would be helpful to understand how the cost-effectiveness analysis in the highest-risk cohort was considered (given different definitions of 'high-risk' group/s utilised in individual therapy trials)
12	It might be helpful if the final guidance could signal that the guidance will apply whilst COVID is an endemic disease and may need to be reviewed in other circumstances
13	It might be helpful if the final guidance could consider whether the use of any remaining stocks of medicines procured by DHSC, which would effectively be available to the NHS at zero additional cost, and therefore only incur the costs associated with their distribution and administration, would represent a clinically and cost-effective use case
14	The draft recommendation of nirmatrelvir plus ritonavir being the only therapy recommended for people in the highest risk group who do not need supplemental oxygen for COVID-19, could mean there is no treatment available for individuals who: ○ Are pregnant (marketing authorisation: not recommended during pregnancy) ○ Are children and adolescents (safety and efficacy in paediatric patients younger than 18 years of age have not yet been established) ○ Have disabilities linked to the medicine's specific cautions and contraindications
15	Section 1: Refers to '*These treatments are recommended through the NHS interim clinical commissioning policy on antivirals or neutralising monoclonal antibodies for people with COVID-19 who are not in hospital*.' – To note treatments are also commissioned through NHS interim clinical commissioning policy 'Treatments for hospital-onset COVID-19'
16	Section 3: Refers to '*The McInnes report was used by the NHS interim commissioning policy on antivirals or neutralising monoclonal antibodies for people with COVID-19 who are not in hospital to define high risk and is a narrower definition than that in PANORAMIC*.' – To note treatments are also commissioned through the NHS interim clinical commissioning policy 'Treatments for hospital-onset COVID-19'
17	Section 3.3: Refers to '*These interim policies and McInnes report's high-risk definition would have influenced the risk level of people who enrolled in PANORAMIC*.' To note that the McInnes report refers to those at 'highest-risk'
18	Section 3.7: Refers to '*Antivirals aim to reduce viral load and viral replication which may reduce risk of severe disease. They are administered orally*.' To note that remdesivir is administered intravenously rather than orally

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Sophie Wheldon

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1	Whilst I am pleased that antiviral access is not planned to be completely revoked, I still have some concerns about the reduction in the amount of treatments available in a community setting. During my two most recent infections with COVID-19 this year, I have required an infusion of sotrovimab in my local COVID Medicines Delivery Unit. Knowing that this treatment was an option felt like a lifeline, which positively contributed to me being able to live as I am. Having a range of different options for community treatments has been very reassuring to me in the past, so it does make me feel anxious as a patient to think that there will now only be one potential community treatment available – one which I have not got any experience with receiving.
2	I am concerned that there could be some access issues if only one community drug is planned to be available for the 500,000 clinically extremely vulnerable people in the UK. If there is a supply issue in the future, how will patients be able to access the treatment that they need? I worry that this could lead to an increase in patients becoming very unwell with COVID, leading to higher hospital admissions and ultimately, increased rates of death, which is terrifying. I would certainly feel extremely anxious if I was to contract COVID-19 again in these circumstances.
3	Being in hospital with COVID-19 when you are immunocompromised is extremely scary and can have a significant physical, psychological and financial impact on patients. If patients aren't able to access community treatments for whatever reason (e.g. not suitable due to contraindications; no community treatments available etc), then this may lead to more patients progressing to a more serious condition with COVID, leading them to require treatment in hospital which would end up costing more money. The hospital admission rates used by NICE in their analysis were based on the Omicron variant, which has typically been reported as a more mild variant of COVID-19. The numbers used in the analysis underestimate the potential impact of future, more severe variants which may result in higher hospital admissions and inevitably increase costs. Patients who end up in hospital will need more options.
4	Further to my points about the reduction in community treatments, I was disappointed to see that the number of hospital treatments has also been reduced. This further increases my anxiety about potential access issues and delays in getting the appropriate treatment for those at high risk of severe infection, including myself.

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	As mentioned above, being hospitalised with COVID-19 as someone who is immunocompromised is very scary. In August 2021, I required a double dose of Remdesivir to help me to fight the infection. I think that this emphasises the point that more options are needed, as the variable response in patients may mean that their treatment will need to be altered or changed in order to get them the best possible outcome. Reducing the number of treatment options will make this much more difficult.
5	I feel that patient preference has been overlooked in this appraisal. I would personally prefer to go to the local COVID Medicines Delivery Unit for an infusion of medication rather than having to wait around for a delivery of tablets. I know of other people who much prefer to receive tablets, because they live far away from a delivery unit. There are many reasons why a patient may prefer one treatment delivery option over another, and I feel that reducing the community treatments down to just one option severely limits this. I understand that it is believed that Sotrovimab is not clinically effective, but I personally had a lot of faith in the treatment as it had made me better on both occasions that I needed it. I feel anxious that Paxlovid is very different to an infusion.
6	Before COVID-19 treatments were made available, the thought of contracting a COVID-19 infection was utterly petrifying, especially as I knew I would not mount a vaccine response as a result of my treatment. To go from that feeling, to being able to access treatments, was like being handed a lifeline. As a young leukaemia patient, I had already spent much of my early 20s in isolation. Just as I was getting back to 'living' again, COVID-19 struck and I was back in an isolated state. Knowing that I could access a range of treatments if I was to contract the virus was a huge relief and has allowed me to continue with my education and employment, allowing me to meet many amazing people and fellow patients, too. However, reality feels quite bleak when I think about the potential decision to axe most of the treatments that I know so well. I feel like this is a big setback and it induces a high level of anxiety for me and uncertainty about the future. I worry that Paxlovid will not be as effective for me, and that I could end up back in hospital if I'm not careful. My point is quite simple. I don't want to go back into isolation – I want to live my life, just as everyone else who is not clinically vulnerable is now able to. Being fully vaccinated against COVID-19 is simply not enough for people like me - we need more support, and more treatment options. Our lives depend on it.

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	Miranda Scanlon (MTA Patient Expert)

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1	I thank the Committee for their work in developing this Draft Guidance. I'm aware that it has been a difficult task in the face of the uncertainty about much of the evidence in a continually evolving situation.
2	Whilst I am commenting from the point of view of kidney patients, I acknowledge that there may be patients with other conditions for whom my comments may be relevant, especially those with other solid organ transplants.
3	I would like to register my deep concern as a kidney patient myself that the only drug recommended for use in the community setting is nirmatrelvir-ritonavir. This is not suitable for individuals with severe renal impairment and has a significant number of drug interactions including with tacrolimus, widely used for immunosuppression in kidney transplant recipients. Unlike other users of immunosuppressants, organ transplant recipients are not able to suspend use of their immunosuppression due to risk of organ rejection. This recommendation therefore leaves the majority of kidney patients in Chronic Kidney Disease (CKD) Stages 4 and 5, on dialysis or with a transplant with no suitable treatment if they contract Covid. I note that the Committee are aware of these facts (3.11, page 19) and considered them in coming to their recommendations. We know that these patients are some of the most vulnerable in terms of hospitalisation and mortality (see later comments) and that many do not respond adequately to vaccines (also noted by the Committee 3.4, p12). The guidance as drafted appears to leave a large population of kidney patients unprotected from Covid which is not only surprising but unfair and unreasonable. This is not a sound and suitable basis for guidance in this group of patients.
4	The Committee did not consider that a sub-group analysis was necessary (3.3 page 11; 3.6 pages 13-14). However, given that the only recommended treatment nirmatrelvir-ritonavir is not suitable for many kidney patients, it could be considered as fair and reasonable for this group of patients to be considered separately to establish the effectiveness and cost-effectiveness of the treatments which are actually available to them. The current models of cost-effectiveness for the other treatments (sotrovimab, molnupirivir and remdesivir) include assumptions pooled across a wide range of high-risk individuals, many of whom are less at risk of serious consequences than kidney patients and for whom treatments may be less effective than in kidney patients. This creates bias in the models which has not been addressed and discriminates against kidney patients. In order to justify a sub-group analysis, I understand that it would need to be shown that kidney patients have differing risks to other high-risk groups considered in the economic model. The following comments address these points.

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5	I am concerned that an appropriate hospitalisation rate has not been used to calculate the cost-effectiveness of available treatments for kidney patients which has disadvantaged this group when considering Covid treatments for them. This comment includes evidence about hospitalisation rates which has not already been taken into account by the Committee and highlights that rates of hospitalisation and mortality are higher in kidney patients than in other high-risk groups as mentioned in my previous comment. The Committee note that the hospitalisation rate is a key driver for the cost-effectiveness models and that for sotrovimab a £37,143 QALY gain was calculated with mean efficacy and a 2.79% hospitalisation rate (this rate derived from a report from GSK from a McInnes group in the DISCOVER-NOW dataset) making it more cost-effective than remdesivir. [For kidney patients, the more cost-effective treatment of nirmatrelvir-ritonavir has to be disregarded; other treatments are not shown in the Draft Guidance due to confidentiality]. Several studies have shown that kidney patients have a much higher rate of hospitalisation and mortality than other high-risk groups. For example, OpenSAFELY (https://doi.org/10.1186/s12916-022-02422-0 showed hospitalisation rates (in 1000 person-years) for Stage 5 CKD, dialysis and transplant of 49.49, 70.73 and 76.08 respectively, compared to 16.45 for those more generally immunocompromised and 4.77 nationally. Kidney patients had rates of hospitalisation 10-16 fold greater than the general population and 3-6 greater than other immunosuppressed individuals. Mortality rates (in 1000 person-years) for Stage 5 CKD, dialysis and transplant were 17.81, 25.71 and 18.9 respectively, compared to 5.08 for those more generally immunocompromised and 1.07 nationally. Although these were rates during the Delta period, these differential risks have remained through successive waves, as shown in a subsequent paper by OpenSAFELY (http://dx.doi.org/10.1101/2022.07.30.22278161). In fact relative hazard risks increased as groups more likely to experience impaired vaccine effectiveness, including kidney patients, did not see the same benefit in COVID-19 mortality reduction as other individuals. **Evidence not previously taken into account by the Committee**, published by Bell et al https://doi.org/10.1093/ckj/sfac173, using Scottish Renal Registry data collected during the Omicron wave (17 December 2021 until 27 March 2022) in triple-vaccinated patients on kidney replacement therapy showed hospitalisation rates of 22% and a mortality rate of 4%. This hospitalisation rate of 22% in kidney dialysis and transplant patients during the Omicron wave contrasts sharply with the rate of 2.79% used in the calculation of cost effectiveness, and well exceeds the bounds of the sensitivity analyses conducted. Using hospitalisation rates applicable to a more widely defined high risk group is unfair to kidney patients who are at greater relative and absolute risk. Using this evidence to include a rate of this magnitude in the calculation would increase the cost-effectiveness of treatments available to kidney patients.
6	I am concerned that the Draft Guidance says ”it is highly uncertain whether sotrovimab is effective against the Omicron variant" and concluded that the WHO’S recommendations against the use of sotrovimab were reasonable. The Committee state that they considered evidence from the Francis Crick Institute but that they were unable to comment on the validity of in vitro data. Leading independent UK virologists are clear that

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	the work resulting in the WHO's recommendation to withdraw Sotrovimab are flawed, resulting from a misinterpretation of the data and is an artefact of a poorly constructed neutralisation assay. The Committee may wish to consult with experts on this point. Data published on 5 December 2022 by OpenSAFELY https://doi.org/10.1101/2022.12.02.22283049 was not available to Committee at the time they published their Draft Guidance. This looks at the real world effectiveness of Sotrovimab compared to Molnupirivir in kidney replacement therapy patients testing positive for Covid and treated with those drugs during the Omicron wave from 16 December 2021 to 1 August 2022. It includes data from both England and Scotland, linked to the renal registries in those countries. Of 1852 kidney patients in England treated with sotrovimab, 1.1% were hospitalised (molnupirivir 515, 3.3%). In Scotland of 723 kidney patients treated with sotrovimab, 1.7% were hospitalised (molnupirivir 270, 2.6%) . Although this study does not include comparative data for those who did not receive treatment, it does include Scottish data from the same source as and for an overlapping time period with the Bell et al analysis https://doi.org/10.1093/ckj/sfac173 where an overall hospitalisation rate was calculated for a similar group of patients (dialysis and transplant, identified by the Scottish Renal Registry) during the early part of the Omicron wave. Whilst not directly comparable, this analysis had a hospitalisation rate of 22% in the first three months of the Omicron wave which suggests a high level of effectiveness for both treatments in this population of kidney replacement therapy patients. This strengthens the evidence that in the real world, sotrovimab is effective in significantly reducing hospitalisation rates for kidney patients and that a high efficacy, high hospitalisation rate model for cost effectiveness would be appropriate. Reworking this calculation of ICER for the sub-group of kidney patients (and excluding nirmatrelvir-ritonavir) would be fair and reasonable and produce a sounder basis to form recommendations.
7	I am concerned that additional costs of Covid in kidney patients have not been adequately recognised. It is known that infections in kidney patients can lead to loss of kidney function and Covid is no exception. For patients with CKD Stage 5, this could reduce their kidney function to a level where they need dialysis which costs in the region of £30-35,000 annually. For transplant patients there is the potential for a serious Covid infection to cause a loss of graft, again necessitating dialysis treatment. As well as the financial cost of dialysis treatment, the mental health impact of starting dialysis, particularly after losing a kidney is devastating, and perhaps particularly if that kidney has been donated by a loved one.
8	I am concerned that the decision not to provide Covid treatments for the majority of kidney patients could affect some people with protected characteristics disproportionately. The 2019 Kidney Research UK report *Kidney Health Inequalities in the UK* stated that in the UK, people from Black and South Asian backgrounds are more likely to suffer from conditions that are risk factors for developing chronic kidney disease and are 3-5 times more likely to start dialysis than those from Caucasian backgrounds. In 2020, the *24th UK Renal Registry Report* shows that of those starting renal replacement therapy 13.9% were Asian (compared to around 7.5% in the general population) and 7.9% were Black (compared to around 3.3% in the population). We also know that Covid

Therapeutics for people with COVID-19 [ID4038]

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	affects those from Black and Asian disproportionately. Removing a treatment which has been available up till now will impact on those populations unfairly.
9	Whilst perhaps not directly in the remit of the MTA Committee, I am very concerned about the effect of these recommendations on the mental health of kidney patients. The Committee acknowledged that the risk of hospitalisation, death and other longer-term impacts of Covid can result in a severe physical and mental burden and I am grateful for that acknowledgement. However, since the publication of the Draft Guidance I have witnessed what is probably best described as a sense of bewilderment and disbelief that NICE could have issued guidance that so disregards kidney patients. This is a group of people who have been disproportionately affected by the Covid pandemic, who have had to radically alter their lives in ways that few others in the country have experienced. It is almost impossible to explain how it feels to literally not step outside your front door for three months, to fear that any human contact will kill you, to not experience any human touch for a year until vaccinations began. Some people with no antibodies to Covid vaccines are still living these lives. For those of us who have relaxed a little, we have known that the safety net of Covid treatments has been available to us. Many people are left unprotected and fearful. None of us know how effective our vaccinations have been, nor how sick we will get with Covid. Treatments have offered us a vital lifeline which has allowed some of us to leave our homes, to meet with friends and family, to begin to get some vague semblance of normality back in our lives. I hope that the Committee will give due regard to the circumstances and understand the loss of hope that the withdrawal of Covid treatments means for kidney patients.
10	I have a further concern that NICE technology appraisals are usually conducted for long term use and are unlikely to have a helpful role in the circumstances of a rapidly changing virus, where drugs are expensive and it can be hard to evaluate their ongoing effectiveness. We have already seen that the majority of the effectiveness evidence comes from trials carried out in waves of variants which are no longer relevant. Waiting for evidence of the current variants in circulation will likely be out of date by the time it is produced. Quite possibly this guidance will be out of date by the time it is published - new variants may arrive on the scene which are susceptible to treatments which are no longer recommended or which are resistance to ones which are. In my personal view, this appraisal seems premature in the current changing climate, and the prescribing landscape needs to be far more agile.
11	I am also concerned that the remit of the MTA was too large, covering treatment of Covid in both community settings and in hospital. My reflection is that, as a result, the Committee were put in a position where they did not have enough time to consider the complex evidence in detail. The two settings could have been appraised separately, with separate Committee meetings which would have given them the necessary time to consider the recommendations.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.

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NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

Draft Guidance comments form

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

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

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

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Comments on the DG received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

I am a chronic lymphocytic leukaemia patient at St James's hospital, Leeds. In 2019 I had chemotherapy and Rituximab. Result MRD negative. When I was well enough to enjoy my retirement, Covid struck. Since Jan 2020 to date I have been shielding along with my wife. We have had no social life, holidays or family events. I have only had 5 Covid vaccines because I had a bad reaction after the fourth. In May this year, 2022 I had a second round of treatment, Venetoclax and Rituximab. I will take Venetoclax until May 2024. I am immunosuppressed due to drugs and CLL and I am not expected to have developed antibodies from the vaccine. I have been hoping the Gov would see sense and follow the other 32 countries using Evusheld. The thought of risking Covid and then having antivirals kept me shielding as I know I am at very high risk of death. This report has left me and my family devastated. The only protection you are proposing for people like me is Paxlovid which is contraindicated to Venetoclax, which I don't want to interrupt. The vaccines have little effect on my depleted immune system as Rituximab affects it for 6 months at least after treatment and Venetoclax also affects my immune system.

With the above in mind, is it the intention of NICE and the British Government to demand the blood cancer, transplant patients and autoimmune patients, many of whom can't take Paxlovid because of other very expensive drugs they are taking, designed to keep them alive, should continue under house arrest with their close family? Or is the NICE and government advice to throw caution to the wind and chance infection, hospital admission and death? This I would suggest is not the actions of a civilised government.

You appear to have based your data on the fact that hospital admissions are lower. Can I suggest that if 500,000 immunosuppressed people are isolating themselves, expecting the government to protect them and come up with a prophylactic drug, the numbers will be lower than if they are forced out into the community without vaccine protection, prophylactic drugs or easily obtained suitable antivirals you might find admissions rise beyond measure. On the other hand after 3 years of isolation with no hope, it's easy to see what the mental health statistics will be. You then need to consider the cost of the treatments and drugs to keep these patients alive. The cost of ICU beds if they are admitted. Why pay the upfront costs if you have no intention of protecting them from Covid.

You need to employ the same urgency for this cohort of patients as Kate Bingham did for the vaccines for the general public. After all you weren't asked if they were cost effective and employing different criteria to the immunosuppressed is discrimination.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

For many people, these recommendations represent a serious reduction in the choice of treatments clinicians have at their disposal and for many it represents a complete withdrawal of useable drugs due to their conditions, medication and contraindicators. This draft proposal clearly underlines the need for more protection for vulnerable patients, such as prophylactics such as Evusheld and any others that may follow in its path. There must be reliable and speedy pathways for the provision of these drugs. Now is not to time to limit options for the most vulnerable.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

Please please please do not take away COVID 10 treatments as paxlovid IS NOT SUITABLE for kidney transplant patients. We are one of the highest groups of death from COVID-19. Paxlovid is not compatible with anti-rejection drugs needed to stay alive. We are already living half-lives as the vaccines DO NOT WORK for us. So we need the existing treatments to stay in place AND we need evusheld to live a half normal life. You CANNOT TAKE AWAY TREATMENTS for an already clinically extremely vulnerable group of people.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No. There is very good real-world data for sotrovimab that seems to have been discounted.

I lead a team that have delivered all COVID therapies to thousands of patients in a large CMDU.

Ergo, we have vast experience on both effect, patient experience, tolerability and

how to deliver therapies.

We have found the same as the real-world data that sotrovimab is well tolerated by the patient, clinically effective in variants (out admission audit is exceptional) and does not have multiple interactions with other POMs. This cannot be said for some of the recommended products.

We were disappointed at the recommendations in regard to sotrovimab from both patient and HCP perspective and would ask that this recommendation be re-examined.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

I am extremely concerned about this draft guidance because if it is finalised, it would leave people with kidney disease with no available therapeutic treatments for Covid-19 unless they become ill enough to need hospital admission. We think that it is disappointing, surprising and unfair. NICE's draft guidance recommends only one of the four community treatments (Paxlovid) and that drug is not suitable for people with late kidney disease, for example those with transplants or on dialysis. These individuals would therefore be left with no community treatment options should they get Covid-19, despite being one of the groups who remain at highest risk of severe illness and death and who have the least protection from their vaccines.

"The Covid-19 therapeutic treatments, particularly Sotrovimab, have been a very important safety net for people with kidney disease. Kidney Care UK strongly supports the UK Kidney Association call for its ongoing availability, particularly given the lack of other options. Furthermore there is presently no access to prophylactic treatments such as Evusheld.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	University College London Hospitals - Pharmacy
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The only antiviral or nMAb recommended in this draft is Paxlovid. Paxlovid is not recommended during pregnancy which means pregnant women have no access to treatment for earlier-stage disease.

- Section 1 – Recommendations, point 1.1

Our experience as a CMDU is that 36% of patients are contraindicated to Paxlovid; mostly due to drug-drug interactions (anticoagulants, transplant drugs) and CKD stage 4-5. NICE should advise whether a second-line treatment option (sotrovimab or remdesivir) can be considered for people who cannot receive Paxlovid.

- Section 1 – Recommendations, point 1.2

NHSE guidance additionally recommends tocilizumab for people with CRP >=75, which reflects RECOVERY inclusion criteria. If the CRP criteria is to be dropped, can the rationale be provided?

- Section 1 – Recommendations, point 1.6 “young people weighing at least 40 kg and adults who do not need supplemental oxygen and have an increased risk for progression to severe COVID-19.”

This draft guidance recommends Paxlovid (nirmatrelvir plus ritonavir) only at this place in therapy. Our experience as a CMDU is that 36% of patients are contraindicated to Paxlovid; mostly due to drug-drug interactions (anticoagulants, transplant drugs) and CKD stage 4-5. NICE should advise whether a second-line treatment option (sotrovimab or remdesivir) can be considered for people who cannot receive Paxlovid.

- Section 1 – Recommendations, point 1.6

No guidance is provided for patients who are immunosuppressed e.g. patients with a haematological malignancy. This cohort currently receive up to 10 days of remdesivir (irrespective of O2 requirement and time from initial infection). Please can specific advice be given for this cohort who are commonly seen in clinical practice.

- Section 1 – Recommendations, point 1.7

We advocate for retaining sotrovimab for clinically-extremely vulnerable (CEV) patients who cannot have Paxlovid, arguing that the in vitro data does support ongoing efficacy against BA.2 and that (in OPENSAFELY supplementary table) the benefit of sotrovimab over molnupiravir is maintained in BA2 era.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01938-9/fulltext

https://www.medrxiv.org/content/10.1101/2022.05.22.22275417v2

- Section 1 – Recommendations, point 1.9

Please be clearer whether the DHSC/NHSE eligibility criteria can be applied, or just the DHSC stock?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I've been shielding for 950 days, I have no response to the vaccines. I cannot take paxlovid as a treatment as I'm other meds contraindicated. I don't see the point in living any more. I had covid in March 2020 and I have never recovered. Are you sure this is cost effective. I've already had 9 months of counselling huge amounts of scans all of which will need to be repeated. This leaves no real options for those severely immunocompromised.
It's terrifying. I don't have a life. Especially if you take these other treatments away.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No it hasn't. One recent study has found to be effective against the BA.5 strain of the Omicron variant. Also, Sotrovimab does look to work effectively against current circulating strains.

Not enough real-world data has been taken into account.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It would be more cost effective to be able to treat the disease in the community and therefore avoiding the need for hospitalization. There is also the long-term effect of covid to individuals who are hospitalized: long-covid causing physical and long-term mental health issues. This is both a trauma to the individual and a long-term drain on costs.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No they most certainly are not. They do not consider the immunosuppressed community. The drugs that are being recommended are not suitable for a cohort of patients - i.e. organ transplant patients. Also, a drug that has been approved and already up and working in 32 other countries, Evusheld, has also been dismissed. The reality is that patients who have low protection from coronavirus vaccination, such as the immunocompromised and those with cancer, are critically dependent on getting access to timely coronavirus treatments following infection, in order to prevent more severe outcomes.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Royal College Obstetricians and Gynaecologists
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I think we need to be careful not to discriminate against pregnant women just because they were not specifically included in the original trial publications. In section 3.24 for example we would favour a stronger recommendation in favour of Tocolizumab – our own wording from V16 of the RCOG Guidance, published soon, will state that: For women meeting the criteria (hypoxic with systemic inflammation), the use of tocilizumab should be strongly considered. It is recommended that any decision to treat with anti-IL6 agents should be taken by an MDT, including obstetric and infection specialists, and given if the benefits outweigh the risks. Although data for the use of tocilizumab in pregnancy in this situation are limited, there is currently no evidence that tocilizumab is teratogenic or fetotoxic.

[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

I was very disappointed to discover these proposals to reduce the number of antivirals available. I was diagnosed with Acute Myeloid Leukaemia last year, I had six months of chemotherapy and then a bone marrow transplant. We have tried to achieve a balanced approach to our lives but now Winter is here outside activities are no longer possible. About a month ago my husband contracted Covid , ironically we believe when he received his Covid jab at our local surgery. I caught Covid from him and received Sotrovimab. My Covid was similar to a head cold and I have no long-term problems. For a very short while I felt a sense of freedom and although I would not be reckless I felt reassured I could do more. I visited a friend, went to a museum and returned to some volunteering roles with my local hospital and foodbank. I feel this now has to stop as any safety net will be removed. Obviously I cannot say that the antiviral made a difference in health terms but it did in terms of my outlook on life and my wellbeing. I can only ask that you do not carry out this proposal and that you continue to make the antivirals available to immunosuppressed people. Thank you

- Has all of the relevant evidence been taken into account?

Yes

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

No because real world evidence has proven that immunocompromised patients have responded well to the treatments which this proposal removes and have avoided hospitalisation as a result. Nirmatrelvir plus ritonavir (also called Paxlovid) cannot be used for people with severe kidney disease particularly those with kidney transplants and/or those on dialysis and will put us, already clinically extremely vulnerable patients, at even greater risk or committing to even stricter ongoing shielding.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No because real world evidence has demonstrated effectiveness against Omicron. Also the suggested use of only Paxlovid for a non-hospital setting will mean that patients with severe kidney disease would have to get hospitalised and be ill enough to need oxygen before they receive any treatment which would be a) much more expensive than administering a treatment before hospitalisation is necessary and b) discriminatory to all kidney disease patients.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not for the reasons stated above and also the two other treatments suggested for hospitalized patients who need supplemental oxygen are: tocilizumab with no current commercial arrangement in place with Roche and baricitinib which does not currently have marketing authorisation in the UK.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes there should be a treatment available to people with severe kidney disease that does not require that patient to be so ill that that they need hospitalisation. This will be fair and equitable to all (avoiding discriminating against those with severe kidney disease) and also cheaper as it will prevent the hospitalisation of many who have continued to shield despite all Covid restrictions being lifted. Without access to treatment outside of the hospital setting it impacts on the quality of life and mental health of all those affected by lack of non-hospitalised treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

I do not think the opinions of people living with immune mediated inflammatory diseases are fully considered here.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not think the broad cost effectiveness has been considered fully. One example is in our family my wife who used to teach small group sessions face to face has had to stop work. This loss of tax revenue is part of the wider cost.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I think that the reduction in choice of treatments in the context of immune modification drugs is discriminatory (e.g. where Paxlovid is contraindicated)

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I think that the reduction in choice of treatments in the context of immune modification drugs is discriminatory (e.g. where Paxlovid is contraindicated)

I am the husband of a person affected and this decision impacts on our whole family life.

I endorse the excellent feedback of Lupus UK.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I can only comment as someone who had a heart transplant 3.5 years ago and is severely immunosuppressed. Despite having shielded for the best part of 2 years I caught Covid a year ago - Delta variant. I was in HDU for 4 weeks and in hospital for 6 weeks. I had each and every drug available that you could give me to help me through. I had to come out on 100% oxygen 24 hrs a day.

When I caught Covid again I was given Sotrovimab and only had a couple of hours in hospital.

If you stop use of this treatment that leaves transplant patients without a safety net if they catch Covid and that is worrying thing. Do you go back to shielding again but indefinitely or you go out and try and live a life but risk your life every single day.

You have already spent a lot of money on giving me a heart transplant to keep me alive but are not prepared to continue to protect me

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

This recommendation is based on analysis which has not properly, thoroughly or accurately incorporated the costs of disabled people's (specifically kidney transplant patients') QALY loss after 28 days post-covid infection; specifically, the increased risk to graft loss through repeated damaging and unattenuated covid infections. This advice provides NO community treatment for kidney transplant recipients. This NICE analysis should also consider the cumulative effect of a) vaccination rates in immunosuppressed people b) lack of preventive treatments for immunocompromised people c) this proposed lack of community treatment for immunosuppressed people.

- Section 1 – Recommendations, point 1.1

Paxlovid is not indicated for kidney transplant recipients taking immunosuppression.
Therefore, there is no early stage covid treatment for kidney transplant recipients. This is discriminatory against the subset of kidney transplant recipient disabled people.
There is not to my knowledge any evidenced link between need for supplemental oxygen and net eGFR reduction. ie. I could be in no need for supplemental oxygen, but my kidney graft could still be seriously damaged. Covid is a vascular disease, not just respiratory; and to limit your criteria to a respiratory criteria is not representative of those patients for whom vascular damage is more adverse. (Including blood vessels and nephrons in the kidney).

In my particular case, covid infection- treated with Sotrovimab- still took 28 days to test negative and cold/flu symptoms to reduce; I am left with long covid symptoms and cardiovascular damage; and my grafted kidney function has been reduced from 40% to 30%, a 25% reduction. At ~10% eGFR, so 2 or so further unattenuated infections later, I will (if lucky) be back on dialysis treatment. I won't go into detail here about the emotional, familial, economic, mental health damage that transition - if preventable - will do. Out of 8 willing live donors, this transplant was the only matching one. I don't have a backup living kidney donor.

It is also highly cost ineffective to compare just those metrics included here. If you are removing covid treatment options for varied life threatening treatments, you must compare costs beyond 28 days. Comparing sotrovimab expense (£-2k) to the *cost benefit* of a functioning kidney graft [vs other renal replacement therapies] (+£24k) results in a *net benefit* to the NHS of £22k over 1 year (assuming 1 covid treatment). Not considering the value of avoiding loss of graft is a short-sighted and unrepresentative comparison. See NHSBT cost benefit info here:

chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://nhsbtmediaservices.blob.core.windows.net/organ-donation-assets/pdfs/Organ_Donation_Registry_Fact_Sheet_7_21337.pdf

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

I agreed to participate in this consultation process, on behalf of the British Infection Society (BIA). However, following NICE registration, I have not heard further from the BIA (and have not received any organisation code) so I am commenting individually.

I think that by (a) treating all McInnes defined High Risk (HR) individually as equally HR (without analysing SEVERELY immunocompromised individuals separately) AND (b) deprioritising efficacy evidence for the Direct Acting Antivirals (DAAs) against previous variants (because specific evidence of activity against current omicron variants is lacking), AND (c) relying on the crude outcomes of hospitalisation and mortality (because everything else is too difficult), the value of DAAs for severely immunocompromised patients (whose severe COVID illness probably differs in its pathology from the hyperinflamatory covid pneumonitis of immunocompetent patients) has been significantly under-estimated. For this group, I think it will be terrible if NICE guidance precludes (i) treating them pre-emptively (ie in early infection, whether in*/out of hosp) with remdesivir if they really can't have paxlovid, and (ii) treating them for established significant covid illness with paxlovid or remdesivir.
*I note that in the NICE analysis of in-patient treatments, pre-emptive Rx of early infection was not assessed!
Meanwhile, there is accumulating evidence about dual Rx for persistent symptomatic infection in severely immunocompromised people. It would be beyond the remit of NICE to recommend such dual Rx. However, in my view, the Consultation document, if published as it stands would result BOTH in increased numbers of severely immunocompromised patients with persistent covid illness AND put the entire burden of paying for their treatment onto tertiary referral centres with multidisciplinary teams and Drug & Therapeutics Committees.

- Has all of the relevant evidence been taken into account?

No. Pre-emptive Rx of early infection in hospitalised patients was not assessed. Perhaps that's because there isn't any evidence about this; if so that should at least be acknowledged.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Personally, I think the baby has been thrown out with the bathwater!

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No. I have concerns about the implications for severely immunocompromised patients who acquire SARS-CoV-2 infection despite having been immunised

- Section 1 – Recommendations, point 1.6

I think severely immunocompromised individuals should be excluded from this non-recommendation

- Section 3 – Committee discussion, point 3.4 ‘Other key risk groups’

Rituximab is indeed a particular extreme of severely immunocompromised because they will be unable to generate any antibody response to vaccine or natural infection. Just because it isn't easy to know which underlying conditions and which drugs really render patients at high risk for bad covid outcomes despite vaccination, doesn't mean this should just be ignored!

- Section 3 – Committee discussion, point 3.5 ‘Age as an independent risk factor’

Unequivocally, age per se was a RF for death in the first wave. But in the current context of very high rates of vaccination (and previous infection) in the elderly, it isn't (irrespective of the protected characteristic/ inequality issue.)

- Section 3 – Committee discussion, point 3.8 “The clinical experts considered that antivirals may have a limited role for people in hospital with COVID-19 because their mechanism of action focuses on blocking viral replication rather than controlling inflammation.”

This is absolutely the case for the vast majority of patients. But the pathology of persistently symptomatic infection in severely immunocompromised individuals is probably a bit different. In any case, to the extent that it is immunologically mediated (as opposed to directly virus mediated) the continuing antigenic drive will be contributing.

- Section 3 – Committee discussion, point 3.9 ‘AG’s indirect comparison approach’

Ultimately, the whole analysis depends on very crude outcomes, with considerable limitations, because it was too difficult to use anything else

- Section 3 – Committee discussion, point 3.10 ‘Generalisability to the omicron variant’

Because there was no evidence about efficacy of DAAs against current variants, the committee assumed that drug resistance might have arisen and therefore deprioritised evidence about efficacy of these drugs against prior variants. I think this was inappropriate given that - so far as I know -genotyping of omicron variants gives no indication of resistance mutations in the relevant viral genes

- Section 3 – Committee discussion, point 3.10 “It could not comment on the validity of the in vitro data and welcomes comments in response to consultation on this.”

WHO issued a rebuttal to the Crick assertion that neutralising monoclonal antibodies have only a reduced effect that may be mitigated by an increased dose: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02306-6/fulltext

- Section 3 – Committee discussion, point 3.11 ‘Relative treatment effects for the non-hospital setting’

There is increasing evidence of safety (of Paxlovid and Remdesivir) in circumstances that have precluded their use up til now

- Section 3 – Committee discussion, point 3.12 ‘Relative treatment effects for the hospital setting’

For the hospital setting analysis, there seems to have been no distinction between early infection (ie giving pre-emptive Rx to prevent severe illness) and established covid-illness. As a result, Paxlovid (and Remdesivir) for the former indication hasn't even been considered! Perhaps there is simply no evidence about this, but if so, that should at least be acknowledged!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	
Please can I confirm what options are available for patients with advanced renal impairment or those on haemodialysis. Literature has confirmed that they are one of the highest risk groups of having adverse outcomes from covid 19. This paper would suggest that Nirmatrelvir plus ritonavir is the only NICE recommended treatment option for patients not on supplemental oxygen however Paxlovid is not recommended or licenced in patients with advanced renal impairment. With NICE not recommending sotrovimab (the previous treatment option), this leaves a significant group of high-risk patients with limited or no NICE recommended treatment options.	

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

These decisions would mean that many in the most vulnerable groups would have no access at all to life-saving treatment, as many treatments and drugs used for transplant patients etc. interact negatively with the remaining therapeutics. Many variants of COVID-19 still remain active, and while there are uncertainties about effectiveness of treatments against new variants, these are absolutely not grounds on which to, for want of a better phrase, throw the baby out with the bathwater. Dosage and effectiveness need to be monitored, but this decision will leave many, quite honestly, to die without proper treatments available.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Absolutely not. The impact of not making more options for COVID-19 therapeutics widely available as we head into yet another unmitigated winter will cost far more, both financially and morally, than putting aside proper budget to treat COVID-19 as an ongoing, very prevalent, very dangerous issue.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Every decision made like this is an egregious breach of human rights for disabled people. The Clinically Extremely Vulnerable, the immunocompromised and the immunosuppressed have been fighting for the last three years to be heard, desperate to have our human rights to safe healthcare, work and education restored. In previous months, despite reassuring us at the beginning of the year that CEV and CV people would have access to adequate testing and treatment, the amount of people actually able to receive these regardless of the severity of their existing illnesses has been highly restrictive already. This further reduction to treatment options leaves many of us without hope, as the treatments that remain cannot be used by many due to drug interactions. We remain imprisoned in our homes, away from family and friends, with the clear message that our lives mean so much less than everyone else. Studies have already proven the impact antiviral treatments can have on a person's prognosis during and after a COVID-19 infection, ranging from milder acute symptoms to less likelihood of developing Long Covid and other post-COVID health issues, another fact being blatantly ignored. Those of us fighting for equal rights, equal treatment and access to safe

healthcare have been shut down repeatedly with arguments that come down to little more than the fact that our lives are apparently not worth the money. I remain deeply disgusted by the continued outlook.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No because real world evidence has proven that immunocompromised patients in other countries have responded well to Tixagevimab plus cilgavimab (also called Evusheld) against Omicron but this seems to be ignored. Also Nirmatrelvir plus ritonavir (also called Paxlovid) cannot be used for people who are kidney transplant patients & those on dialysis as it negates our immune suppressant medication and will put us at even greater risk or ongoing shielding.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No because real world evidence from other countries has demonstrated effectiveness against Omicron. Also the suggested use of only Paxlovid for a non - hospital setting will mean that patients with severe kidney disease would have to get hospitalised with supplemental oxygen before they receive any treatment which would be a) much more expensive than administering a treatment before hospitalisation is necessary and b) discriminatory.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not for the reasons stated above and also the two other treatments suggested for hospitalized patients who need supplemental oxygen are: tocilizumab with no current commercial arrangement with Roche and baricitinib which does not currently have marketing authorisation in the UK.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes there should be a treatment available to people with severe kidney disease that does not require that patient to be so ill that that they need hospitalisation. This will be fair and equitable to all (avoiding discriminating against those with severe kidney disease) and also cheaper as it will prevent the hospitalisation of many who have continued to shield despite all Covid restrictions being lifted. Without access to treatment outside of the hospital setting it impacts on the quality of life and mental health of all those affected by lack of non-hospitalised treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

Agree that highly effective Paxlovid should remain a treatment but more consideration should be given to the removal of Sotrovimab as a treatment option.

1. There should be a community COVID treatment option for those high-risk patients who cannot have Paxlovid in order help prevent hospitalisation or disease progression.
2. Some Immunosuppressed patients who may not have had a good vaccine response and cannot have Paxlovid will be left with no outpatient treatment option. Is this correct?
Paxlovid has some interactions and restrictions including pregnancy, and some liver conditions, age. e.g. What treatment would be prescribed for a pregnant immunosuppressed patient? Or a 15-year-old transplant patient?
3. Ethics. Is removing Sotrovimab ethical if there is a chance it might still be effective?
4. Cost effectiveness, is it more expensive to treat these patients if admitted to hospital?
5. Has the following evidence been looked at when considering efficacy of Sotrovimab/nmabs and should this be explored further before removing Sotrovimab?

The following reports published 06/10/2022 suggest Sotrovimab (and perhaps other treatments) may still be effective. Has this been considered?

I would like to draw attention to this paragraph published 06/10/2022

"... it would be reasonable to retain the use of sotrovimab, especially in extremely clinically vulnerable patients who test positive for COVID-19 and have few other options."

"In the case of sotrovimab, the combined evidence from our in-vitro neutralisation and real-world clinical efficacy data supports its continued use against circulating omicron variants, including BA.4 and BA.5."

"We found that sotrovimab neutralised BA.4, BA.5, and BA.2 to similar extents (EC50=1490 ng/mL; 95% CI 881–2517), suggesting that sotrovimab would remain effective against BA.5. Similarly, a second-generation BA.2 variant, BA.2.12.1, was neutralised to a greater extent than parental BA.2 (EC50=1211 ng/mL; 95% CI 844–1738), in line with preliminary pseudotyped lentivirus neutralisation data on a wider set of second-generation omicron sublineages, including BA.2.75.2.14 In light of this evidence, it would be reasonable to retain the use of sotrovimab, especially in extremely clinically vulnerable patients who test positive for COVID-19

and have few other options."

https://www.uclhospitals.brc.nihr.ac.uk/news/monoclonal-antibodies-remain-effective-against-latest-sars-cov-2-variants

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01938-9/fulltext

- Has all of the relevant evidence been taken into account?

I have attached a study in case it hasn't been considered
https://www.uclhospitals.brc.nihr.ac.uk/news/monoclonal-antibodies-remain-effective-against-latest-sars-cov-2-variants

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The consideration of immunosuppressed who cannot have Paxlovid

- Section 3 – Committee discussion, point 3.23 'Equality issues'

Effectiveness of Sotrovimab using the information below should be more definitively established first. The decision to remove Sotrovimab from those unable to have Paxlovid (if there is still any chance of being effective) may disproportionately impact society's most medically vulnerable and their families, it may affect their ability to work, attend school, university, medical settings, social events, see family.
This in turn could reduce life chances, increase mental ill-health, and overall not be cost effective or ethical. In some cases children may be lose a parent and placed into care. This decision must not be taken lightly and Effectiveness of Sotrovimab should be clearly established before completely removing.
Some immunosuppressed have only resumed social activities due to the availability of these treatments.

https://www.uclhospitals.brc.nihr.ac.uk/news/monoclonal-antibodies-remain-effective-against-latest-sars-cov-2-variants

- Section 3 – Committee discussion, point 3.9 'Generalisability to the Omicrom variant'

Has this evidence been considered published 06/10/2022

"We found that sotrovimab neutralised BA.4, BA.5, and BA.2 to similar extents (EC50=1490 ng/mL; 95% CI 881–2517), suggesting that sotrovimab would remain effective against BA.5. Similarly, a second-generation BA.2 variant, BA.2.12.1, was neutralised to a greater extent than parental BA.2 (EC50=1211 ng/mL; 95% CI 844–1738), in line with preliminary pseudotyped lentivirus neutralisation data on a wider set of second-generation omicron sublineages, including BA.2.75.2.14 In

light of this evidence, it would be reasonable to retain the use of sotrovimab, especially in extremely clinically vulnerable patients who test positive for COVID-19 and have few other options."

https://www.uclhospitals.brc.nihr.ac.uk/news/monoclonal-antibodies-remain-effective-against-latest-sars-cov-2-variants

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01938-9/fulltext

- Section 3 – Committee discussion, point 3.25 'Conclusion'

Is there a possibility of Sotrovimab to be offered privately if found to be effective and if NHS cost is an issue?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Need to include cost of the NHS making the treatments available within the NICE costing assessment. As the NHS could be doing something else instead of providing these treatments

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes, however NICE need to include cost of the NHS making the treatments available within the NICE costing assessment. As the NHS could be doing something else instead of providing these treatments

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No. This, for instance has not: https://doi.org/10.1002/ana.26536

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, since the practical clinical element is missing - see my other comments.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I am concerned about the lack of second line treatments in the pre-hospital setting for those in whom Paxlovid is contraindicated because of drug interactions of which there are loads!

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Paxlovid is contraindicated in pregnancy and sotrivumab / remdesivir can be currently given when clinically necessary. Non-availability in this setting can be considered a discrimination against pregnant women.

- Section 1 – Recommendations

Pre-hospital setting

As a consultant neurologist looking after patients with autoimmune neurological disorders like mutiple sclerosis, I am concerned that there is no alternative to Paxlovid in the pre-hospital setting. Paxlovid has many drug interactions with drugs many of these patients are on, and the current availability of sotrovimab has come to the rescue many times. I strongly advise a second line drug to be considered for this situation, and a monoclonal antibody is probably the least likely to interact.

Hospital setting

As a principal investigator of a study looking at the effect of dexamethasone and/or remdesivir on the incidence of neurological complications during covid (https://doi.org/10.1002/ana.26536), I cannot see that this has been modelled. Mortality is no longer really relevant in the changing covid landscape and more important is to model the consequences of untreated covid on the patient's long-

term health which can be costly. Neurological complications leave the patient with long-term disability and are amongst the most costly. Our study has shown that treatment with dexamethasone, remdesivir, or both in patients hospitalized with COVID-19 was associated with a lower frequency of neurological complications in an additive manner, such that the greatest benefit was observed in patients who received both drugs together.

Paxlovid is contraindicated in pregnancy and sotrivumab / remdesivir can be currently given when clinically necessary. Non-availability in this setting can be considered a discrimination against pregnant women.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

It isn't clear if/how non-randomised evidence relevant to this MTA which my colleagues and I have generated, comparing sotrovimab and molnupiravir, has been taken into account in this assessment. https://doi.org/10.1136/bmj-2022-071932 . This is of specific interest for this MTA, but also of wider relevance given NICE's stated aim to make better use of real-world evidence in decision making. The evidence in our BMJ paper suggests sotrovimab may retain a beneficial effect, even against recent variants. The committee's view seems to be that there is uncertainty about whether sotrovimab has any benefit, and to therefore recommend against its use. This would seem more compatible with stronger evidence that sotrovimab is in fact ineffective, rather than uncertainty.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The cost effectiveness estimate of >£90,000 per QALY gained for sotrovimab treatment is difficult to interpret. What is the estimate of effectiveness that contributes to this calculation and where does it come from? What would the calculation be assuming effectiveness in line with the estimates from our OpenSAFELY study? What are the uncertainties around this estimate? Does it vary by relevant risk group? What level of effectiveness would meet a more acceptable cost/QALY, and is there evidence to suggest such a level of effectiveness is unlikely to be met? The precise estimate quoted doesn't reflect the importance of uncertainty and potential variation.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations regarding sotrovimab seem unsound as they will prevent usage due to uncertainty about its effectiveness rather than confidence about a lack of effectiveness. In part this uncertainty is based on giving little weight to non-randomised evidence. The current evidence suggests to me that there indeed remains some uncertainty about the question of effectiveness of currently available

treatments, but that there is at least some evidence that sotrovimab remains effective. For this to be investigated further, it would require usage of sotrovimab to continue. Without data arising from such usage, we will not generate any further evidence about whether sotrovimab is effective or not and the uncertainty will remain. This potentially precludes useful treatment being available to patients who have limited treatment options.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	National Axial Spondyloarthritis Society
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

This seems to leave people like me, with blood cancer (Chronic Lymphocytic Leukaemia) with no treatment unless we get really ill. Nirmatrelvir/ritonavir (Paxlovid) has contraindications with my cancer treatment Venetoclax and several other drugs I take. There seems to be no treatment as a prophylactic against Covid or to treat it at an early stage. For people like me who are most at risk from becoming seriously ill with Covid, this is extremely distressing and condemns us to

remaining in isolation (coming up to three years now) or risk getting seriously ill before we can be treated. What happened to prevention being better than a cure?

- Has all of the relevant evidence been taken into account?

Has it been taken into account the mental anguish of the immunocompromised who have less and less options to live any sort of meaningful life?

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

What about the clinical cost of having to admit the immunocompromised to hospital when they become seriously ill with Covid. What about the economic cost of us not being able to return to work and return to society?

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I believe those with blood cancer, which counts as a disability, are being discriminated against. The rest of society is protected by vaccines. The vaccines do not work for many of us and there is no protection for us and less and less treatment available.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

It is very concerning that so many of these therapeutics, particularly in the non-hospital setting, are planned to be withdrawn. Vulnerable people in the UK do not have access to any prophylactic therapies and many have not mounted an adequate response to the vaccines, so they are relying on these treatments to keep them safe should they catch covid-19. Without access to these treatments, more vulnerable people will end up seriously ill and require hospital treatment, or develop long covid, making the treatments more cost-effective in the long-term.

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes - withdrawing so many of these treatments will discriminate against people on the grounds of race, disability and pregnancy.

- Section 1 – Recommendations, point 1.1

Nirmatrelvir plus ritonavir (Paxlovid) is contraindicated for many people. This will leave many vulnerable patients with NO access to community therapeutics.

- Section 1 – Recommendations, point 1.7

Sotrovimab has been a very effective community therapeutic for the treatment of covid-19 in the vulnerable cohort.

- Section 1 – Recommendations, point 1.8

Tixagevimab plus cilgavimab is being used successfully in many other countries as both a prophylactic and a treatment for covid-19. There is strong evidence of its efficacy from both the Provent and Tackle trials, as well as with real-life data.

- Section 3 – Committee discussion, point 3.25 ‘Addressing health inequalities’

Those more vulnerable to covid-19 have already faced a greater burden of health inequality during the pandemic, with most having to shield or greatly reduce contact with other people. Children in these families have missed more school than other children during the pandemic. Adults have had to adjust their work or even leave their jobs altogether. It is therefore unacceptable that they should have to face more health inequality from the withdrawal of these treatments.

- Section 3 – Committee discussion, point 3.2 ‘The rapidly evolving SARS-CoV-2 virus’

Hospitalisations have likely reduced due to the availability of these therapeutics. Withdrawing these treatments will likely result in an uptick in hospitalisation rates amongst the vulnerable cohort.

- Section 3 – Committee discussion, point 3.9 ‘Generalisability to the Omicron variant’

Real world evidence shows that these treatments have remained effective during the Omicron wave. New variants are emerging all the time and efficacy could either decline or improve for each one. Even when efficacy declines, it is far better for vulnerable patients to have some protection than to have none at all.

- Section 3 – Committee discussion, point 3.17 ‘Long COVID costs’

It is extremely concerning and misleading that the per person management cost of long covid has been based on the costs of treating people with chronic fatigue syndrome (ME/CFS). ME/CFS has been underfunded for decades and the true costs both to people's livelihoods and mental/physical health is vastly under-estimated.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

NHS staff here, a scientist, faced gross medical negligence by the hospital to my health requiring a kidney transplant. Kidney function stable but low. Five covid vaccines so far with zero antibodies detected. A sixth dose given but do not expect any antibodies. Kidney transplant recipients cannot take any of the suggested drugs or treatments suggested. You cannot give a patient drugs with contraindications and hope for the best. We need sotrovimab and Evusheld and in fact the government should be investing in pre prophylaxis treatments going forwards.

It is shocking that a British citizen and NHS staff that I have to read your recommendations. There is no humanity or care in some of these decisions. This is my current situation:

Medical negligence, still ongoing. I was in ICU twice.

Kidney transplant with immunosuppression.

Lower Kidney function.

6 doses of vaccines with 5 showing no antibodies.

NHS Oxford scientist forced out of my job, forced to be redeployed twice and stuck working from home.

Loss of my career as scientist, loss of salary and now expected to lose my life.

Facing discrimination and elimination from society.

The UK had the worst death record during covid. It is not something to be proud of. I am proud of the real scientists who developed the vaccines.

I am not sure what cost-effective means when it comes to people's lives here. How cost effective is it to have patients in ICU and then try and treat them? I am wondering if NICE need to speak to real patients and stop using this one size fits all type of analysis. You must know that when a patient is waiting for a kidney transplant, there is a lot of science involved and one of these is called tissue typing. This shows how unique we all are as individuals hence my own personal health including my genetics cannot be compared to someone else. I am

wondering if I am missing something here, and if there is a plan B or C in the pipeline? I do understand we are in the endemic stage of covid, but make no mistake there are over 500,000 of us and our families who have been forgotten and still suffering. We also want to get on with our lives and not always be talking about covid as well as living in fear. I was always taught in life that when it comes to health, prevention is better than cure. I still stand by this statement

Covid Apartheid

Covid came for all of us, like a thief in the night, unannounced. Where there was light and hope, doom and gloom soon followed. The world went silent, the world stopped. Locked in our homes, we were told to keep safe and stay in our bubbles. God forbid, if you disobeyed the track and trace detectives.
I was forced to shield, to hide, to stay silent, never to be seen or heard by society. Banished, forced into solitary confinement. I am a medical criminal guilty because I want to live my life. You must hide and stay safe, they said. They labelled me as "Clinically Extremely Vulnerable". Those who were "Normal" amongst us carried on. Humanity's true colours was exposed. Inequalities, discrimination, segregation all showing their ugly faces. I felt angry to be left behind, forgotten by the rest of society. How dare they segregated us. How dare you destroyed my life. This is not what humanity does to others. Survival of the fittest, they do say. My true identity taken away from me within a blink of an eye. Dark clouds descended upon me. I lost friends, relationships, and my identity. Those who stood by me, I salute you. Thrown out of my job, I was forced to work from home. No shopping, no travelling, no cinema, no socialising, no laughing, **No Life**. It was too unsafe to come out, too dangerous, too unpredictable. Ducking and diving, playing hide and seek with a deadly virus that no human could see, I tried to remain normal. I endured all the suffering, followed the science, cried till my eyes ran dry. I retreated into a deep dark hole, experienced the ups and downs of the pandemic. They said I was depressed, I felt judged, yet again. Do you want another tablet to help you, they said. I rolled my eyes and sighed. Time went by very slowly. Nearly three years, I have come out stronger. I am a warrior and navigate this world with my silent confidence and knowledge. I do not speak, but my actions will always speak volumes. We march forwards knowing that this too will not last forever.

By [redacted]

The true measure of any society can be found in how it treats its most vulnerable members, Mahatma Ghandi.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	
If you go ahead and remove sotromivab the IC like myself will have no treatment available if we can catch Covid. I have previously had this treatment in sept this year after catching Covid. The treatment was successful in the fact that I only had mild symptoms of Covid.	

Considering I shielded for 2 1/2 years with my wife and was very scared if I was to catch Covid, I had some reassurance of fighting it as sotromivab was available and I knew it was effective.
You are casting IC adrift again. This is once again shameful and a disgrace. Do you actually care for the 0.5m people and their families still shielding - what protection have we against Covid since the jabs are ineffective for us?
Please reconsider your proposals.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

By not recognising age as a risk factor you are discriminating against the elderly population that are dying from COVID in hospital most commonly. The vaccines were rolled out by arbitrary age cut offs. It is not clear why that is acceptable but allowing Paxlovid in the community for those over 65 is not (as in the US).

- Section 3 – Committee discussion, point 3.10 ‘Generalisability to the Omicron variant’

Feels that all the nmabs have been swept into the same basket when actually they all work at different sites and targets. Feels like the Crick Institute's thoughts have been ignored on Sotrovimab. No mention of RECOVERY research group just the 'Long COVID research group' current sotrovimab arm open that is collecting data right now with omicron inpatients in RECOVERY. Is early data available from this to see if big reason to suspect doesn't work against omicron?

- Section 3 – Committee discussion, point 3.25 ‘Conclusion’

Throughout the document there appears to be no comment re: nosocomial COVID which represents a significant proportion of cases. If patients are high risk and would get Paxlovid in the community they should be allowed it in hospital. This should be clear so patients aren't excluded from this treatment on the basis of social care needs (for example).

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

My partner has Cardiac Sarcoidosis. On Mexiletine. Cannot mount response to six vaccines. Cannot take Paxlovid. He has no protection against covid either prophelactic, or now he has extremely limited treatment options. You must protect the vulnerable - make Evusheld available to this group as prevention. You cannot leave them totally unprotected.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No because real world evidence has proven that immunocompromised patients have responded well to the treatments which this proposal removes and have avoided hospitalisation as a result. Nirmatrelvir plus ritonavir (also called Paxlovid) cannot be used for people with severe kidney disease particularly those with kidney transplants and/or those on dialysis and will put us, already clinically extremely vulnerable patients, at even greater risk or committing to even stricter ongoing shielding.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No because real world evidence has demonstrated effectiveness against Omicron. Also the suggested use of only Paxlovid for a non-hospital setting will mean that patients with severe kidney disease would have to get hospitalised and be ill enough to need oxygen before they receive any treatment which would be a) much more expensive than administering a treatment before hospitalisation is necessary and b) discriminatory to all kidney disease patients.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not for the reasons stated above and also the two other treatments suggested for hospitalized patients who need supplemental oxygen are: tocilizumab with no current commercial arrangement in place with Roche and baricitinib which does not currently have marketing authorisation in the UK.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes there should be a treatment available to people with severe kidney disease that does not require that patient to be so ill that that they need hospitalisation. This will be fair and equitable to all (avoiding discriminating against those with severe kidney disease) and also cheaper as it will prevent the hospitalisation of many who have continued to shield despite all Covid restrictions being lifted. Without access to treatment outside of the hospital setting it impacts on the quality of life and mental health of all those affected by lack of non-hospitalised treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

It would appear that this proposal offers no treatment for people with kidney disease or kidney transplant recipient until they are hospitalised. Surely this is discriminatory and counter-productive. There is a drug available that is safe for kidney patients to take, and if this prevents them from becoming seriously ill with COVID-19, then what is the rationale for not making it available to them at an early stage of their COVID-19 illness? Why does NICE deem it necessary to wait until that already vulnerable patient is seriously ill in hospital before offering them a suitable drug?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

No, I believe that some evidence regarding tixagevimab and Cilgavimab has not been considered there are more up to date studies that show these monoclonal antibodies do have some effect in a positive manner against Omicron (New England journal of medicine). Also the fact that over 120 Clinicians are backing its release, including Dr Lennard Lee and there are French clinicians that believe it is effective as well as Independent SAGE.

It is also still being used in thirty-two other countries including the USA and the FDA have actually supplied it free of charge to those who need it.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, not all factors have been taken into consideration, for example most Kidney solid organ transplant patients cannot take Paxlovid because of complications with their medication, i.e. Tacrolimus.
Also these are not normal times, so normal processes should not be used when dealing with immunosuppressed patients, for them Covid is NOT over!

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not in the case of immunosuppressed patients, real world scenarios have not been taken into account nor mental health issues caused by long term shielding.
Mental health reasons were a factor in the governments reasoning for removing restrictions, this guidance is based on cost effectiveness and clinical outcomes, not a holistic approach!
#forgotten500k REAL PEOPLE, real lives, this could be YOU!

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

There is definitely discrimination against immunosuppressed people in the way a general approach is being taken, THESE ARE NOT NORMAL TIMES, it is not normal that immunosuppressed people can't go to the Cinema, theatre, concerts, restaurants or mix in crowds of people and family, so do not use normal processes! The vaccines were given emergency clearance for use by the general population, but immunosuppressed people who have little or no protection from vaccines are being treated in the same way as the general population, this is not morally acceptable!

YES, Immunosuppressed people have been disabled by the refusal to release EVUSHELD for use on the NHS, therefore there is a definitive case of discrimination on health grounds and also cost if purchased privately, this is completely unacceptable and needs to be reconsidered as these people have the right to a life just like everybody else! THESE ARE NOT NORMAL TIMES. #forgotten500k

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

No because real world evidence has proven that immunocompromised patients have responded well to the treatments which this proposal removes and have avoided hospitalisation as a result. Nirmatrelvir plus ritonavir (also called Paxlovid) cannot be used for people with severe kidney disease particularly those with kidney transplants and/or those on dialysis and will put us, already clinically extremely vulnerable patients, at even greater risk or committing to even stricter ongoing shielding.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No because real world evidence has demonstrated effectiveness against Omicron. Also the suggested use of only Paxlovid for a non-hospital setting will mean that patients with severe kidney disease would have to get hospitalised and be ill enough to need oxygen before they receive any treatment which would be a) much more expensive than administering a treatment before hospitalisation is necessary and b) discriminatory to all kidney disease patients.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not for the reasons stated above and also the two other treatments suggested for hospitalized patients who need supplemental oxygen are: tocilizumab with no current commercial arrangement in place with Roche and baricitinib which does not currently have marketing authorisation in the UK.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes there should be a treatment available to people with severe kidney disease that does not require that patient to be so ill that that they need hospitalisation. This will be fair and equitable to all (avoiding discriminating against those with severe kidney disease) and also cheaper as it will prevent the hospitalisation of many who have continued to shield despite all Covid restrictions being lifted. Without access to treatment outside of the hospital setting it impacts on the quality of life and mental health of all those affected by lack of non-hospitalised treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

The guidance does not stratify or group those at risk of progression to severe disease. Certain groups with severe immunocompromise are likely to have much higher risk of progression than others, in which case for these groups the NNT and subsequent cost-effectiveness estimates for pre-emptive therapy are likely to be lower. The guidance should attempt to address this in view of maximal benefit,

fairness and equity.

The models of cost-effectiveness may not adequately account for reduction of PASC (long covid) after pre-emptive therapy. There is evidence for the reduction of PASC from Paxlovid pre-emptive therapy (1) - this benefit is in addition to the benefit given from avoiding hospitalisation. It is reasonable to extrapolate this effect to pre-emptive remdesevir as this has a similar efficacy in reducing progression to hospitalisation (as evidenced in the PINETREE study.) Could the guidance consider this?

The guidance does not make it clear how those with hospital onset infection (HOCI) will be considered. At the moment HOCI do not seem to be covered by the guidance for non-hospitalised patients, nor the guidance for hospitalised patients without oxygen requirement. This latter group appears to refer to treatment of admissions of acute COVID disease, rather than those who develop HOCI who may benefit from pre-emptive therapy. Clarity over guidance for HOCI is sought.

Evidence from OpenSafely [2] that sotrovimab has clinical effect as pre-emptive therapy in BA.2 era is mentioned but not considered. The result of this study causes me to question the weight given in the guidance to in vitro data on neutralisation and its extrapolation to clinical efficacy.

These points taken together suggest the guidance may not adequately consider the efficacy and benefits of treatments, especially for certain severely immunocompromised (at risk) groups.

[1] Yan Xie, Taeyoung Choi, Ziyad Al-Aly Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19. medRxiv 2022.11.03.22281783; doi: 10.1101/2022.11.03.22281783

[2] Zheng B et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform. BMJ. 2022 Nov 16;379:e071932. doi: 10.1136/bmj-2022-071932. PMID: 36384890

- Has all of the relevant evidence been taken into account?

Evidence from OPENSafely on the clinical effectiveness of sotrovimab as pre-emptive therapy on variants with reduced susceptibility (i.e BA.2) is not considered. [1]

[1] Zheng B et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform. BMJ. 2022 Nov 16;379:e071932. doi: 10.1136/bmj-2022-071932. PMID: 36384890

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Clinical efficacy of sotrovimab as pre-emptive therapy is based on in vitro data and does not take into account the clinical effectiveness seen in OPENSafely [1].

The consideration given in the cost-effectiveness models is given to reduction in PASC (long COVID) from pre-emptive therapy is not clear. Those not hospitalised

after pre-emptive therapy likely benefit from decreased risk of PASC [2] independent of the reduction in risk of hospitalisation.

[1] Zheng B et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform. BMJ. 2022 Nov 16;379:e071932. doi: 10.1136/bmj-2022-071932. PMID: 36384890

[2] Yan Xie, Taeyoung Choi, Ziyad Al-Aly Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19. medRxiv 2022.11.03.22281783; doi: 10.1101/2022.11.03.22281783

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No, there has been no consideration for those who are extremely at risk of severe illness as a result of COVID infection and who are not able to be treated in the community with Paxlovid because of various health conditions such as Organ transplants or those who take cointradictive medications such as Leflunomide. This would mean that they would only get treatment in hospital if they already have contracted an extremely severe, life threatening COVID infection risking death or serious damage to lungs etc. Also these people have not been given a suitable prophylactic medication such as Evusheld and vaccines are not effective for them.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

This does not take into account the full cost of having immunocompromised individuals in hospital with a severe COVID-19 infection and on oxygen as is likely to happen if these 5 medications are withdrawn without having alternative treatments available. As above, many cannot be treated with Paxlovid and are therefore likely to progress to more severe illness. It should be noted that the cost of a year's supply of the prophylactic treatment Evusheld, with a high % success rate of preventing hospitalisation, for one immunocompromised person is actually significantly LESS THAN the cost of treating this unprotected person in hospital if they become severe ill with COVID19.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Definitely NOT.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or

belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

As above, you have not considered the effect that this will have on the most vulnerable, most at risk of severe illness/death from contracting COVID19. So much so that the Government advised this group to SHIELD by isolating themselves whilst rates of COVID infections are high - they are higher now than when this measure was advised. Therefore this is gross discrimination on grounds of disability.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No because real world evidence has proven that immunocompromised patients have responded well to the treatments which this proposal removes and have avoided hospitalisation as a result. Nirmatrelvir plus ritonavir (also called Paxlovid) cannot be used for people with severe kidney disease particularly those with kidney transplants and/or those on dialysis and will put us, already clinically extremely vulnerable patients, at even greater risk or committing to even stricter ongoing shielding.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No because real world evidence has demonstrated effectiveness against Omicron. Also the suggested use of only Paxlovid for a non-hospital setting will mean that patients with severe kidney disease would have to get hospitalised and be ill enough to need oxygen before they receive any treatment which would be a) much more expensive than administering a treatment before hospitalisation is necessary and b) discriminatory to all kidney disease patients.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not for the reasons stated above and also the two other treatments suggested for hospitalized patients who need supplemental oxygen are: tocilizumab with no current commercial arrangement in place with Roche and baricitinib which does not currently have marketing authorisation in the UK.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes there should be a treatment available to people with severe kidney disease that does not require that patient to be so ill that that they need hospitalisation. This will be fair and equitable to all (avoiding discriminating against those with severe kidney disease) and also cheaper as it will prevent the hospitalisation of many who have continued to shield despite all Covid restrictions being lifted. Without access to treatment outside of the hospital setting it impacts on the quality of life and mental health of all those affected by lack of non-hospitalised treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Evusheld for the UK
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

If people have to continue to shield due to the withdrawal of some of the treatments as outlined in the question below. The long-term effects on the mental health of this group need to be taken into consideration. Many have already been shielding for 2.5 years already. This is not acceptable.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes. As if some of these treatments are withdrawn. It will leave some immunocompromised patients, particularly the kidney transplant patients without prophylaxis or Covid treatment options. This is very worrying for some of our group. This is not acceptable. This leave no option but for people to continue to shield as there is now no fall back.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

These recommendations represent a significant decrease in the treatment options open to immunocompromised patients (and their clinicians). For many such

patients, the medications they are on preclude the use of the recommended treatments, leaving them with no treatment options at all if they catch Covid. Until prophylactic treatments such as Evusheld are made available in the UK for immunocompromised individuals, NICE should keep as many treatments available as possible to these people, to avoid the accusation that they are intentionally enabling the premature and avoidable death of immunocompromised people to avoid affordable costs to the NHS

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Without a sufficient range of treatments, patients who cannot take Paxlovid may decide the risk of working is too great. And when such patients get covid but can't receive prompt treatment, the interaction of more severe illness and their existing conditions may prevent them returning to work long term/permanently. Has the cost of this been factored in? These people will be lost to the work force & contributing taxes.

Additionally, these people's existing chronic illness burden is likely to increase if their covid is not treated promptly - adding predictable additional costs for the NHS to look after these complex patients.

Providing, albeit expensive, covid treatments keep skilled workers in the workforce, bring in more tax income and reduce health costs associated with treating complex patients with covid and the exacerbations of their conditions/disability during and post-covid.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Disability Discrimination. How will the discrimination against people disabled by Lupus be addressed if Sotrovimab is withdrawn? Can Sotrovimab remain available for certain groups? Sotrovimab is the only treatment compatible with my medication and disease (and this is the case for many other Lupus patients). The decision to discontinue Sotrivimab is likely to make me more socially disabled or medically more disabled, or both. I am full time academic, mother of 3 with Lupus. My disease and my medications give me a higher risk of a) catching covid and b) developing severe covid. My 6 vaccinations have provided very little antibody protection due to immunosuppression. As a result, before Sotrovimab was available, I had to avoid close contact even with my own children for more than 18 months (as well as the wider public). When Sotrovimab became available I could live more normally at least at home around my family. When I caught covid (from

my son), prompt treatment with Sotrovimab was effective. I will not be able to take Paxlovid due to its toxic interaction with colchicine (taken for active Lupus Pericarditis). Without the safety net of Sotrovimab I will return to a life of fear in my own home around my family, a fear that affects them as much as me - disabling us all from reasonable participation in family life and society. In response, I am considering stopping my colchicine treatment (against medical advice) in order that I can live with the reassurance that I can take paxlovid if needed. So this decision to remove Sotrovimab creates a very unfair 'personal choice' between a) becoming more socially excluded even in my home and restricted to 'working from home' or b) allowing lupus pericarditis to progress untreated by colchicine. (NB It is not possible to simply pause Colchicine whilst taking paxlovid - it takes a considerable time to clear the body). People disabled by Lupus in this situation will be discriminated against if Sotrovimab is withdrawn.

- Section 1 – Recommendations, point 1.7 “have an increased risk for progression to severe COVID-19.”

Disability Discrimination. How will the discrimination against people disabled by Lupus be addressed if Sotrovimab is withdrawn? Can Sotrovimab remain available for certain groups? Sotrovimab is the only treatment compatible with my medication and disease (and this is the case for many other Lupus patients). The decision to discontinue Sotrivimab is likely to make me more socially disabled or medically more disabled, or both. I am full time academic, mother of 3 with Lupus. My disease (which has affected lungs and heart) and my medications give me a higher risk of a) catching covid and b) developing severe covid. My 6 vaccinations have provided very little antibody protection due to immunosuppression. Therefore, before Sotrovimab became available, I had to avoid close contact even with my own children for more than 18 months (as well as friends and colleagues). But when Sotrovimab became available I could live more normally at least at home around my family. When I caught covid (from my son), prompt treatment with Sotrovimab was effective. I will not be able to take Paxlovid due to its toxic interaction with colchicine (taken for active Lupus Pericarditis). Without the safety net of Sotrovimab I will return to a life of fear in my own home around my family, a fear that affects them as much as me - disabling us all from reasonable participation in family life and society. In response, I am considering stopping my colchicine treatment (against medical advice) in order that I can live with the reassurance that I can take paxlovid if needed. So this decision to remove Sotrovimab creates a very unfair 'personal choice' between a) becoming more socially excluded even in my home and ongoing restriction to 'working from home' or b) allowing lupus pericarditis to progress untreated by colchicine. (NB It is not possible to simply pause Colchicine whilst taking paxlovid - it takes a considerable time to clear the body). People disabled by Lupus in this situation will be discriminated against if Sotrovimab is withdrawn.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

The decision has been made by the government not to purchase Evusheld apparently due to lack of evidence of its effectiveness and longevity. NICE is now looking into Evusheld too and it seems that it is not going to be authorised in the UK for use due to lack of effectiveness. I'm not sure how this can be said when over 30 other countries are using it and supplying live evidence of its effectiveness.

It seems a tad contradictory to me that the Government wants me to keep having vaccines every 3 - 4 months which are ineffective in me and other immunosuppressed but it will not supply us with a drug which will help protect us more.

I am very sad and feel very let down that I will have to continue wearing heavy masks to protect me and my family and I will continue to lead restricted lives to help keep me alive.

The irony is if I catch Covid-19, I will cost the NHS a lot of money, with the treatment of me and then the inevitable medical retirement that would follow. More than Evusheld would cost.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

This proposal contains NO options for kidney transplant patients outside of hospital admission. This group has been shown to be at the highest risk from Covid of severe illness and death. They have the least protection from vaccines as they are on immunosuppressants. In addition, there is no prophylactic treatment. This is discriminatory.

- Has all of the relevant evidence been taken into account?

No. Have you considered how many at risk individuals are STILL shielding? They are protecting themselves, they don't catch Covid and so skew the numbers

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. You have completely excluded the highest risk group - kidney transplant patients

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No. You have completely excluded the highest risk group - kidney transplant patients

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any

group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes. The highest risk group, kidney transplant patients, are completely excluded from any community-based treatment. You only want to treat them when they become so sick they have to be admitted to hospital. This is blatant disability discrimination - they are not being treated equally to other at-risk groups.

- Section 1 – Recommendations, point 1.1

This is NOT suitable for kidney transplant recipients so what should they do? It's proven they are the highest risk group from Covid

- Section 1 – Recommendations, point 1.2

Again, not a community-based treatment for kidney transplant patients

- Section 3 – Committee discussion, point 3.25 'Conclusion'

What do Kidney Transplant patients do? Die? Shield for the rest of their lives? You must address this group given their risk.

- Section 5 – Evaluation committee members and NICE project team

Where are the medical experts in specific fields? Charities?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No: insufficient evidence has been provided and/or considered to show how the changes will protect those people with dysregulated immune systems (for example those with multiple neurological conditions e.g. multiple sclerosis and CIDP) who are vulnerable to Covid AND who cannot receive vaccinations on medical advice (for example due to adverse reactions from said dysregulated immune system) AND who cannot receive any of the Covid treatments not being suggested for withdrawal. As it stands, a straightforward one-off outpatient infusion of Sotrovimab may avoid such a person being hospitalised or worse (I know this, because this was me in August 2022): I tested positive for Covid and on day 1 developed neurological and inflammatory symptoms concerning to the CMDU doctor who assessed me over the phone that day. On day 2 I had Sotrovimab by outpatient infusion - this was the only treatment assessed as suitable for me. By day 3 I had turned a corner and was improving. I can see no consideration for what will be offered or available in such a circumstance if Sotrovimab is withdrawn. It's a costly drug, but I contribute far more in UK taxes each year than the cost of a dose of the drug, and costly hospitalisation was avoided.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No: my life may well have been saved in August 2022 by an infusion of Sotrovimab: certainly concerning and unusual day 1 neurological and inflammatory Covid symptoms where resolving by day 3, the infusion having been given in outpatients on day 2. It was the only treatment option assessed as suitable for me, and seems to have been extremely clinically effective in my case.

The cost of an infusion of the drug is high, but in my case, I contribute far more in taxes each year than the price of a dose of the drug. Costly hospitalisation was avoided in my case after Sotrovimab, despite the Professor of Neurology saying earlier in the pandemic that he would not expect me to have a good outcome when I encountered Covid. Removing this drug from those approved by NICE for clinically vulnerable people who on medical advice cannot protect themselves by being vaccinated leaves such people with zero options to keep themselves safe, aside from the remainder of their life in strict isolation, given the advice to others is to 'avoid those more vulnerable' (we're not bright green with flashing lights on our head - nobody can avoid us if we're leading any sort of life outside the home). This situation is unconscionable in a civilised society.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, for the reasons given above.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes: in my personal case, my dysregulated immune system means (a) I'm likely extremely clinically vulnerable to Covid; and (b) I cannot protect myself with Covid vaccines (I have CIDP alongside MS, and had a neurological ADR to one dose of AstraZeneca, then a year later when we tried a dose of Pfizer I developed lasting cardiac issues, so I have been advised by Prof Alex Richter that I cannot receive more vaccinations). My disability places me at a potentially fatal disadvantage in the circumstances, and the proposal to withdraw Sotrovimab is discriminatory, given there would appear to be no alternative routes by which I can protect myself, aside from spending the rest of my life apart from my husband, friends, family and society if this drug is withdrawn from approval for use in cases like mine.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

I struggle to understand the decisions behind this and how this has been costed appropriately. To take away early treatment so more immunocompromised end up in hospital requiring more intensive treatment is surely not cost effective. Total economic madness as well as unethical. It seems the 500k+ vulnerable are yet again being discriminated. Newer more dangerous variants can progress in the immunocompromised, therefore surely it makes no sense not to withdraw certain treatments. My husband is 48 and was hospitalised with Covid. He was given remdesivir and thinks that was the drug that saved him. Very sad on the decision on this. Shame on all involved.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

I am shocked that the proposal in the UK is that there will be no access to Evusheld, no Covid-19 specific infection control procedures in society including in health care settings and a reduction in the treatments for people with Covid-19. My husband has CLL and is on active treatment, which includes taking Venetoclax. I understand that Paxlovid is contraindicated by Venetoclax. To say we are terrified by this proposal is an understatement. This draft proposal needs reviewing urgently to consider how immunosuppressed individuals will be treated in the likely event that they catch Covid 19. They have the right to the same level of protection from the NHS as other individuals.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Not if you consider immunosuppressed people for whom Paxlovid is contraindicated.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No - they discriminate against people who are immunosuppressed and cannot take Paxlovid.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Discrimination against immunosuppressed individuals for whom Paxlovid is contraindicated.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

As a general comment, I find it quite remarkable that the list of stakeholders does not include the nationwide Covid Medicine Delivery Units or CMDUs. These have been running since December 2021, and the staff of the CMDUs have vast experience and expertise relating to prescribing sotrovimab, molnupiravir and paxlovid, and of the outcomes of these treatments. I heard about this consultation by chance, with very little notice, despite there being an email address book for all the CMDUs that NHS England can access (the single point of contact). i.e. the CMDUs could easily have been contacted for their input.

I wonder whether anyone involved in drafting these guidelines has had any first-hand experience of treating high risk patients who are unwell with covid-19 and at risk of severe illness. If so, I find it most unlikely that a guideline with only one treatment option would have been put together. What shall we do with the transplant patients and cancer patients on complex chemotherapies, those with advanced renal disease or liver cirrhosis, many of whom have no antibodies and are at very high risk of disease progression. There is NO evidence that sotrovimab doesn't work - it seems to be a cost analysis, but not based on the vast amounts of money already invested in these patients' complex health care. I sincerely hope that NICE reconsider this approach, and indeed apologise for not contacting CMDUs for their input. So many people have worked tirelessly 7 days a week on top of their normal jobs to try to help these patients, and the proposals in this document would lead to the reasonable conclusion - what is the point of continuing this service through the coming winter? What hope do these patients have come March? What shall we do when we assess a high-risk patient, establish that they are sick but ineligible for paxlovid, often with their first covid infection (and many many high-risk patients have not yet had covid)? Explain that unfortunately there are no treatments available, no current trials and that we can't predict their outcomes? But that we have some good treatments available if they end up in hospital? With also the unpredictable effects of long covid to factor in? I wonder whether it would be ethical to set up a trial of paxlovid vs no antiviral treatment in this high-risk group of patients. I think not. I really dread having those conversations with patients, especially as all the current data suggests that sotrovimab remains effective in real life. What we would really be saying is, yes, there is a treatment that could help, but the NHS can't afford it. It would cost you £3000-£4000 (drug plus infusion cost) if you went private. (But there won’t be that option).

I think my main concern with the proposed NICE advice is that the individual patient does not seem to be at the centre of the discussion. The fact that no subgroup analysis has been undertaken for patients who cannot be treated with

paxlovid lumps all the high-risk groups together, but that simply isn't fair as many of the very highest risk are ineligible for paxlovid. That, taken with the flimsy in vitro evidence around reduced sotrovimab binding efficacy (which cannot be extrapolated to loss of clinical effectiveness), as so eloquently debunked in the Francis Crick group document, makes it very hard to follow the scientific argument, but also the cost effectiveness argument, around withdrawing sotrovimab. We trust the experts to make wise decisions, but I have lost my faith in this process.

- Has all of the relevant evidence been taken into account?

No -
1) I do not believe that CMDUs who have nearly a year of experience of delivering these antivirals (which includes nMABS) have been consulted. Many of them hold plenty of evidence on the relative efficacy of paxlovid, monupiravir and sotrovimab, mostly during the omicron era. You could ask them whether they have data on 1) number of patients treated (this is in foundry) 2) what with (also in foundry) 3) admission rates within 28 days (due to covid vs not due to covid) (wildly inaccurate in foundry) and 4) covid vs non covid deaths by 28 days (inaccurate in foundry).
2) I did not find, though may have overlooked?, a reference to a very helpful paper on risk of severe covid-19 post vaccination from the Lancet: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01656-7/fulltext#seccestitle150
This helpfully shows how important a risk factor age is, as well as how much at risk the transplant patients are (who will be excluded from antiviral therapies if the proposed removal of sotrovimab from the therapeutic armoury goes ahead. It also shows admission rates amongst the whole population, vaccinated, from dec21 to feb 22, which were basically 9% (accepting that delta would also have been circulating then).
3) I don't think that specialty collected information on the risk of hospital admission with covid-19 in specific high-risk groups has been sought. For example, the ABN has data on patients with MS treated with b-cell therapies or S1P inhibitors, suggested around a 10% hospitalisation rate post vaccination. It seems highly likely that other specialty organisations have been monitoring the outcomes of their patients, which would provide further evidence that the 0.77% admission rate used from the Panoramic trial, and the basis of the cost effectiveness analysis, is way off the mark for the highest risk patients. It is really hard to imagine that this baseline is being used for people with transplants, receiving b-cell therapies, cancer chemotherapy etc. I believe the phrase is: 'this lacks face validity'.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not think so.
1) It was hard to understand what level of clinical efficacy was used in the sotrovimab calculations - the 710-page associated document was too much to the read in the couple of days available to me before the consultation closed. I believe it was 0.2, though I did not fully understand what that meant (but it seemed similar to paxlovid, which is appropraite). That sounds similar to the 80% mark - implying that 20% may still be admitted, but that is far and away above the data that we hold in CMDUs. Perhaps I misunderstand this, but the covid admission rates amongst the highest risk groups treated with paxlovid or sotrovimab are remarkably low 0.2-1.3%, in our own cohort of over 1000 patients. (That is not an insignificant overall number when you look back at the published trials.)

2) The baseline QALY is not representative of the highest risk population. Neither does the amount of money already spent on the care of e.g. transplant patients and complex cancer patients seem to have been taken into account. This is not a 'normal' patient group, and the argument that subgroups cannot be considered seems odd, considering that it is subgroups (up to 40%) that will be excluded from treatment given that they cannot receive paxlovid. I strongly feel that the cost-benefit analysis should consider two groups separately - those that can, on the whole, be treated with paxlovid and separately, those who are definitely excluded from paxlovid (eg. transplant patients, CKD4&5, liver cirrhosis, on anticoagulants or clopidogrel, certain cancer chemotherapies)

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Not in my opinion. The evidence provided against the use of sotrovimab is flimsy and not backed up by real world data or pharmacological theory.

If I have understood correctly, the high efficacy estimate for sotrovimab is 33,840 per QALY which only just misses the 30k cut-off. If the drug costs 2600ish and administration costs bring it up to about 3000, that implies that you would need to treat 10 of the highest risk patients to prevent a death? I think the real problem here is that you do not know what the admission and mortality rates are in the highest risk patients (post vaccine, in the omicron era, in a group of patients who were effectively excluded from trials), which renders this assessment invalid for the group of patients who are ineligible for paxlovid. Though, I suppose we will find out the answer pretty quickly if nMABs are no longer a treatment option from March.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I would say that age is a very important characteristic to consider given the ongoing elevated risk in older people. Similarly, discriminating against those with transplants, complex cancer chemotherapies (where there are unknown potential drug interactions) or on dialysis/CKD4/5 or those with liver disease by not offering them any treatment instead of paxlovid requires stronger justification that 'a concern' around in vitro neutralisation data. Pregnant patients have also been excluded, as paxlovid is not allowed in pregnancy.

- Section 1 – Recommendations, point 1.1

Paxlovid is well tolerated and effective. It is a great first line treatment but prescribing takes time and the interactions are complex. The current in and out of hospital guidelines make it difficult to prescribe paxlovid if you come in with covid (and eg. delirium, falls etc) but not with respiratory covid.

It is important that the new guidance allows equal access to treatment, whether at home, in hospital, or in other institutional establishments (including prisons). The factors to consider need to be whether they have covid, any symptoms attributable to covid, a high risk factor, and that they are not on oxygen. The place of care

should be irrelevant but is not mentioned here. This really matters and should be simple to correct.

- Section 1 – Recommendations, point 1.5

I agree with this. PANORAMIC has clearly shown lack of efficacy of molnupiravir. Noting that the very highest risk patients were not included here, we have never-the-less, seen lengthy admissions and several deaths in a small number of high-risk patients treated with molnupiravir in Dec, Jan and Feb 22 in our own CMDU and discontinued it on that basis. I would not be waiting until March to withdraw this medication as a treatment option.

- Section 1 – Recommendations, point 1.9

This is very confusing. so, we can use sotrovimab as we already bought it (because it works!) but we can't have any more? how will we explain that to patients? Or is the assumption that the expiry date will be passed by March, so we can use it up this winter. It doesn't seem to be an evidence-based recommendation, though is a welcome allowance for the winter.

- Section 1 – Recommendations, point 1.7

I strongly disagree with this recommendation and have commented on that extensively in other sections. As stated earlier, there is NO evidence that it does not work in real life (none that I have seen and none referenced here), and it is the only option for many patients. It is far more cost effective than remdesivir (which has quite a shaky evidence base).

- Section 1 – Recommendations, point 1.9 “But, it is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab (all neutralising monoclonal antibodies) are effective against the Omicron variant.”

It isn't reasonable to ask for nMABs to be re-trialled every time a new variant comes along. Look at the data from the Francis Crick institute. Plus 9 months of real-world evidence in the UK, and the open safely data. What matters is not how well it binds, but the EC50. If you give lots of antibodies that bind a little less well, you will be protected. That is the whole principle of the booster campaign, so why does it not apply to nMABs? The scientific argument is logical, we have nothing else to offer the very highest risk patients, there remains a small amount of uncertainty, why not err on the side of offering a treatment, with careful monitoring of outcomes (which CMDUs are well placed to do, if that was mandated when prescribing sotrovimab - though NHS digital ought to be able to solve the alignment of admissions and deaths within 28 days. I think this is complicated by many admissions being for sotrovimab treatment, massively skewing the data).

- Section 1 – Recommendations, point 1.9 “The cost-effectiveness estimates are highly dependent on hospitalisation and mortality rates. These rates are lower with the Omicron wave than earlier variants in the pandemic. Lower rates increase the cost-effectiveness estimates.”

Whilst omicron may be less severe, the hospitalisation rate of interest is in the high-risk population. We don't have good estimates of this, given that the antiviral trials basically took obese, diabetic, hypertensive unvaccinated patients as the

high-risk arm. That is not the same as the CMDU cohort, by a long way. There is some data from organisations such as the ABN showing a 10-15% admission rate amongst patients on ocrevus and fingolimod after vaccination, but prior to CMDU treatments. Have you explored these admission rates with specialist organisations, that often have their own registers? The PANORAMIC trial data is useful in terms of a background admission rate in less high-risk individuals, but it cannot reasonably be extrapolated to the highest risk patients.

- Section 1 – Recommendations, point 1.9 “cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources.”

how do you apply a general cost effectiveness model to people who have complex cancer care, transplants etc. 2-3 thousand pounds is a drop in the ocean of their care. The model should be based on the highest risk patients, not the general QALY. I did find it hard to understand these calculations in the associated document, which no doubt reflects my lack of familiarity with the NICE process, but I would again emphasise that these are a very particular group of patients - ones that doctors have generally put at risk with their treatments, and so are we not duty bound to offer the licensed effective alternative to paxovid if they cannot have that treatment? This is a pretty unique situation.

I imagine the risk that patients would not go ahead with a treatment for their underlying condition with associated disability etc if they knew they could not have paxlovid has not been factored in here. Or they may choose less potent, safer alternatives. I'm thinking mostly about IMIDs here - and we have known from decades of epidemiology before these high efficacy treatments became available of the considerable morbidity from these diseases. This is a real risk - and already dominates consent conversations in terms of elevated risk from covid-19. It will get very complicated if a paxlovid assessment is needed at that time too - because surely that is a very real risk that a reasonable patient would wish to know about before agreeing to start an immunotherapy? i.e. the fact that they are at high risk from covid but no treatments are available to them?

- Section 3 – Committee discussion, point 3.23 ‘Uncaptured benefits’ “enabling other NHS healthcare services to proceed (for example, routine operations and reducing impact on waiting lists)”

surely this is a pretty critical factor to consider. Please see other comments on very lengthy hospital admissions in those high-risk patients that were not treated

- Section 3 – Committee discussion, point 3.23 ‘Uncaptured benefits’ “because it mostly spreads when people are asymptomatic.”

this is an interesting comment given that this data was based on earlier variants of covid. With omicron, many people do not test positive until days 2-3 on lateral flow, implying that they are not infectious at an earlier stage. I am surprised that this is not considered in the document, given the emphasis on the changing face of covid into omicron everywhere else.

- Section 3 – Committee discussion, point 3.24 ‘Equality issues’ “These alternative treatments had substantially higher ICERs and were not considered a cost-effective use of NHS resources”

please see my earlier comments. You would effectively be discriminating against the up to 40% of highest risk patients that cannot take paxlovid by failing to offer sotrovimab. The evidence provided to support this decision is tenuous. Patient groups will no doubt speak vocally on this subject, especially as they were denied access to evushield too.

It is interesting that there is a rather unique situation here, in that sotrovimab has been available to treat patients for almost a year, and it will be well over a year by March. Thus NICE will be in an unusual position, not of suggesting that a drug cannot come into clinical practice due a lack of cost effectiveness, but that it will be removed from clinical practice, without the evidence (either of inefficacy or of lack of cost-effectiveness) to back that up. I suspect that that will be even less easy to understand by the patient groups at risk than finding a treatment to be unsuitable in the first instance.

- Section 3 – Committee discussion, point 3.24 ‘Equality issues’ “The committee noted the McInnes report did not include age as an independent risk factor.”

that is not entirely true. It is included in the advice on patients with HIV. And the Lancet paper I mentioned earlier clearly shows ongoing risk with age alone post vaccination. Surely it is unfair to exclude those who may benefit from paxlovid on the basis of age alone?

- Section 3 – Committee discussion, point 3.24 ‘Equality issues’ “Pregnancy and or maternity”

Paxlovid is absolutely contraindicated in pregnancy. So this is another group (albeit fortunately a small group of high risk patients) that are left out of the guidance, given there is no treatment recommended other than paxlovid. sotrovimab can be used in pregnancy, where the benefits outweigh the risks (and what risk is there - some covid antibodies crossing the placenta? pregnant, high-risk patients who are really unwell with covid have been happy to receive infusions, though the numbers are very small.)

- Section 3 – Committee discussion, point 3.25 ‘Addressing health inequalities’ “Even considering greater flexibility, the ICERs of alternative treatments were substantially higher than what is considered a cost-effective use of resources.”

that ('substantially higher') is clearly not true for sotrovimab as it only just failed to meet the 30K cut-off in the arguably not very representative modelling used so far. A small change in the range (eg. admission rates, QALY based on high-risk populations) would make it cost-effective

- Section 3 – Committee discussion, point 3.1 ‘Impact of COVID-19’ “patient experts explained that the increased risk of hospitalisation and death has led to changes in treatment, lifestyle and behaviour during the COVID-19 pandemic because of the need to shield. Patient organisations emphasised the need for treatments to prevent progression to severe COVID-19.”

this is so important. The majority of high-risk patients have still not had covid. In our CMDU, we have 20,000 high risk patients, and around 6000 have been

referred (some of them more than once, included in that figure). The most common phrase on the phone is 'I can't understand why I have it now after all this time'. They remain careful, curtailing their lifestyles, afraid to travel to see relatives or to make holiday plans, because of the risk of covid-19. Are we really going to leave them high and dry with only paxlovid as an option?

Please could you also consider whether patients would be able to access a course of paxlovid to take with them if they travel? They would still require CMDU assessment to take it (via their mobile phone). It would mean the chance to live a normal life (including seeing family and friends overseas) after 3 years, for many people.

- Section 3 – Committee discussion, point 3.2 ‘The rapidly-evolving SARS CoV-2 virus’ “People may stay longer in hospital, but this is to avoid potential onwards transmission to people with underlying conditions rather than because of complications.”

I am not sure that is entirely true and would question what this is based on. My analysis of 27 high risk patients (who flagged to CMDU through the pillar one addition to webview) since august 22 (i.e. with BA.5 most likely), who were admitted with covid, which was thought to be incidental and therefore not treated, found that between them they were admitted for 527 days (average 3 weeks), then 17% were readmitted for 13 days. This is a huge number of bed days. Our overall analysis of those not treated as inpatients was that 9% died and they spent an average of 18 days in hospital. This compares with 0.2 days per patient treated (n=1166) as an outpatient through CMDU, and 0.09% mortality if you exclude molnupiravir (which had a 2.1% mortality rate in 142 patients)

- Section 3 – Committee discussion, point 3.3 ‘Key definitions’ “These interim policies and McInnes report's high-risk definition would have influenced the risk level of people who enrolled in PANORAMIC”

That is correct. Few of the highest risk patients were recruited to Panoramic as they were receiving treatments through CMDUs. Therefore, the admission rates in Panoramic cannot be extrapolated to the highest risk groups.

- Section 3 – Committee discussion, point 3.3 ‘Key definitions’ “slightly different definitions of high risk”

basically, the trials did not include the CMDU's high risk patients. Mostly they were excluded. Risk was obesity, hypertension and diabetes in an unvaccinated population. This does not equate to the McInnes group definitions.

- Section 3 – Committee discussion, point 3.3 ‘Key definitions’ “But 1 patient expert thought that subgroups should be considered separately because considering a mixed group of risk definitions disadvantages the highest risk groups.”

This is a good point, especially when thinking about limiting treatment options to paxlovid - because certain patient groups (particularly the transplant patients who remain at such high risk) are automatically denied treatment then. As well as those with liver cirrhosis, which are already often a disadvantaged group. And the CKD4&5 patients, and those on complex cancer chemotherapies, and those on

anticoagulants or clopidogrel. splitting the analysis into those who generally could have paxlovid, and those who generally could not, would be highly informative.

- Section 3 – Committee discussion, point 3.4 ‘Other key risk groups’ “particularly if they are having rituximab.”

B cell therapies remain a significant risk factor overall. MS treatments include ocrelizumab and ofatumumab (b-cell therapies) rather than rituximab. S1P phosphate inhibitors such as Fingolimod, Siponimod and Ponesimod also are very risky, with data showing not only the B cell, but also the T cell, response is depleted here.

- Section 3 – Committee discussion, point 3.5 ‘Age as an independent risk factor’ “The committee noted that age is a protected characteristic and any recommendation including age would need to be assessed for impact on equity of treatment.”

This is an interesting argument, as surely the converse is true. By not recognising age as the very significant risk factor that it is, we continue to deny effective treatments (paxlovid) to the elderly. Age >50 is included in the McInnes group guidelines in relation to HIV, for example. That paragraph relating to HIV is particularly well worded, leaving scope to use clinical judgement. Panoramic may have something to add to that when the paxlovid arm reports. The Lancet article does a good job at trying to answer this question:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01656-7/fulltext#seccestitle150

Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales
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Open AccessPublished:October 15, 2022DOI:https://doi.org/10.1016/S0140-6736(22)01656-7

- Section 3 – Committee discussion, point 3.6 ‘High-risk definition conclusion’ “It assumes that people have general population survival, have a starting age of 56.6 years and the same hospitalisation rate as PANORAMIC.”

I would challenge these assumptions.
1) They are not like the general population. Far from it. Many are also quite a lot younger than in Panoramic. We treat many people in their 20s-50s. They have a great many years, potentially, ahead.
2) PANORAMIC was not able to include the highest risk patients, so whilst it may be as good as we can get, it will undoubtedly be an underestimate. I have commented more on this point elsewhere.

- Section 3 – Committee discussion, point 3.6 ‘High-risk definition conclusion’ “The committee considered that a single definition of high risk should be used because of the model limitations..”

I understand the rationale, but this does not take into account that some of the very highest risk patients are ineligible for paxlovid. So their risk and outcomes are diluted by lower risk patients. The highest risk patients seem to be those on b-cell therapies, transplant recipients and haematological malignancies. Closely followed by neurological disease, sickle disease and CKD5. Again, see the lancet paper.

- Section 3 – Committee discussion, point 3.6 ‘High-risk definition conclusion’ “Additional functionality would be required to make differential subgroup recommendations and this would not be practical or proportionate to the decision problem”

I think this misses the point of the high-risk individuals who won’t have any treatment options as they can't have paxlovid. That it likely to be anywhere from 10-40% of the highest risk cohorts treated by CMDUs. That isn't insignificant, and is surely proportionate to the decision problem?

- Section 3 – Committee discussion, point 3.8 ‘Treatments for severe COVID-19 in hospital’ “The clinical experts considered that antivirals may have a limited role for people in hospital with COVID-19 because their mechanism of action focuses on blocking viral replication rather than controlling inflammation.”

it is interesting that so much remdesevir is prescribed in hospitals in the treatment of covid pneumonia when there is clear evidence that it doesn't help. Whereas it might help prevent progression to covid pneumonia but is very hard to provide through CMDUs due to the need for 3 consecutive days of iv infusions. What a huge waste of money. Why wait until March to stop that? Especially as it seems remdesevir is in short supply, so there aren't stocks to use up.

- Section 3 – Committee discussion, point 3.10 ‘Generalisability to the Omicron variant’ “All experts and the committee considered it appropriate to consider how the clinical evidence would generalise to the Omicron variant and its subvariants.”

interesting, seeing as CMDUs have treated 10s of thousands of patients throughout omicron. In fact, I think nationally it is now hundreds of thousands. Vast numbers, and surely enough to take a view. You would think we would have some local data relating to outcomes?! I've offered our local data many times to NHS England, but I'm told this is all collected on Foundry. The trouble is that Foundry is wildly inaccurate, suggesting around a quarter of our NMAB treated patients have been admitted (presumably miscounting many day case admissions for sotrovimab infusions) whereas it is 1.5-3.1% (covid vs not covid) in our cohort. I do wonder why this guidance has not sought to obtain local data from CMDUs.

- Section 3 – Committee discussion, point 3.10 ‘Generalisability to the Omicron variant’ “The Francis Crick Institute's COVID surveillance unit suggest that neutralising monoclonal antibodies have only a reduced effect that may be mitigated by an increased dose.”

exactly. This is basic pharmacology. This entire document seems to be based on one single observation, around how tightly sotrovimab binds to various omicron variants in a dish. But that isn't the whole story. An antibody that binds, but less well, will still work if you give enough of it. that is the basis of booster campaigns. So, the data from the Francis Crick unit shows that the EC50 to neutralise various omicron variants remains many, many fold below the concentrations achieved with sotrovimab treatment. It is the EC50 that matters. Both the Francis Crick institute and the OPENSAFELY data provide strong theoretical and real world data that sotrovimab works. CMDUs have plenty more data. So why take this option away?

- Section 3 – Committee discussion, point 3.10 ‘Generalisability to the Omicron variant’ “The committee also could not comment on altering dosages outside of marketing authorisations because the risk–benefit profiles of increased doses have not been assessed by the Medicines and Healthcare Regulatory products Agency (MHRA)”

They don't need a higher dose. The Francis Crick institute argue that the EC50 is 64-fold below the mean peak serum concentration of sotrovimab for BA.2. This was similar with BA.4 and .5. So that is the theory, and opensafely and CMDU data provide the practice. The theory is also similar to the concept of booster vaccinations - more antibodies that don't necessarily bind as well can still work as well as fewer antibodies that are more specific. The only evidence against sotrovimab is the in vitro binding, and that is a very weak argument in the face of strong science in favour of its use. Plus, it is important to balance this argument with the fact that it is very safe and well tolerated, and a significant proportion of the highest risk patients cannot have paxlovid. It would be terrible to remove this treatment option without any evidence that it isn't working and leave these patients on their own against this much feared disease. The only remaining argument can be the cost, but it is not that much in comparison to the cost of a transplant, ongoing care, dialysis, cancer chemotherapies etc. I am really struggling to follow the logic here.

- Section 3 – Committee discussion, point 3.11 ‘Relative treatment effects for the non-hospital setting’ “It noted that PANORAMIC was also recruiting a nirmatrelvir plus ritonavir treatment arm.”

Indeed. The results of which will surely impact on these recommendations for paxlovid, one way or another.

- Section 3 – Committee discussion, point 3.11 ‘Relative treatment effects for the non-hospital setting’ “The committee would have preferred to see the results from PANORAMIC alone”

these are available in preprint

- Section 3 – Committee discussion, point 3.12 ‘Relative treatment effects for the hospital setting’ “The committee considered that remdesivir's mechanism of action may not fit the stated treatment aims. This is because antiviral activity would be expected to work more effectively before onset of the hyperinflammatory stage of the disease that is associated with hospitalisation. This could reduce the relative effect of treatment with respect to a disease with lower mortality.”

This is well put, and there seems little place for remdesevir once covid complications have set in. I suppose it may possibly be of benefit in immunocompromised patients who have not cleared the virus. I wonder if that has been taken into account - those patients who are still positive on lateral flow have a high viral load, and if that is still the case on presenting with covid pneumonia, remdesivir might do something helpful.

- Section 3 – Committee discussion, point 3.13 'Model structure and key drivers of cost-effectiveness' "hospitalised with or without COVID-19"

This is very binary and ignores the potentially protracted admissions in high-risk individuals with covid, which can often worsen their underlying risk condition illness too.

- Section 3 – Committee discussion, point 3.14 'Hospitalisation rates' "The rate is likely to vary substantially based on types of underlying conditions in the high-risk group, with potentially higher rates for severely immunocompromised people, such as transplant recipients and people having chemotherapy."

Exactly, and this is the very group that will be excluded from treatment by removing sotrovimab. They should be modelled separately.

- Section 3 – Committee discussion, point 3.14 'Hospitalisation rates' "G used a hospitalisation rate of 0.77% from PANORAMIC in its base case to generate the decision-making incremental cost-effectiveness ratios (ICERs)"

see previous. This will be a substantial underestimate for high-risk untreated individuals. Our own CMDU data on molnupiravir in the highest risk groups had an admission rate of 4.9% out of 142 patients treated from late December 21 to mid Feb 22. the very highest risk patients were given sotrovimab, but there weren't enough infusion slots for everyone to have it, so again, this is very much the low-risk end of the high risk groups and an underestimate. Our CMDU admission rate for sotrovimab treated patients is 3.1% including non-covid admission and 1.5% covid only out of 550 patients. For paxlovid, it is 0.6% (0.2% for covid) out of 474 patients. These are all treated admission rates. 0.77% is not a reasonable number in the context of admission rates if we do not treat the highest risk patients. Remember, up to 40% of them may not be eligible for paxlovid. I wonder how using admission rates of 5% and 10% for the very highest risk groups would affect the cost-benefit analysis for sotrovimab?

- Section 3 – Committee discussion, point 3.14 'Hospitalisation rates' "18.4% (study of people with primary and secondary immunodeficiency [Shields et al. 2022]"

This is likely much closer to the mark with the highest risk patients. Remarkably higher than the 0.77% mark

- Section 3 – Committee discussion, point 3.15 'Time to discharge' "for example, waiting for a negative COVID-19 test"

Isn't that relevant if the antiviral therapies speed up clearing of the virus (which PANORAMIC suggested might be the case)?

- Section 3 – Committee discussion, point 3.15 ‘Time to discharge’ “However, it considered these were difficult to disentangle from the evidence available.”

Perhaps CMDUs might have some more evidence?

- Section 3 – Committee discussion, point 3.16 ‘Utility value assumptions’ “The committee agreed with the AG's rationale and the long COVID utility decrement assumptions.”

This paragraph is very hard to understand if you have never come across utility decrements

- Section 3 – Committee discussion, point 3.17 ‘Long COVID costs’ “But, it also provided scenario analyses with increased average yearly costs (£2,500).”

How can these effects have minimal impact on the cost effectiveness, given sotrovimab treatment is about 2-3K? And if you were to get covid once every 2-3 years?

- Section 3 – Committee discussion, point 3.18 ‘Administration costs’ “However, future delivery may be in primary care, which would likely reduce these costs”

How exactly is primary care going to do it more cheaply? Also, those costs were based on spending before the arrival of paxlovid, which takes on average 45 mins to safely prescribe, unlike molnupiravir which was 5-10 mins.

- Section 3 – Committee discussion, point 3.18 ‘Administration costs’ “permanent staffing structure.”

I wonder where these staff are coming from? Most CMDUs are run on overtime, as there are no staff to employ (and also because they have not been commissioned for more than 6 months at a time)

- Section 3 – Committee discussion, point 3.20 ‘Non-hospital setting’ “mean efficacy”

What does this actually mean? You have been very clear about the hospitalisation rates used, but not the efficacy used. Was this different for nMABs vs Paxlovid? I can see some further description of this in the 700+ page accompanying document, but I didn't fully understand what 0.2 meant in that context. It wasn't quite as small a number as paxlovid - but the patient populations receiving the treatments are NOT the same. Transplant patients, for example, are only in the sotrovimab treatment group, and they remain the very highest risk group.

- Section 3 – Committee discussion, point 3.20 ‘Non-hospital setting’ “£37,143 per quality-adjusted life year (QALY) gained”

This headline figure is difficult to disentangle as:

1) What was the efficacy rate used?

2) The baseline population for QALY wasn't the same as the high-risk transplant and complex cancer patients, for example.

3) The 30K QALY doesn't generalise to this high risk population where vast sums of money have already been spent. Is there a number needed to treat with sotrovimab to prevent an admission or death that might inform this better? Within that highest risk population?

- Section 3 – Committee discussion, point 3.20 ‘Non-hospital setting’ “remdesivir (a) £96,485 per QALY gained (b) dominated (more expensive and less effective than standard care)”

This cost is huge. I imagine the same questions about what mean efficacy means apply, but even so, why is this currently the second line treatment for CMDUs at present? above molnupiravir and more particularly above sotrovimab, which we already bought? None of this makes sense. If we stopped using remdesevir now, we would have lots more money to spend on sotrovimab in March.

- Section 3 – Committee discussion, point 3.21 ‘Hospital setting without supplemental oxygen’ “The committee did not consider any interventions were likely to be a cost-effective use of NHS resources compared with standard care.”

Fair and well explained - but why wait until March.

- Section 3 – Committee discussion, point 3.25 ‘Conclusion’ “no technologies recommended”

Why isn't paxlovid in here? It is daft that you can have treatment for covid-19 if you stay at home, but not if you e.g. trip and fall as you feel unwell (not uncommon if you have covid) and end up in hospital (but not with covid pneumonitis). I commented on this at the start. Treatment should be based on evidence and need, not on the place of care. There also doesn't seem to be any consideration of hospital-onset covid-19 in this overview table. So, if you are in hospital with e.g., myasthenia on strong immunosuppression, just starting to improve and you get covid, tough luck? I suspect this is an oversight that could be quite easily corrected. At least, I hope that is the case.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

No because real world evidence has proven that immunocompromised patients have responded well to the treatments which this proposal removes and have avoided hospitalisation as a result. Nirmatrelvir plus ritonavir (also called Paxlovid) cannot be used for people with severe kidney disease particularly those with kidney transplants and/or those on dialysis and will put us, already clinically extremely vulnerable patients, at even greater risk or committing to even stricter ongoing shielding.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No because real world evidence has demonstrated effectiveness against Omicron. Also the suggested use of only Paxlovid for a non-hospital setting will mean that patients with severe kidney disease would have to get hospitalised and be ill enough to need oxygen before they receive any treatment which would be a) much more expensive than administering a treatment before hospitalisation is necessary and b) discriminatory to all kidney disease patients.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not for the reasons stated above and also the two other treatments suggested for hospitalized patients who need supplemental oxygen are: tocilizumab with no current commercial arrangement in place with Roche and baricitinib which does not currently have marketing authorisation in the UK.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes there should be a treatment available to people with severe kidney disease that does not require that patient to be so ill that that they need hospitalisation. This will be fair and equitable to all (avoiding discriminating against those with severe kidney disease) and also cheaper as it will prevent the hospitalisation of many who have continued to shield despite all Covid restrictions being lifted. Without access to treatment outside of the hospital setting it impacts on the quality of life and mental health of all those affected by lack of non-hospitalised treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	
This is appalling. How are CEV supposed to carry on "living" with no covid protection (vaccinated 6 times) and now the antivirals are being withdrawn? Where	

is our safety net? How can we continue safely? This is absolutely barbaric. You really need to procure evusheld asap!!!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Shionogi
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Not all relevant evidence has been considered, because the evidence considered was predominantly limited to published empiric evidence available at the outset of this evaluation. For all significant and relevant parameters, pragmatic approaches such as qualitative expert opinion, should be used to address any important evidence gaps. This additional evidence is particularly valid, given the changing nature of COVID (e.g., different variants, with varying levels of severity) and the need for non-naïve indirect comparisons of treatment effect of the interventions (e.g., due to trials conducted at different waves of COVID, with varying patient populations). Absence of available evidence should not be a satisfactory justification for uncertainty and new evidence should be generated (either by the AG or the committee, using qualitative exert opinion if necessary) for all significant and relevant parameters. At numerous points in this draft guidance, it appears that the committee had 'given up' and justified assumptions or conclusions based on lack of empiric evidence. The four examples below illustrate this point:

- Section 3.9 is illustrative, and critical since it explains the committee's conclusions regarding relative treatment effect. The AG highlighted significant limitations and uncertainty (e.g., due to the changing nature of COVID and heterogenous trial populations), and the section concludes by outlining that the committee considered it (i.e., the 'low-high' scenario analysis) to be '…an attempt to address some aspects of uncertainty in the absence of alternative methods to model the uncertainty.' There are opportunities for improvement here, by using alternative methods such as qualitative expert opinion, which could have improved from 'an attempt' to 'the best possible attempt'.

- Hospitalisation rate is another key driver, for which a more substantial use of expert opinion would have been warranted. Having observed the committee meeting, it was clear (at least from the public part 1) that the committee made some attempt to elicit expert views on this parameter, but this was largely unsuccessful, leading to the rather inconclusive position stated in section 3.14 of the draft guidance. Earlier and more comprehensive expert elicitation on this key parameter – which was identifiable as a critical model input at the scoping stage – by either the AG and or NICE and its committee could have significantly reduced this uncertainty.

- Section 3.13 states that the committee '…considered the model appropriate to capture the important outcomes, given the available evidence'. It is unclear whether this means the committee think that given all the evidence on COVID, all the important outcomes have been identified (and then modelled); or that the

committee think there is limited evidence to support estimating the magnitude of certain (important) outcomes, and therefore it is better not to model them. The second viewpoint would be unsatisfactory, given that new evidence (albeit based on subjective expert opinion) should always be available.

- Section 3.18 contains similar (unclear) wording explaining the committee's view on uncaptured benefits (see comment in response to Q2, below).

Overall, this draft guidance suggests that NICE (via their AG and committee) could have taken a more robust and practical approach to key areas of the evidence and analysis, which were predictably uncertain, given the evolving nature of COVID and the timing/nature of clinical trials for the interventions. Given that the aim of NICE (and other HTA agencies across the devolved nations) is to 'recycle' and build on the EEPRU model used for this MTA for future STAs, we suggest that steps should be taken to pro-actively address key areas where there are evidence limitations and uncertainty, to ensure that the model is better able to inform decision-making.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is not possible to judge whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, because key sections of this draft guidance are not detailed or clear enough. Specifically, the committee's conclusions regarding key parameters are not visible or precise enough for stakeholders to see whether/why their recommendations are reasonable. These examples from four sections of the guidance illustrate:

Section 3.13 states that the key driver of outputs in the non-hospital setting was the baseline rate of hospitalisation. Based on contents elsewhere in the guidance (and particularly in section 3.20), this seems to be incomplete as it omits relative treatment effect as the other key driver.
Section 3.18 is unclear:
- It is unclear why the committee think CMDU costs will be similar in the future, given the arguments and evidence to the contrary earlier in this section. The rationale outlined in final sentence ('This is because the resource required to deliver the treatments would be proportionately similar although in the format of a permanent staffing structure') would benefit from better explanation.
The contents of section 3.20 are not complete or clear enough to judge whether the summaries are reasonable interpretations. Specifically, the committee's 'most plausible' assumptions - and therefore the most likely ICERs - are unclear. For example:
- It is not sufficiently clear why the committee preferred the mean and low (and not the high) efficacy effects, by simply noting limitations in section 3.9; section 3.9 does indeed highlight limitations and uncertainty, but it does not indicate any systematic bias in the evidence that warrants discounting the high efficacy evidence.
- The committee should state their most plausible point-estimate assumption for hospitalisation rates and specify what is meant by 'in the middle of the range' (when explaining the ICERs for nirmatrelvir plus ritonavir); if this is 1.78% (the average of 0.77% and 2.79%), then the guidance should clearly state so.
- The committee should state their most plausible point-estimate assumption for relative treatment effects. As for hospitalisation rate, if this is midway between the mean and low effects, then the committee should clearly state so, and then the guidance should provide those quantitative estimates.

- The guidance should also be clearer regarding ICER ranges. For example, it is impossible to judge whether the committee's recommendation not to recommend molnupiravir is reasonable, unless the ICER ranges are more visible. Section 3.20 states that '…the range of ICERs was likely to be substantially above…' the threshold. It would be far more informative to clearly state what the ICER range is, and the proportion of that range which is above/below the threshold.

Section 3.23 states that for certain uncaptured benefits '…there is limited evidence to support them.' It is unclear whether this means that the committee think there is limited evidence to support their existence, or whether the committee think there is limited evidence to support estimates of their magnitude.
- If the former, NICE guidance should clearly explain why the committee think this, given that clinical experts appear to think the opposite. The committee note about community treatments not limiting transmission because it mostly spreads when people are asymptomatic is illogical; there can only be an absence of transmission impact if it entirely spreads when people are asymptomatic.
- If the latter, this is not an adequate justification to not consider them (see point above, in response to consultation Q1).
We suggest that the final guidance should be more precise and clearer, so that stakeholders can understand exactly what conclusions the committee made about key parameters, and therefore how their subsequent decisions were justified based on those conclusions.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations themselves are probably as sound as they can be, given the evidence that the committee considered. However, as described in response to Q1, NICE should have ensured that the evidence base considered by the committee was more complete. NICE's approach to a limited evidence base will need to adapt if the intention is to use a single EEPRU model for future STAs that will issue guidance covering the whole of the UK. In particular, a more robust methodology for indirect treatment comparisons – given limitations of the COVID NMA Initiative and PANORAMIC study framework - will be increasingly important. Also, the rationale for the recommendations is insufficiently clear, for the reasons described in response to Q2.
We hope that for future evaluations, NICE will take better measures to address key evidence limitations and uncertainty – and will document the committee's decision-making and rationale more clearly in its guidance.
Furthermore, we suggest that for future evaluations of COVID therapeutics, there are some key 'learnings' from this initial evaluation that need to be considered, to ensure that the evaluation scope/methodology, evidence base, and committee decision-making are satisfactory.
Specifically, NICE's focus will need to shift in accordance with the evolving nature of COVID:
- As highlighted in section 3.23, there are numerous outcomes that clinical experts consider to be relevant, and which need to be modelled to avoid underestimating the benefits of treatment.
- An additional component to be included in the future assessment is 'diversity' value; given the possibility of resistance (as highlighted in section 3.10), this should also be considered for COVID therapeutics (as for antibiotics), particularly if multiple agents within a given 'class' of therapeutics for COVID become available.
We hope that in future evaluations of COVID therapeutics, NICE makes adequate consideration of these broader factors.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No comments

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

My son is a transplant patient and is taking the drug Tacrolimus. Tacrolimus interacts with Paxlovid so it was recommended he have an alternate antibody treatment via infusion when he was ill with Covid in March. Judging by this recommendation it appears that if it is approved, no treatments will be available for transplant patients taking tacrolimus unless they are hospitalised with severe Covid. This seems ridiculous when other prophylactic treatments such as Evusheld are not available on the NHS. If this recommendation goes through, there would be no treatments available for my son unless he was severely ill or we could pay the very high private fees for Evusheld. How is this looking after vulnerable patients? Looking at your last paragraph it appears that this decision was made on cost. Why spend large sums of money on providing people with transplants and then not provide those people with the means of maintaining their health. Seems like a false economy to me.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

We believe so in regard to published literature.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
-

I believe they are reasonable interpretations of the published evidence but overlook small subgroups of high-risk patients, who may benefit from antivirals and in whom there will be little chance of available data due to small clinical numbers.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No as far as I am aware

- Section 1 – Recommendations, point 1.1 “have an increased risk for progression to severe COVID-19, as defined in the independent advisory group report commissioned by the Department of Health and Social Care.”

Our concern is that by considering the clinical efficacy or cost-effectiveness of remdesivir in the entire cohort of patients hospitalised with COVID-19, or those at high-risk of severe COVID-19 as defined by the McInnes report, a sub-group of ultra-high-risk patients are being overlooked and disadvantaged.

In particular we have local experience of a case series of significantly immunocompromised patients (post haematopoietic stem cell transplantation or receiving anti-CD20 medication for haematological malignancy) who, despite prior vaccination, have developed a phenotype of persistent COVID-19 with recurrent admissions with fevers and late progressive viral pneumonitis (requirement for oxygen), with an inability to achieve immunological control of SARS-CoV-2. Following formal MDT discussion of these patients, use of remdesivir, often in combination with nirmatrelvir plus ritonavir, has led to marked treatment responses in fever and respiratory symptoms, with some evidence of virological response or clearance. There is currently a lack of clear trial evidence on the optimal management of this cohort of patients, however available antiviral medication has a clear mechanistic rationale with local anecdotal experience on their successful use.

We are concerned that by listing remdesivir as not recommended for any indication, access to remdesivir may be limited for this group of ‘ultra-high-risk’ patients (which would represent a narrower subset of the McInnes definition). Please consider acknowledging within the guideline that a subset of patients with profound immunocompromise are being noted to develop a phenotype of persistent COVID-19 and that despite a current absence of evidence for benefit, there may be a role for antiviral medication, including remdesivir in these patients following specialist MDT discussion.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	
• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	

I am writing this response in a personal capacity as the Clinical Lead of the South-West London CMDU, based at St George's University Hospitals Foundation NHS Trust.

I would like to acknowledge that this technology appraisal is complex with many uncertainties and difficulties in obtaining precise estimates of treatment effectiveness and key outcomes due to a lack of data on these treatments with the current population that we are prescribing to and that the draft guidance covers. I commend the committee on this hard work so far.

Early treatment for Covid-19 in the UK is limited to those defined as being in the 'highest risk groups' by the McInnes report, therefore the recommendations made by NICE only apply to early treatment in these groups. The reliance on the PINETREE study for effectiveness estimates of early treatment of remdesivir in 'high risk' patients is misleading. In the UK, the highest risk groups have been defined by the McInnes report to be broadly those receiving chemotherapeutic agents, those receiving other immunosuppressive drugs, those with severe renal or liver failure, those with inherent immunodeficiencies and those with advanced HIV immunosuppression. The PINETREE study recruited patients with an identified 'risk factor' for severe Covid-19 pneumonitis but only a very small proportion had current cancer (5.3%) or immunosuppression (4.1%). Even in this relatively low risk population. PINETREE found an 87% risk reduction in the hospital admission/death composite endpoint. In the draft guidance, the committee notes that this large risk reduction was driven by reduced hospitalisation rates as there were no deaths in either arm. However, the committee fails to comment on the size of the study, which was clearly not powered to detect this less frequent outcome. The PINETREE trial authors provide a power calculation and aimed to recruit 1264 patients into the study, however the study recruitment was stopped early and the number of patients enrolled was approximately half the projected total needed for adequate power for the composite outcome. Therefore, the committee should not include these results in their evidence synthesis for treatment benefit estimates.

The low estimate used for hospitalisation rate also seems flawed - the OPENSAFELY paper looked at people treated with sotrovimab and molnupiravir and found hospitalisation/death rates of 1.45% and 2.05% respectively. Given that we now know that molnupiravir does not show a survival or hospitalisation benefit from the PANORAMIC results, surely the upper hospitalisation rate for the molnupiravir group should be taken as a proxy for the baseline hospitalisation rate in this cost effectiveness analysis.

In terms of calculating costs, it is not clear whether the committee have taken into consideration the cost of delivering Paxlovid to intended recipients. Whilst some patients are able to send someone to pick up Paxlovid, because of the time pressure of needing to initiate treatment within 5 days, CMDUs are currently having to use courier services to deliver oral antivirals where this is not possible. This is a significant drug-associated administrative cost and will still be incurred even if dispensing moves to the community.

It is my opinion that there are sufficient uncertainties in the estimates of clinical effectiveness, costs incurred and baseline hospitalisation rates that the current recommendations for early treatment may need to be revised.
It would also be much more transparent if the cost effectiveness calculations were

more explicitly laid out, with upper and lower bounds of confidence in all the estimates used in the models.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

As the committee is aware, many people with symptomatic early Covid-19 in the highest risk groups are not eligible for Paxlovid due to drug-drug interactions, low creatinine clearance or decompensated liver disease. The committee does not seem to have considered the impact on equality of only recommending paxlovid for early treatment.

I have taken a data-driven approach to provide you with evidence of how this draft recommendation will restrict access to early treatment disproportionately in groups of patients with protected characteristics.

We analysed data of 5664 patients that were triaged by our service between 15th March and 5th December 2022. Of these 5664 patients, 1674 were deemed eligible for early treatment. Over half (58%) of eligible patients were eligible for Paxlovid, 19% were prescribed remdesivir, 16% were prescribed Sotrovimab, 3% were prescribed molnupiravir, and 4% declined treatment.

When examining ethnicity (ethnicity available in 898 patients): people of Black/Black British or Mixed origin were less likely to be eligible for Paxlovid (5.3% of people eligible for Paxlovid were Black or Black British, compared with 6.6% of those not eligible for Paxlovid).

The median age also differed: 56 years for those eligible for Paxlovid (IQR 43-66); 59 for sotrovimab (IQR 46-71); 60 for remdesivir (IQR 48 to 70), and 68 for molnupiravir (IQR 54 to 80).

Men referred to our service were less likely to be eligible for Paxlovid: only 52.9% of men compared with 61.4% of women eligible for treatment could be prescribed Paxlovid.

When looking at Index of Multiple Deprivation, there was no difference in the proportion of people in IMD deciles 1&2 between those eligible for Paxlovid and those not eligible (this was low at 3.6% of our treated patients).

Our data from South-West London shows that older patients (who are more likely to have polypharmacy and therefore drug-drug interactions) are less likely to be eligible for Paxlovid; that Black or Black British people are less likely to be eligible for Paxlovid, and that men are less likely to be eligible for Paxlovid.

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It would also be much more transparent if the cost effectiveness calculations were more explicitly laid out, with upper and lower bounds of confidence in all the estimates used in the models.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any

group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I am writing this response in a personal capacity as the Clinical Lead of the South-West London CMDU, based at St George's University Hospitals Foundation NHS Trust.

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Our data from South-West London shows that older patients (who are more likely to have polypharmacy and therefore drug-drug interactions) are less likely to be eligible for Paxlovid; that Black or Black British people are less likely to be eligible for Paxlovid, and that men are less likely to be eligible for Paxlovid. This may be evidence of discrimination on the grounds of protected characteristics.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	BNSSG ICB
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

This is difficult to comment on as new evidence emerging all the time therefore how often will this be reviewed in light of new emerging evidence. How reactive will NICE be in change in evidence base.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Some of costings are not disclosed therefore would need to see further cost modelling to comment. What will be allocated to local systems to support this as likely to cause a cost pressure. Based on current known/disclosed acquisition costs.

As above evidence emerging all the time so reactiveness to update and incorporate this in timely manner.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Only one treatment option paxlovid and nothing else in CMDU service (non-hospitalised patients).

Regardless of what is published will the NICE document be updated as evidence is changing as further evidence emerges. For example updated clinical commissioning document changes 28/11/22.

As offer is oral Paxlovid (non-hospitalised) which limits the offer for a number of the highest risk patient groups including those with solid organ transplants, renal impairment. As well as this drug interactions being an issue.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Pregnant women in any category are not left with any options as paxlovid not suitable for pregnant females. How would we treat pregnant women?

- Section 1 – Recommendations, point 1.1

Agree. We are giving comments from a Treatments for Highest Risk Non-Hospitalised Patients (Adults and Children) with COVID-19 perspective as we run BNSSG CMDU service

- Section 1 – Recommendations, point 1.9 “molnupiravir, remdesivir”

could these options be utilised for patients who can’t have paxlovid? How would these patients be treated without another treatment choice.

- Section 1 – Recommendations, point 1.3 “marketing authorisation”

We will review detail post marketing authorization

- Section 1 – Recommendations, point 1.5

Would potentially consider this as 3rd line option in line with interim clinical commissioning policy 28/11/22 for those who are unable to have paxlovid? Limited option of just paxlovid isn’t suitable for all patients.

Remdesivir did appear to reduce hospital mortality significantly in the high risk cohort in earlier waves.

Accept that no apparent impact on mortality and was pre-omicron and there are concerns that this will be a much smaller benefit now, but rather than no alternative for the large number of people who cannot have paxlovid within the transplant cohort would it not be better to trial/audit it rather than withdraw it?

- Section 1 – Recommendations, point 1.9

clinicians may need to consider an alternative appropriate option for people with COVID-19 that are unable to have paxlovid.

- Section 1 – Recommendations, point 1.6

Could remdesivir be used as an option for example 2nd line option with interim clinical commissioning policy 28/11/22 for those who are unable to have paxlovid? Limited option of just paxlovid isn’t suitable for all patients.

- Section 1 – Recommendations, point 1.7

Agree in line with cost implications and WHO guidance

- Section 1 – Recommendations, point 1.8

We never used this option

- Section 3 – Committee discussion, point 3.25 ‘Conclusion’

Only offer is oral Paxlovid which limits the offer for a number of the highest risk patient groups including those with solid organ transplants, renal impairment. As well as this drug interactions being an issue. The new renal dose recommendations are not based on high quality recommendations, pregnant women in any category are not left with any options.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

I agree that Paxlovid should remain available as an anti-viral treatment option. However, more consideration should be taken to the removal of other anti-virals such as Sotrovimab and Molnupiravir. Sotrovimab and Molnupiravir have far fewer drug interactions than Paxlovid. No consideration seems to be given to the groups of patients who will be left with no outpatient treatments at all (under 18s, transplant patients taking Tacrolimus/Cyclosporin, anyone who takes a drug contraindicated with Paxlovid).

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

There are currently no anti-viral treatments available for anyone unable to have Paxlovid. This is unacceptable. If one such patient (i.e. transplant patient) were to develop serious disease due to Covid, isn't it more expensive to treat these patients if admitted to hospital for weeks, at £400 a night? Compared to the approx. £2000 cost of Sotrovimab treatment as an outpatient.

Even if Sotrovimab is considered as "may not be effective against Omicron variants", I feel strongly that if anti-virals such as Sotrovimab are the only treatments some patients can have, such treatments should not be removed. No treatment is ever absolute. Has all evidence been considered before removing Sotrovimab as a treatment?

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Access to Sotrovimab will provide an outpatient treatment option to those patients who are at high risk and unable to take Paxlovid. Molnupiravir, taken as a tablet, will allow patients to be treated at home. This will relieve pressure on the NHS, as many of those patients will be less likely to develop serious disease requiring inpatient treatment, at a time when the NHS is under severe strain.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Efficiacy of anti-virals such as Sotrovimab and Molnupiravir should be looked at more closely if they are the only treatment options available for some patients on

the grounds of age (under 18s cannot have Paxlovid); pregnancy and disability; who take medications contra-indicated with Paxlovid. Is it ethical to leave such patients with no anti-viral treatment options at all, on the basis of "effectiveness/cost to the NHS"?

As an example. A liver transplant patient under 18 would have had transplant surgery costing the NHS £50,000+. Is it then ethical to deny that patient any outpatient treatment, based on the fact the only treatment available to them (Sotrovimab), at £2000 is not considered cost effective to the NHS. If they were then to develop serious disease as a result due to Covid, would it not be more expensive to provide that patient with extensive inpatient treatment, increasing pressure on the NHS as a result, and requiring their parents to take time off work to care for them if they develop serious disease or long Covid.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

There will be no provision for transplant recipients to receive any treatment in the community to avoid serious illness. Paxolovid cannot be taken with the main immunosuppressant Tacrolimus.

I note that the other 2 treatments recommended in the draft guidance tocilizumab and baricitinab are subject to commercial and authorisation measures so not even approved.

Current experience is that patients can become very unwell being monitored by phone before hospital admission for monoclonal antibodies. They are unwell for longer.

Evidence from peers shows their medical condition worsens, employment and family etc are affected. Surely prevention is better.

Hospital treatment for the above is a postcode lottery. Hospital capacity is getting worse. There is a five-day window for these kinds of treatments currently. Off the list for treatment if you do not get it in time or symptoms get worse later

Double standards are being applied to us. Vaccines could be rolled out in the hope of being effective against future variants i.e. Omicron in Spring 2022 but our hope for at least some protection in March Evushield was rejected because of Omicron. Patients in 32 other countries had months of freedom. A percentage is safer than nothing.

Many of us have had to pay privately for antibody tests to assess our risk of severe Covid illness. My results and many others after 6 vaccinations is no protection.

Our lives are restricted not much change since lockdowns expected to ‘live’ with Covid without the protection of treatments that are available elsewhere and privately.

We are still living semi shielding live our mortality figures are lower because we are having to live these restricted half-lives.

Just be honest we are not worth the cost. Transplants are given because they are cost effective. I led a normal life. I pay taxes and used to spend on the economy until my life was so restricted by Covid for travel, socialising work. The mental health cost is growing.

Our mortality figures are not as high as they might be because we semi shield still. It affects families.

If money is the priority and transplant patients are not worth protecting what is the point of the transplant programme? Why give a transplant to live a shielded life afterwards?

I have looked after my transplant for 16 years. Since Covid my life has shrunk. NICE members think how threatened you felt in the first lockdowns before vaccination we are still in that position! Plus in the early months we were told not to leave home at all.

Some of us also have the added risk of age. Transplantees are living longer. Dialysis costs thousands of pounds more but our previously normal lives are just not worth protecting. We are not really LIVING with Covid into 2023.

Be honest NICE recommend the tools for us to live properly to live let the NHS be honest and stop the transplant programme. They cannot afford the proper medical protection after the procedure.

Your draft statement looks as though once again we are abandoned to more useless vaccines (in our case) to tick a box and pretend we are protected. This consultation looks like a pass the buck exercise from the Dept of Health to save money and shelve the issue for the worst winter months. No report till March while we struggle in a society that pretends there is no longer any risk to any group.

With no co

- Has all of the relevant evidence been taken into account?

No

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any

group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Discrimination against transplant patients taking Tacrolimus. Thus all kidney patients stage 5 and above and other transplant patients

Hospital based treatments recommended not even approved.

Access to hospital treatment a post code lottery and patients have to be very unwell to antibodies. Different standards are being applied to us for whom vaccines do not protect compared to other people. For example vaccinations not specifically targeted to omicron were rolled out to all in January to August 2022 in the hope they would protect. No vaccine is 100%. Yet an antiviral Omicron was rejected due to Omicron. Patients in 32 countries had months of some additional safety and freedom from semi shielding denied. A percentage efficacy against serious illness, expensive hospitalisation and extended sick leave etc is better than none

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	University Hospitals Sussex NHS Foundation Trust
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes I think it has

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Our areas of uncertainty:

1. We have performed a local audit that demonstrates the current overuse of both dexamethasone and tocilizumab. The majority of covid positive patients in hospital are ill with other non-covid diagnosis and the hypoxic cohort of the covid positive group are more often breathless for non-covid-19 reasons such as CCF, bacterial pneumonias, COPD exacerbations. The time has come to be explicit about the indications for dexamethasone, baricitinib and tocilizimab treatment. We would ask that instead of saying "Covid-19 positive....and oxygen requirement (in the case of dexamethasone and tocilizimab)", the terminology be changed to "clinico-radiological evidence of Covid-19 pneumonitis....and oxygen requirement". This is a different disease with a different incidence and too many patients that are swab Covid-19 positive are being misdiagnosed with Covid-19-pneumonitis and being given potentially harmful drugs. We are also missing opportunities to make alternative diagnoses as by proxy covid-19 +ve and hypoxic is still being regarded

as most likely covid-19 pneumonitis. O2 requirement is no longer a specific surrogate for early identification of moderate to severe covid-19 pneumonitis in the covid positive patient. Ultimately this is a radiological diagnosis primarily - that should be reflected in the guidance now that we have decreasing numbers and the time and tools to make the diagnosis accurately. The key is the word "pneumonitis" which does not appear to be seen in these recommendations or in any of the interim clinical commissioning policy prose.

2. We are uncertain about paxlovid for symptomatic inpatients not on oxygen, within the time frame and in a high-risk group, as they would qualify for treatment if not an inpatient. We think we need to clear that these patients can be considered for treatment. This is what happens in practice in hospitals.

3. There needs to explicit guidance on the CRP thresholds for the use of tocilizumab to avoid overuse in an unsafe or non-cost effective fashion. In practice, in the context of Omicron, this is increasingly less frequently needed in Covid cases likely due to dexamethasone and the increasingly covid-immuno experience of the population. However a lack of clarity about the CRP threshold will lead to an increase in the risk of overuse in a drug that currently is not frequently needed in real world practice.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No there are none

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	British Society for Rheumatology
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Paxlovid has been very effective in the real world of the NHS in reducing the severity of COVID-19 in non-hospitalised significantly immunosuppressed patients, including those who are on long term pulses of rituximab. We are particularly concerned about this group of patients as they may not have mounted such a good response to the COVID-19 vaccines. It is important that there is another option beside Paxlovid for those patients who are eligible for anti-virals but cannot receive Paxlovid for example because of potential drug interactions, being pregnant, paediatric patients. We feel that the OPENSAFELY data (section 3.10) show a good effect when sotrovimab is used. We feel it should also be available to severely immunocompromised non-hospitalised patients with COVID-19 who cannot receive Paxlovid. We feel it is a more effective option than molnupiravir with the current Omicron variants, but this could change as the virus mutates and should be kept under review.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Age and pregnancy could be discriminators as outlined above, i.e. young people or pregnant people when Paxlovid is contraindicated and no other anti-viral option is available to them.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

It seems mad that there is such a delay in getting prophylactic treatment such as Evusheld that is proven to work worldwide to give some protection to the CEV when vaccines do not work for some due to condition or treatment. As for cutting back on treatments when admitted to hospital with covid is sheer blindness and stupidity.

- Has all of the relevant evidence been taken into account?

I doubt it

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Probably not

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Probably not once again

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Just try and protect the CEV with correct medication rather than blanket vaccinations that do not work for some due to condition or treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	London Kidney Network - Transplant
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Kidney transplant recipients have an inferior response to SARS CoV2 vaccines despite 3 and 4 doses (1) and therefore remain at risk of severe infection and hospitalisation. The OCTAVE data was referenced in the consultation but it should be noted that this contains minimal immunogenicity data on kidney transplant recipients (2). Published data demonstrates the efficacy of sotrovimab in kidney transplant recipients to reduce the progression to severe COVID-19 infection (3). As far as we are aware there is no published safety or efficacy data of Paxlovid in kidney transplant recipients. This is likely to be related to the significant drug interactions of ritonavir and calcineurin inhibitors such as tacrolimus and cyclosporin. The majority of kidney transplant recipients receive calcineurin inhibitors as part of their immunosuppression.

1. Thomson T, Prendecki M, Gleeson S, Martin P, Spensley K, De Aguiar RC, Sandhu B, Seneschall C, Gan J, Clarke CL, Lewis S, Pickard G, Thomas D, McAdoo SP, Lightstone L, Cox A, Kelleher P, Willicombe M. Immune responses following 3rd and 4th doses of heterologous and homologous COVID-19 vaccines in kidney transplant recipients. EClinicalMedicine. 2022 Nov;53:101642. doi: 10.1016/j.eclinm.2022.101642. Epub 2022 Sep 9
2. Kearns, P, Siebert, S et al. Examining the Immunological Effects of COVID-19 Vaccination in Patients with Conditions Potentially Leading to Diminished Immune Response Capacity – The OCTAVE Trial. http://dx.doi.org/10.2139/ssrn.3910058.
3. Villanego F, Mazuecos A, Cubillo B, Merino MJ, Poveda I, Saura IM, Segurado Ó, Cruzado L, Eady M, Zárraga S, Aladrén MJ, Cabello S, López V, González E, Lorenzo I, Espí-Reig J, Fernández C, Osma J, Ruiz-Fuentes MC, Toapanta N, Franco A, Burballa CC, Muñoz MA, Crespo M, Pascual J. Treatment with sotrovimab for SARS-CoV-2 infection in a cohort of high-risk kidney transplant recipients. Clin Kidney J. 2022 Jul 28;15(10):1847-1855. doi: 10.1093/ckj/sfac177. PMID: 36147706; PMCID: PMC9384612.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Solid organ transplant recipients who are at the highest risk of severe infection despite primary extended vaccination course and boosters (1), currently receive community treatment, including sotrovimab and molnupiravir, for COVID 19 infection. Current treatments will no longer be available if the draft guidance is finalised. Paxlovid will not be administered to kidney transplant recipients (as contraindicated in patients with severe renal impairment and those taking concomitant medication dependent on CYP3A metabolic pathway) and these

patients will then be at increased risk of progression of COVID-19 infection and hospitalisation. We therefore do not believe the clinical and cost effectiveness analysis takes account of the increased risk of hospitalisation in solid organ transplant patients.

1. Agrawal U, Bedston S, McCowan C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. Lancet (London, England) 2022; 400(10360): 1305-20.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

For kidney transplant recipients with early COVID-19 infection, we do not feel that these recommendations are suitable for guidance to the NHS. The dose adjustment required for calcineurin inhibitors to facilitate Paxlovid treatment of complex and it is unlikely that transplant units will be able to undertake this safely. The Crick and OpenSAFELY data, referenced by the consultation, supports the continued access to sotrovimab for transplant recipients (1,2) and have also recently published on the benefits of sotrovimab over molnupiravir (2,3). We strongly suggest that solid organ patients should continue to have access to sotrovimab in the community to treat COVID-19 infection.

1. Wu MY, Carr EJ, Harvey R, et al. WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed. Lancet (London, England) 2022.
2. Zheng B, Green ACA, Tazare J, et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform. BMJ (Clinical research ed) 2022; 379: e071932.
3. The OpenSAFELY Collaborative, Bang Zheng, Jacqueline Campbell, Edward J Carr, John Tazare, Linda Nab, Viyaasan Mahalingasivam, Amir Mehrkar, Shalini Santhakumaran, Retha Steenkamp, Fiona Loud, Susan Lyon, Miranda Scanlon, William J Hulme, Amelia CA Green, Helen J Curtis, Louis Fisher, Edward Parker, Ben Goldacre, Ian Douglas, Stephen Evans, Brian MacKenna, Samira Bell, Laurie A Tomlinson, Dorothea Nitsch, The LH&W NCS (or CONVALESCENCE) Collaborative.
Comparative effectiveness of sotrovimab and molnupiravir for preventing severe COVID-19 outcomes in non-hospitalised patients on kidney replacement therapy: observational cohort study using the OpenSAFELY-UKRR linked platform and SRR database. medRxiv 2022.12.02.22283049; doi: https://doi.org/10.1101/2022.12.02.2228304

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No but it is worth noting that low socio-economic status and black ethnicity are associated with kidney disease and a higher prevalence is therefore seen in kidney transplant patients compared to the general population. Removal of access to

community treatment is likely to increase anxiety in this vulnerable patient group and may exacerbate health inequalities.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

As well as mortality rates the impact of Covid on quality of life has been disregarded. My husband has had ME for over 30 years and has had Diffuse B cell NHL. This has left considerable scar tissue in his lungs. He has been hospitalised with a "normal "viral infection. Even a normal cold has a severe impact on his health.ME Association reports significant relapses from ME people who have caught Covid. We are still shielding as although he was identified as CEV we are unsure if he would be eligible for Paxlovid. I do not want him to have to crawl up the stairs on hands and knees again or be bed bound for months at the very least.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Vasculitis UK
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

We have some concerns about the lack of treatment options in the vasculitis community as the preliminary recommendation only recommends one treatment in non-hospitalised setting, nirmatrelvir and ritonavir (Paxlovid).

According to the Patient Information Leaflet for Paxlovid (https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid/patient-information-leaflet-for-paxlovid), the medication has a wide range of contra-indications making it a non-recommended treatment for many vasculitis patients as severe renal disease is common amongst our community. Furthermore, a lot are on medication contradicting taking Paxlovid.

Patients having vasculitis and other autoimmune illnesses are at highest risk of getting severely ill from COVID-19 and therefore were included in the NHS antiviral treatment plan. The antiviral treatment helped patients with vasculitis to stay out of hospital. When vasculitis patients get seriously ill and need hospitalisation they decline extremely fast so if the option for those who cannot have Paxlovid is to be ill enough to need hospitalisation and oxygen their risk will increase further.

We ran a short survey in our community, 100% of those who responded stated that it is very important to be able to access antivirals to prevent the progression of

COVID-19 to severe illness. Of those that had covid and were treated with antivirals (87.18% didn't need hospitalisation, even though 66,67% felt very ill) 48.72% have renal involvement.

23.08% of the vasculitis patients responding to our survey are still shielding and another 13.89% would start shielding again if they know that they will not be able to have an antiviral treatment unless getting severely ill. The majority of our members (72.50%) are being extra cautious and try to avoid exposing themselves to the risk of getting covid, but many of them work or have families with children at school age therefore it is impossible not to come in contact with covid.
The impact on the mental health is immense. The feeling of isolation and the anxiety are not gone for these people. After reading the draft proposal for Covid - 19 treatments 92.11% said they are worried.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The assertation in the preliminary recommendations, ''…it is highly uncertain whether casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab are effective against the Omicron variant'' make us be concerned that the recommendations are based on an incomplete review of evidence. The committee noted the WHO's recommendation against using casirivimab plus imdevimab and sotrovimab for the Omicron variant. This recommendation has been challenged (WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed, Mary Y Wu at.al., published 6th October 2022, https://doi.org/10.1016/S0140-6736(22)01938-9
As vasculitis patients up to now could access antiviral treatment when non-hospitalised there is no evidence of the cost that will result from many of them not being able to have the antiviral treatment as it is not recommended for those with severe renal involvement. Generally, immunocompromised patients need longer time to heal and are in risk of sepsis therefore they will need prolonged hospitalisation. Furthermore, a severe infection is a common trigger for flare ups that need medical attention.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

If the draft recommendations were to be applied, they would disproportionally negatively affect people from the vasculitis community (and other chronically ill patients) as many of them are on medications or have comorbidities that exclude them from taking the only non -hospital antiviral treatment. As many don't create immune response to the vaccines getting antivirals is the way to protect these patients of hospitalisation and higher risk of mortality.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

It is a discrimination against patients with certain disabilities who because of their comorbidities and treatment will not be able to have the treatment needed to avoid getting severely ill from Covid-19. The committee considered it, but treating these patients is not cost effective for NHS. Maximising public health will put these

patients in higher risk of hospitalisation and increase their mortality risk.

A different treatment available for these patients should be considered. It is equity that patients like me need.

NICE National Institute for Health and Care Excellence

In vitro data on neutralising monoclonal antibodies for COVID-19: interim methods framework

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Background

NICE has published a suite of guidelines on COVID-19. We are also developing a multiple technology appraisal (MTA) on therapeutics for people with COVID-19, and a single technology appraisal (STA) on tixagevimab plus cilgavimab for preventing COVID-19. The MTA includes the neutralising monoclonal antibodies (nMAbs) casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab for treating COVID-19 in people with severe COVID-19 or mild COVID-19 at high risk of progressing to severe disease. The STA covers tixagevimab plus cilgavimab for pre-exposure prophylaxis of COVID-19 in people who are unlikely to mount an adequate immune response to COVID-19 vaccination or in people for whom COVID-19 vaccination is not recommended.

The SARS-CoV-2 virus that causes COVID-19 evolves over time resulting in new variants and subvariants. Current clinical-effectiveness evidence for nMAbs is from clinical trials conducted before the Omicron variant became the predominant variant. Because the SARS-COV-2 virus is evolving rapidly, it is difficult to do clinical trials in real time. This means clinical trials on new variants will not be completed in time to help us understand how effective nMAbs are against those variants before the virus evolves again. It is also unlikely that findings from observational studies will be reported in the timeframe required to inform decision-making. We therefore need to develop methodology to help understand whether nMAbs developed for a previous variant can be used for people infected with, or at risk of infection with, a newer variant.

With little clinical trial and observational data on the efficacy of nMAbs against newer variants, policy makers are using in vitro data. In vitro data is generated from laboratory studies outside of a living body and usually involves cell culture. For these reasons, in vitro studies are not thought to fully replicate the conditions seen in humans, and the evidence type and quality differs from

clinical trial evidence. In vitro data on nMAbs is from laboratory studies investigating their neutralisation effect on cells infected with the COVID-19 variant of interest.

In general, some in vitro data suggests that some nMAbs may have reduced neutralisation against some of the more recent variants in circulation, such as the Omicron variant and subvariants. We are in a position where we need timely decisions on whether these nMAbs should be recommended for pre-exposure prophylaxis and treatment of COVID-19. However, the clinical-effectiveness and in vitro data cover different situations because clinical-effectiveness data was obtained when previous COVID-19 variants were dominant and in vitro data has been generated from newer circulating variants. The fundamental challenge for decision-making is around how in vitro data translates into clinical and health economic outcomes in the absence of clinical studies in people infected with, or at risk of infection with, new COVID-19 variants.

This document outlines a framework to assist technology appraisal and guideline committees in making these decisions.

Scope of this framework

This framework applies to in vitro data on neutralising monoclonal antibodies for pre-exposure prophylaxis or treatment of COVID-19 only. Although there has been some suggestion that antivirals (for example, paxlovid) could work differently against different variants, this hasn't transpired to date and therefore, the principles outlined here do not cover those treatments.

How this framework was developed

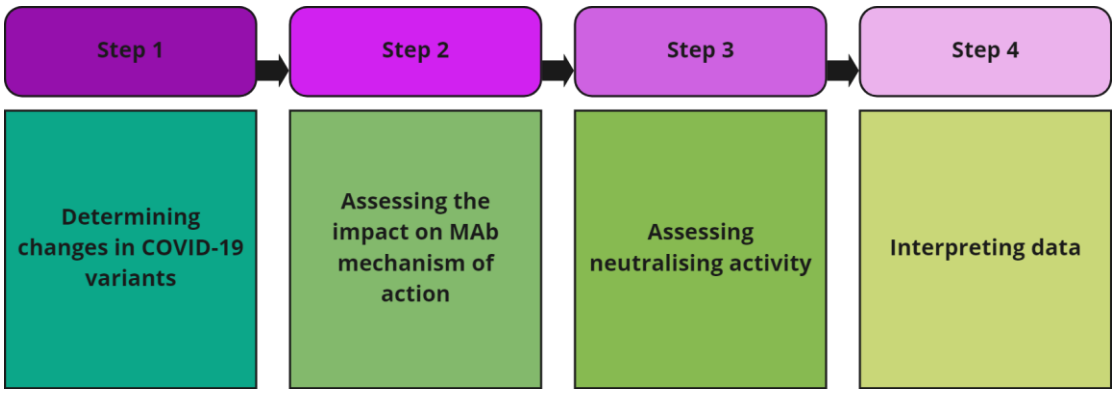
In December 2022, NICE established an in vitro data expert advisory group (IVAG, see Appendix 1) including people with expertise in using and understanding COVID-19 in vitro data or making clinical and health economic

decisions in the setting of uncertainty. The main aims of this group were to advise on translating in vitro evidence on neutralising activity of nMAbs into clinical and health economic outcomes to aid decision-making for NICE guidance. This is to determine when nMAbs are likely to be less effective or ineffective in the event of a new variant emerging, and to describe the uncertainty around those decisions. The group also advised on the type of data required to inform decision rules and how to use the data. The group met 4 times during December 2022 and the discussions were used to generate this interim framework and decision rules.

This is a living framework and will be updated as new information emerges.

Framework overview

Figure 1: summary of key considerations for using in vitro data on the effectiveness of nMAbs against new variants



Step 1: Determining changes in COVID-19 variants

Anticipated future trajectory of circulating variants

The IVAG acknowledged the uncertainty around predicting the incidence of future variants, with reduced COVID-19 testing in the UK adding to this uncertainty. However, reflecting on the patterns and emergence of previous variants, the IVAG anticipated that the following principles will apply:

- It is certain that new SARS-CoV-2 variants will emerge with significantly different antigenic properties. It is also possible but less likely that new variants will have different properties in terms of transmissibility, cell tropism and disease severity. It is expected that there will continue to be 2 types of evolution of the virus: 1) frequent incremental changes leading to small changes in antigenicity and 2) infrequent antigenic shifts leading to selective sweep of a new fit variant.
- There is a certain level of standing genetic diversity which can fluctuate over time and 'changes' to viral genotype are a continuous process. Historically there has been a major sweep approximately every 6 months. What constitutes a major sweep of a new lineage is somewhat subjective. Less dramatic changes are a continuous process; at any given time, some lineages will be growing and slowly replacing other lineages. Antigenically similar previous variants are unlikely to re-emerge because of population immunity but cannot be ruled out. It is possible that a new lineage could emerge which is partially or completely ancestral to a previous lineage like Delta, but this would likely be antigenically distinct.
- A future variant could be neutralised by a given nMAb where this hasn't been observed for previous variants.

Based on the above assumptions, the IVAG supports steps for regular monitoring of the emergence of variants and determining whether further action is needed.

Surveillance and identification of new emergent variants

The UK Health Security Agency (UKHSA) has a surveillance system in place for monitoring the emergence of changes to COVID-19 variants. This intelligence will be shared with NICE.

Additionally, the World Health Organization (WHO) defines variants of concern as those meeting the following criteria:

- increase in transmissibility or detrimental change in COVID-19 epidemiology, or
- increase in virulence or change in clinical disease presentation, or
- decrease in effectiveness of public health and social measures or available diagnostics, vaccines and therapeutics.

The WHO also has a list of variants which it monitors. NICE will also use this information as a source of intelligence. However, it's recognised that the WHO's information isn't always relevant to the UK because there have been previous variants of concern recognised by WHO (for example, Beta) that have been important globally but have never become dominant in the UK.

Monitoring increasing prevalence of a variant (or subvariant)

Variants of interest are typically antigenically different from previous variants and generally exhibit 'immune escape', that is, the person's immune system is no longer able to recognise and eliminate the virus. For this reason, the variants tend to quickly increase in prevalence across a population over a period of weeks to months.

Threshold for determining a new 'dominant' variant (or subvariant)

Predicting when a variant will become dominant is a complex task and depends on expert interpretation of evidence regarding the relative growth rates of cocirculating variants and interpretation of functional mutations in novel variants. There is also a distinction between genetic difference (such as a genetic shift away from a predominant variant) and immune escape, which links to the ability of a subvariant to increase in prevalence and replace other variants. The IVAG indicated that it is usually clear if a variant will replace others once it has reached about 10% sample frequency and has a logistic growth rate of over 25% per week. Intelligence from the UKHSA and the WHO

should indicate which variants are emerging and increasing in prevalence and should be used as a trigger to move to the next step in this framework.

Actions in this step of the framework:

- UKHSA shares surveillance intelligence on emerging variants that it anticipates will increase in prevalence or become dominant in the UK.
- NICE considers the UKHSA data in addition to the WHO's information on variants of concern.
- NICE, with input from the UKHSA, will decide whether there has been a step-change in variants from those which informed the decisions when the guideline recommendations were developed.

Decision point: If a new variant is becoming dominant, NICE will move to the next step on assessing impact on nMAb mechanism of action.

Step 2: Assessing impact on monoclonal antibody mechanism of action

Monoclonal antibodies and mechanism of action

Monoclonal antibodies have different mechanisms of action in terms of which proteins they bind to, meaning they can neutralise the SARS-CoV-2 virus in different ways. This is important when considering the monoclonal antibody of interest. Some treatments include a combination of 2 antibodies and it is possible that one but not the other may retain activity against a variant. NICE is evaluating the clinical and cost effectiveness of 3 nMAbs; these have the following reported mechanism of action against the SARS-CoV-2 virus:

- **Casirivimab plus imdevimab (Ronapreve)** is a combination of 2 non-competing recombinant human IgG1 monoclonal antibodies. This combination targets 2 distinct epitopes (the part of the virus to which the nMAbs attach) binding simultaneously to the S protein receptor binding

domain. Casirivimab plus imdevimab block the virus's interaction with the angiotensin-converting enzyme 2 (ACE2) receptor that is used by the virus to enter host cells.

- **Sotrovimab (VIR-7831)** is a dual-action, engineered human IgG1 monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. Amino acid substitutions in the Fc region result in a median half-life of 49 days while retaining the ability of the antibody to recruit effector functions.
- **Tixagevimab and cilgavimab (Evusheld)** is a combination of 2 recombinant human IgG1 monoclonal antibodies, with amino acid substitutions in the Fc regions that extend antibody half-life. Tixagevimab plus cilgavimab have longer half-lives of 87.9 and 82.9 days respectively. Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain of SARS-CoV-2.

The IVAG noted that the nMAbs exhibit dose-linear and proportional pharmacokinetics across the range of doses at which they've been studied. What this generally means in practice is that if the dose is doubled, the concentrations in serum are doubled, and if the dose is halved then the concentration in serum is halved.

The majority of currently available nMAbs were developed in the context of early SARS-CoV-2 variants. Some in vitro data has shown that many of them may be less effective at neutralising newer variants resulting in a perception that they may work less well in people infected with or exposed to new variants.

Considering the mechanism of action of nMAbs with relation to new variants, NICE sought advice from the IVAG to determine whether it is likely that nMAbs could retain neutralising activity. For example, if a specific nMAb target epitope is lost in a new variant, this could be a potential trigger for considering whether neutralisation activity is reduced or lost.

Based on their experience, the IVAG indicated that:

- Neutralisation activity of combination treatments may be more resilient to changes in variants because they tend to have a broader mechanism of action.
- Drug-selected resistance has been observed during use against susceptible variants (up to Omicron BA.1).
- Marked reductions in neutralisation have been reported since Omicron BA.2 and subsequent sub-lineages emerged.
- Neutralisation can also be compromised when mutations occur outside of the specific epitope because of the overall impact on protein structure.

Actions in this step of the framework:

- Determine whether the nMAbs' mechanism of action is still effective against the new variant.
  - The main impact is expected when a variant has a mutation eliminating the target epitope of the nMAb or a mutation outside of the specific epitope that compromises neutralisation.
  - Assessment of impact will require a combination of evidence on mechanism of action and expert input.

Decision point: If there is a potential impact on the effectiveness of the nMAbs' mechanism of action move to next step of assessing neutralising activity.

Step 3: Assessing neutralising activity

Determining the evidence base

NICE requires in vitro data to inform discussions on whether the nMAbs included in NICE guidance still have neutralising activity against the new dominant variants. NICE's search strategy for identifying published evidence

is outlined in Appendix 2. NICE may obtain additional data from the UKHSA, regulators and manufacturers of nMAbs.

Relationship between in vitro neutralisation data and clinical effectiveness

Neutralisation assays are considered the gold standard for determining antibody efficacy against viruses. The results of these in vitro ELISA assays, usually reported as the 50% and 90% effective concentrations (EC50 and EC90), tell us the concentration of drug needed to neutralise 50% or 90% of the virus. The goal of neutralisation is not necessarily to neutralise the virus completely, but to reduce the growth rate of the virus to below a self-sustainable level. The IVAG indicated that different nMAbs may remain effective despite having reduced neutralising activity against a different variant than that prevalent when the clinical trial which led to marketing authorisation was done. This may occur if the concentration of the treatment used in clinical practice is, for example, 100-fold higher than that needed to reduce the viral level. In this example, the nMAbs may have a similar effect on viral growth rate even if there is a 100-fold reduction in neutralising activity against a new viral variant compared with original studies against older variants. In an attempt to maximise a positive outcome in clinical trials some companies have used the highest dose possible initially followed thereafter by lower doses. For example, a clinical trial on casirivimab plus imdevimab used doses of 8.0 g, 2.4 g and 1.2 g (O'Brien et al. 2021).

This is important to note when considering the neutralising activity of the nMAbs.

The gold standard for assessing clinical effectiveness of medicines is through blinded randomised clinical trials (RCTs). In the absence of RCTs on the effectiveness of nMAbs against new SARS-CoV-2 variants, we need to establish whether there could be a plausible link between in vitro neutralisation data and clinical and health economic outcomes. While there is

no consensus on the exact relationship between in vitro neutralisation data and clinical outcomes for COVID-19 (such as reducing hospitalisation rates or mortality), the IVAG concluded that it's plausible that an association exists. The main reason for this conclusion is because scientists have consistently used in vitro neutralisation data to select antibodies and doses for further testing in RCTs for several decades of antiviral pharmacological research. The IVAG noted, however, that a link between in vitro data showing a fold change in neutralisation activity against newer variants and clinical outcomes is difficult to establish because of how a new variant may impact disease severity.

One of the key methodological steps in the usual process of reviewing evidence of clinical effectiveness is to appraise the clinical trials to critically to assess quality and robustness, risk of bias and generalisability. There is no validated tool for appraising in vitro neutralisation data. Therefore, the IVAG discussed key components of quality for studies on in vitro neutralisation and identified important characteristics to consider when assessing studies. The IVAG was also aware of the ongoing work of the Department of Health and Social Care Antivirals and Therapeutics Taskforce which aims to standardise aspects of in vitro neutralisation studies.

Key components of in vitro neutralisation studies

Virus and cell lines

In vitro neutralisation studies typically use either pseudovirus or live virus. Pseudoviruses do not replicate and have their surface envelope proteins replaced with those of SARS-CoV-2. The IVAG agreed that it preferred studies using live SARS-CoV-2 virus but acknowledged that both types of virus were associated with uncertainty. The IVAG agreed that in vitro data from pseudovirus generally agrees with in vitro data from live virus, and the advantage is that results from pseudovirus are generated quicker.

The IVAG noted it is also important that the cell line used for viral culture has been clonally selected and that the batch of virus has been sequenced, characterised and reported in the studies. This would enable NICE to assess the consistency across studies.

Reproducibility of assays

The IVAG agreed that in vitro neutralisation assays should be reproducible, so studies should clearly detail the methods used.

Different manufacturers of nMAbs assume different degrees of tissue penetration, and some, but not all, companies also include a margin of error (up to 10-fold) in their assays. According to the IVAG, few companies use EC50 because inhibiting only 50% of replication is not a recognised basis for efficacy of medicines to prevent or treat viral illnesses, and EC90 is at least 9-fold higher than EC50.

The IVAG concluded that EC50 values would be acceptable to initially assess whether an nMAb has lost efficacy against new variants relative to older variants. But, when detailed pharmacokinetic and pharmacodynamic (PK/PD) assessments are needed, EC90 should be used.

Repeatability of results

When new SARS-CoV-2 variants emerge, it is likely that numerous groups of scientists will generate and publish in vitro data. The IVAG considered it important that results are broadly consistent across studies. The IVAG noted, however, that fold-differences in neutralisation between different variants have generally been more reproducible than the absolute concentrations of nMAb required for neutralisation.

Comparator

The IVAG discussed that in vitro neutralisation studies should report fold change in EC50 against the new variants relative to the ancestral or reference variants.

Measuring uncertainty in the results

The IVAG discussed that using 95% confidence intervals (95% CIs) when reporting EC50 and EC90 point estimates would be helpful for measuring uncertainty in the results. For example, comparing 2 absolute EC50 values without a 95% CI could be misleading. However, the IVAG acknowledged that 95% CIs are not always reported in the literature.

Actions in this step of the framework:

- Search for in vitro data to determine if there are any studies that report neutralisation data for nMAbs against new variants of interest.
- Determine the quality and reproducibility of the data using the appraisal approach outlined in Appendix 3.

Decision point: If there is in vitro data available that is of sufficient quality and reproducible, move to next step of interpreting the data.

Step 4: Interpreting changes to in vitro neutralisation by monoclonal antibodies

In vitro data presentation

There are generally 2 presentation types for in vitro data used in the published literature: heat maps (for example, as shown in Wang et al. 2022) and concentration dose–response curves (for example, as shown in Planas et al. 2022). These present the concentration of nMAbs needed to neutralise the variant in vitro to a stated degree (for example, EC50). Heat maps show the nMAbs drugs in columns, and the variants in rows. A red colour represents a loss of neutralising activity while no colour reflects maintained neutralising activity. A dose–response curve plots drug concentration on the x axis as a function of percent viral inhibition on the y axis. With separate plots per treatment, each neutralisation curve reflects neutralisation activity of therapeutic monoclonal antibodies against variants of interest. Although the

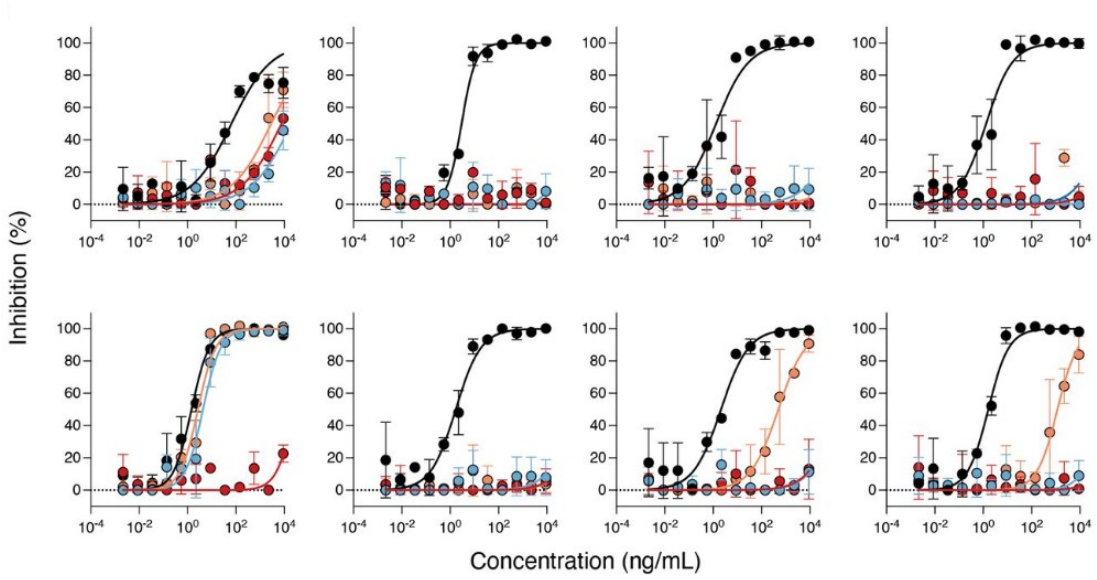
IVAG acknowledged that heat maps provide a good summary of a lot of data, the IVAG concluded that it preferred dose–response curves because they provide more information. Specifically, they enable assessment of whether the slope of the concentration response curve changes between variants. If the slope changes (showing that higher concentrations of nMAbs are needed to retain neutralisation), the EC90 moves even further away from the EC50 and, in some cases, the nMAb cannot achieve EC90.

Figure 2. Example heatmap from [Wang et al. 2022.]

IC$_{50}$ (μg/ml)	NTD	NTD-SD2	SD1	RBD Class 1				RBD Class 2				RBD Class 3											RBD Class 4	Evusheld
	C1520	C1717	S3H3	S2K146	Omi-3	Omi-18	BD-515	XGv051	XGv347	ZCB11	COV2-2196	LY-CoV1404	XGv289	XGv264	S309	P2G3	SP1-77	BD55-5840	XGv282	BD-804	35B5	COV2-2130	10-40	
D614G	0.002	0.125	0.022	0.004	0.004	0.012	0.010	0.001	0.002	0.002	0.002	0.002	0.002	0.001	0.023	0.001	0.003	0.002	0.001	0.011	0.014	0.007	0.049	0.003
BA.4/5	0.001	0.209	0.014	0.090	0.023	0.013	0.010	0.050	3.450	4.868	>10	0.001	0.038	0.002	0.514	0.002	0.005	0.009	0.001	0.019	>10	0.021	2.414	0.035
BQ.1	0.001	0.666	0.019	0.585	0.860	0.131	0.343	0.159	2.830	>10	>10	>10	0.425	0.494	0.600	1.608	>10	0.034	0.020	>10	>10	>10	>10	>10
BQ.1.1	0.003	1.117	0.025	0.527	0.804	0.170	0.377	0.191	3.311	>10	>10	>10	1.013	>10	2.140	>10	>10	>10	0.093	>10	>10	>10	>10	>10
BA.4/5-R346T	0.002	0.141	0.009	0.081	0.019	0.009	0.006	0.042	2.166	2.560	>10	0.001	0.045	0.003	1.726	0.041	>10	1.447	0.001	>10	>10	>10	5.069	>10
BA.4/5-K444T	0.002	0.116	0.009	0.104	0.016	0.010	0.006	0.040	4.766	3.731	>10	>10	0.161	0.273	0.552	1.245	4.007	0.038	0.006	>10	>10	>10	6.976	>10
BA.4/5-N460K	0.002	1.166	0.016	0.542	1.279	0.186	0.431	0.152	3.046	>10	>10	0.002	0.353	0.003	0.934	0.003	0.009	0.012	0.002	0.122	>10	0.030	>10	0.063
BA.2	0.002	0.561	0.016	0.028	0.015	0.005	0.012	0.001	0.003	0.012	1.924	0.001	0.067	0.003	0.833	0.002	0.006	0.014	0.001	0.036	0.827	0.009	8.770	0.019
XBB	>10	0.836	0.016	0.223	1.181	0.468	0.555	>10	>10	>10	>10	>10	>10	>10	0.343	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10
XBB.1	>10	0.693	0.019	0.190	1.705	0.605	0.803	>10	>10	>10	>10	>10	>10	>10	0.405	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10
BA.2-V83A	0.001	0.354	0.015	0.036	0.019	0.007	0.015	0.002	0.003	0.013	3.039	0.001	0.070	0.002	0.641	0.002	0.007	0.019	0.001	0.045	1.274	0.011	>10	0.025
BA.2-Del144	0.002	0.501	0.011	0.026	0.016	0.004	0.011	0.002	0.002	0.008	4.134	0.001	0.063	0.002	0.455	0.002	0.005	0.014	0.001	0.031	0.341	0.010	8.766	0.021
BA.2-H146Q	0.001	0.356	0.011	0.032	0.011	0.004	0.009	0.002	0.002	0.010	2.924	0.002	0.055	0.002	0.641	0.003	0.007	0.019	0.001	0.044	1.107	0.009	9.106	0.019
BA.2-Q183E	0.002	0.307	0.019	0.034	0.018	0.006	0.014	0.002	0.003	0.013	3.098	0.001	0.067	0.003	0.649	0.002	0.008	0.020	0.002	0.028	1.019	0.011	9.251	0.022
BA.2-V213E	0.002	0.406	0.013	0.030	0.014	0.004	0.010	0.002	0.002	0.006	2.177	0.001	0.047	0.003	0.720	0.002	0.006	0.014	0.001	0.026	1.247	0.009	8.198	0.018
BA.2-G252V	0.001	0.577	0.013	0.030	0.012	0.004	0.008	0.002	0.003	0.008	2.258	0.001	0.048	0.002	0.564	0.002	0.005	0.012	0.001	0.032	0.939	0.011	>10	0.026
BA.2-G339H	0.001	0.485	0.017	0.034	0.020	0.006	0.012	0.002	0.002	0.010	3.876	0.002	0.114	0.002	0.302	0.002	0.007	0.040	0.002	0.050	0.661	0.012	8.575	0.023
BA.2-R346T	0.003	0.372	0.012	0.017	0.010	0.003	0.007	0.001	0.002	0.007	2.109	0.002	0.048	0.004	1.433	0.007	>10	1.442	0.001	0.112	>10	>10	7.767	1.486
BA.2-L368I	0.003	0.453	0.019	0.027	0.010	0.004	0.010	0.002	0.001	0.006	2.603	0.001	0.030	0.002	0.605	0.002	0.005	0.021	0.001	0.026	0.324	0.008	3.202	0.018
BA.2-V445P	0.001	0.433	0.019	0.026	0.009	0.004	0.009	0.002	0.002	0.008	2.313	>10	>10	1.141	0.428	>10	0.007	0.144	>10	1.582	0.486	>10	6.311	3.135
BA.2-G446S	0.002	0.367	0.012	0.021	0.009	0.004	0.009	0.001	0.003	0.008	2.614	0.002	0.026	0.004	0.686	0.002	0.004	0.014	0.022	0.026	0.965	0.017	5.774	0.029
BA.2-N460K	0.002	1.323	0.012	0.132	0.784	0.013	0.358	0.007	0.004	0.073	1.756	0.001	0.355	0.003	0.878	0.002	0.011	0.017	0.001	0.058	1.957	0.013	>10	0.025
BA.2-F486S	0.002	0.677	0.008	>10	0.583	0.011	0.017	>10	>10	>10	>10	0.001	0.049	0.003	0.581	0.002	0.006	0.009	0.002	0.060	2.264	0.011	>10	0.023
BA.2-F490S	0.001	0.428	0.014	0.022	0.033	0.004	0.008	0.001	0.004	0.012	1.105	0.001	0.030	0.002	0.564	0.002	0.006	0.011	>10	0.048	>10	0.013	5.337	0.016
BA.2-R493Q	0.003	0.338	0.024	0.005	0.006	0.006	0.006	0.001	0.001	0.002	0.034	0.001	0.045	0.002	1.109	0.002	0.007	0.022	0.000	0.010	1.175	0.010	3.419	0.008

>10	1-10	0.1-1	0.01-0.1	<0.01

Figure 2. Example concentration dose–response curves from Planas et al. 2022



In vitro neutralisation activity interpretation

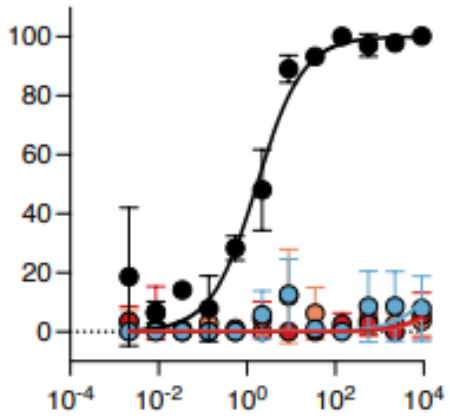
The IVAG discussed different scenarios (see table 1) of changes in neutralising activity against variants compared to the reference strains. It concluded that some scenarios had a clear interpretation that could inform recommendations made by technology appraisal or guidelines committees. These scenarios are when there can be no plausible argument for continuing efficacy for the antibodies against a new variant (see table 1). However, there will also be scenarios where the fold change in neutralising activity, particularly at higher concentrations of drugs, will be harder to interpret without further information. The IVAG indicated that if the in vitro data shows a fold change, but in vitro neutralisation is still achieved at concentrations that could be achieved in serum, then the nMAb may still be effective at a higher dose. However, the IVAG considered that this may require higher dosages than licensed and acknowledged that NICE must make recommendations based on the licensed dose only.

Table 1: Scenarios for changes in the in vitro neutralising activity relative to the reference variant (either ancestral variant or predominant variant in pivotal RCT) - applicable to prophylaxis and treatment

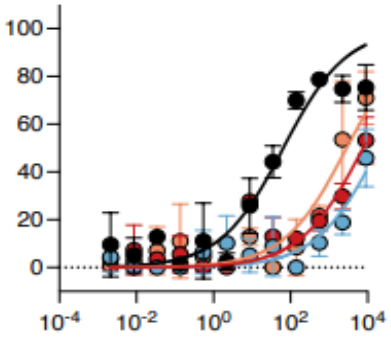
Scenario	Agreed action	Rationale
No or minimal fold change in neutralising activity relative to the reference variant	Use existing RCT evidence for decision-making	We are confident that the neutralising activity has been minimally impacted therefore the conclusions from the RCT hold
No or minimal neutralising activity at very high concentrations	Move to decision to not recommend a nMAb	These concentrations could not be achieved in the body Clear in vitro evidence that nMAbs will not be clinically effective (or by extension cost effective)
Some neutralisation at higher concentration, but substantial fold change compared with the reference variant	Insufficient information to make a decision	If there is a substantial fold change, PK/PD data is needed to attempt linking of the data to clinical outcomes

Visualising the scenarios

The following example from Planas et al. 2022 shows no or minimal neutralising activity at very high concentrations for the variants in blue and red compared with the black reference variant:



The following example from Planas et al. 2022 shows some neutralisation at higher concentrations:



Pharmacokinetic and pharmacodynamic (PK/PD) data

The IVAG stated that simply interpretating the fold-difference in an nMAb's ability to neutralise a variant without considering the compartmental pharmacokinetics, including how the drug interacts in different bodily compartments, does not give a complete picture.

In general terms, the plausibility of continued efficacy of a nMAb against new viral variants requires consideration of the plausibility of the antibody still achieving sufficient neutralisation activity in patients, and this requires an understanding of the pharmacokinetics. The nMAbs exhibit dose-linear and

proportional pharmacokinetics. What this means in practice is that if the dose is doubled, the concentrations in serum are doubled, and if the dose is halved then the concentration in serum is halved. The IVAG indicated that there is an important step in understanding the compartmental pharmacokinetics that correspond to the clinical-effectiveness measures achieved in RCTs. This includes the doses of nMAbs needed to neutralise and how a double dose that doubles the concentration in serum, for example, might overcome an expected fold reduction of neutralisation in vitro.

The IVAG concluded PK/PD data is required to try to link in vitro neutralisation data to clinical outcomes where there is a substantial fold change but some neutralisation is retained in vitro. Without this data, it is not possible to determine how this fold change may be associated with clinical outcomes.

The IVAG considered it essential to know the minimum concentration required to neutralise the ancestral (or reference) viral strain and if this differs from the licensed dose of a nMAb treatment. If this dose was substantially above the minimum concentration, then there is potentially still a tolerance to accommodate a large fold reduction in neutralisation in vitro. If the neutralisation activity achieved by the dose was close to the minimum needed for effectiveness in the ancestral (or reference) viral strain, then there is a high possibility that even a small fold change in neutralisation would render the nMAb clinically ineffective.

The IVAG agreed that clinical trials reporting failed doses provide important information. Although they did note that the more data points presented, the more confidence this adds to the dose-clinical response relationship. From this data we know what concentration of drug or level of neutralisation of virus the investigators found to be clinically ineffective. Unfortunately, for most nMAbs, IVAG acknowledged that this PK/PD data is not available, and suggested that the regulators and NICE should encourage companies to

collect this data in registrational trials to allow rapid assessment based on in vitro data.

Differences between the monoclonal antibodies

The IVAG noted that there is some in vitro data showing that tixagevimab and cilgavimab for pre-exposure prophylaxis of COVID-19 does not neutralise newer dominant variants of the virus. According to the IVAG, sotrovimab shows some neutralisation if the concentration used in vitro is increased. However, the higher concentrations of sotrovimab needed to inhibit some variants in vitro were much larger than the drug dosages used in published RCTs. Additionally, the IVAG indicated that the mechanism of sotrovimab differs from other nMAbs and that it may have additional beneficial effects beyond neutralisation through 'effector functions'. The IVAG acknowledged that this may be an additional benefit, but is hard to quantify. Overall, the IVAG concluded that evidence of in vitro neutralisation is a necessary requirement, and evidence of an effector function effect alone is insufficient to conclude clinical benefit.

Actions in this step of the framework:

- Use the appraised in vitro data to determine which scenarios from table 1 apply.
- Use the scenarios outlined in table 1 to determine the appropriate action.
- Seek expert advice on interpreting in vitro data and the proposed action.

Decision point: There are 3 outcomes in this step of the framework:

1. No or minimal fold change in neutralising activity of a drug against a viral variant relative to the ancestral variant: no action needed; continue to monitor.
2. No or minimal neutralising activity at very high concentrations: determine if need to update recommendation.

3 Some neutralisation at higher concentrations, but substantial fold change compared with ancestral variant: insufficient information to make a decision; seek expert input and ask companies for dose-failure data.

Appendix 1: IVAG members

Amanda Adler (Chair)	Director, Diabetes Trials Unit, University of Oxford
David Bauer	Group Leader & Head, RNA Virus Replication Laboratory. The Francis Crick Institute
Rupert Beale	Clinician Scientist Group Leader, Consultant Nephrologist, The Francis Crick Institute, UCL Division of Medicine
Sanjay Bhangani	Consultant Physician and Honorary Associate Professor, Royal Free Hospital and University College London
Neil Ferguson	Director, MRC Centre for Global Infectious Disease Analysis, Imperial College London
Neil Hawkins	Professor of Health Technology Assessment, University of Glasgow
Mark Jit	Professor of Vaccine Epidemiology, London School of Hygiene and Tropical Medicine
Saye Khoo	Professor in Pharmacology, Hon Consultant Physician in Infectious Diseases, University of Liverpool
David Lalloo	Director, Liverpool Tropical School of Medicine
Siraj Misbah	Consultant Clinical Immunologist, Oxford University NHS Foundation Trust
Andrew Owen	Professor of Pharmacology, University of Liverpool
Derek Smith	Professor of Infectious Disease Informatics, Zoology Department at Cambridge University
David Stuart	MRC Professor of Structural Biology, University of Oxford
Mark Sutton	Scientific Leader - Healthcare Biotechnology, and Professor for Antimicrobial Therapy, UKHSA and King's College London
Laurie Tomlinson	NIHR Research Professor, Honorary Consultant Nephrologist, London School of Hygiene and Tropical Medicine
Erik Volz	Reader in Population Biology of Infectious Diseases, Faculty of Medicine, School of Public Health, Imperial College London

Appendix 2: Search strategy

Pubmed: (omicron[TI] OR XBB[TI] OR BQ.1[TI] OR BQ1[TI] OR BA4[TI] OR BA5[TI] OR BA.4[TI] OR BA.5[TI] OR BA4/5[TI] OR BA.4/5[TI])OR BA2.75[TI] OR BA.2.75[TI])AND (mabs[ti] OR antibod*[ti] OR neutral*[ti] OR vitro[TI] OR in-vitro[TI] OR sotrovimab[ti] OR casirivimab[ti] OR imdevimab[ti] OR tixagevimab[ti] OR cilgavimab[ti])

Europe PMC: ((TITLE:"omicron" OR (TITLE:"XBB") OR (TITLE:"BQ.1") OR (TITLE:"BQ1") OR (TITLE:"BA4") OR (TITLE:"BA5") OR (TITLE:"BA.4") OR (TITLE:"BA.5") OR (TITLE:"BA4/5") OR (TITLE:"BA.4/5") OR (TITLE:"BA2.75") OR (TITLE:"BA.2.75")) AND ((TITLE:"mabs") OR (TITLE:"antibody") OR (TITLE:"antibodies") OR (TITLE:"neutralising") OR (TITLE:"neutralizing") OR (TITLE:"neutralisation") OR (TITLE:"neutralization") OR (TITLE:"vitro") OR (TITLE:"in-vitro") OR (TITLE:"sotrovimab") OR (TITLE:"casirivimab") OR (TITLE:"imdevimab") OR (TITLE:"tixagevimab") OR (TITLE:"cilgavimab")) AND (SRC:PPR))

Appendix 3: Appraisal of the evidence

The risk of bias assessment is to be completed using the adapted Toxicological data reliability assessment tool (TOXRTOOL). The following 23 questions are allocated a score of 0 or 1.

Criteria		
No	**Criteria I: Test substance identification (monoclonal antibody)**	**Score**
1	Was the monoclonal antibody named/described in the study?	
2	Is information on the source/origin of the monoclonal antibody given? *Generally, only authentic product provided by the manufacturer should be accepted for interpretation of the findings. This should include manufacturer name.*	
3	Does the test substance accurately reflect monoclonal antibodies used in clinical practice?	
		0
	Criteria II: Test system characterisation (neutralisation assay)	
4	Is the test system described**?** *At a fundamental level, comparison of in-vitro data across laboratories is hampered by the use of different cell lines that may be infected by SARS-CoV-2 variants to different extents.* *Emerging evidence suggests that MAbs binding outside of the RBD may be sensitive to ACE2 expression levels and this should be considered.*	
5	Was the neutralisation assay appropriate? *It is expected that all neutralisation assays would be ELISA assays conducted in at least two independent experiments.*	
6	Is information given on the source/origin of the test system, and is there data available on the validity of that test system? *This could include:* • *Laboratory/scientist providing cell lines* • *Commercial provider of test systems* • *A description of how the reactivity of the nMAB was validated* • *Origin of tissues and primary cells*	
7	Are necessary information on test system properties, and on conditions of cultivation and maintenance given? (Type of assay, type of virus, type of cell line, type of media) *There is broad agreement that in vitro methodology should employ authentic SARS-CoV-2 isolates, and that routine sequencing of virus stocks is needed*	

	since cell culture adaptation and mutations can occur and can change replication of virus in cells. It is currently unclear whether variants isolated from different countries will behave the same in cell culture since a large study comparison has not been reported. There is evidence that some methods to propagate the virus have led to additional mutations. *Pseudovirus assays present several advantages over live virus which include the speed at which data can be generated after emergence of a new variant, and the lack of reliance upon BSL-3 facilities, and the controlled evaluation of the effect of specific mutations. However, limitations are also evident since the pseudovirus may not contain the full suite of mutations or may not function like an authentic virus in every way. Therefore, it is suggested that data from pseudovirus assays should be considered based on a clear understanding of the inherent benefits and limitations of the data.* *Widely available cell lines should be used such as VeroE6 and VeroE6-TMPRSS2, Calu-3 cells and A549 cells.*	
8	Has sufficient detail been reported on the methods to replicate the study?	
9	Does the study confirm that an appropriate cell line has been used? *Investigators may use cell lines which have been shown to be inappropriate for assaying certain classes of monoclonal antibodies.*	
		0
	Criteria III: Study design description	
10	Are doses administered or concentrations of test substances analysed given?	
11	Are frequency and duration of exposure as well as time-points of observations explained? (duration of incubation with virus, duration of assay) *Timing of assay readouts should be validated.*	
12	Have a range of antibody concentrations been tested that are relevant to those required for neutralisation in serum? *A limitation of many in-vitro studies is the range of antibody concentrations tested, which are often lower than the average maximum serum concentrations.*	
13	Were negative controls included?	
14	Were positive controls included?	
15	Is the number of replicates (or complete repetitions of experiment) given?	
16	Is the study methodology likely to produce reliable comparison data? *For example, have the study investigators utilised an assay calibrated with the WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reporting of neutralisation titres in International Units – an assay useful for standardised comparisons of different monoclonal antibodies against various variants.*	

	Testing should be conducted on an ancestral strain of the virus or reference strain used in an RCT in parallel to the variant under investigation.	
		0
	Criteria IV: Study results documentation	
17	Are the study endpoint(s) and their method(s) of determination clearly described? *A 4-paramater, variable slope dose response analysis has been proposed as the most effective way to determine EC_{50} and EC_{90} parameters.* *Luciferase endpoints for pseudovirus assays and nucleocapsid measurements (anti-N with high content imaging) for authentic live virus have been highlighted as providing reliable readouts.* *Cytopathic effect (e.g. measured by cell titer glo) has been reported to be heterogeneous between different variants studied to date.* *qPCR readouts have an excellent signal to noise ratio but may not be applicable to pseudovirus assays.*	
18	Is the description of the study results for all endpoints investigated transparent and complete?	
19	Are the outcomes appropriate, and clearly and transparently reported? *EC_{50} and EC_{90} values should be generated as outcomes from the in vitro testing.*	
20	Were the study outcomes determined prior to analysis?	
21	Are the statistical methods for data analysis given and applied in a transparent manner?	
22	Are confidential intervals included? *CIs are important in evaluating the uncertainty of any possible changes in neutralisation; particularly when considering IC_{90} values, which lie close to the plateau of the dose–response curve and are inherently noisy.*	
		0
	Criteria V: Plausibility of study design and data	
23	Are the quantitative study results reliable?	
		0
	Total score	0

Based on the total score, studies are allocated to category 1, 2 or 3 as indicated below. Category 1 is assigned if the total score is ≥20, category 2 is assigned for scores >16, and for all scores <16, category 3 is assigned.

Category	Definition

1- Reliable without restrictions	“Studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline (preferably performed according to GLP) or in which all parameters described are closely related/comparable to a guideline method.”
2- Reliable with restrictions	“Studies or data from the literature, reports (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.”
3- Not reliable	“Studies or data from the literature/reports in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment.”

Appendix 4: Glossary of terms used

Ancestral: the original strain of SARS-CoV-2 identified in Wuhan.

Cell line: a defined population of cells that can be maintained in culture for an extended period of time and can be used for in vitro experiments.

Clonal selection: the process of generating cell lines from a single cell.

Conserved epitope: is an epitope retained by multiple strains of virus as a key target of a broadly neutralising antibody.

EC50: concentration needed to neutralise 50% of the virus population leaving the remaining 50% of the virus to be able to replicate.

EC90: concentration needed to neutralise 90% of the virus population. Concentration is at least 9-fold higher compared with EC50.

Effector functions: antibodies can induce innate and adaptive immune responses beyond neutralisation, including antibody-dependent cellular cytotoxicity.

Epitope: structure on the surface of an antigen that is recognised by and can bind to a specific antibody.

Immune escape: this occurs when the immune system of a host is unable to respond to an infectious agent, such as a virus.

In vitro*:* tests and experiments that researchers perform outside of a living organism in a controlled environment, for example a test tube or petri dish.

Neutralising monoclonal antibodies: ‘mAbs’ that bind to and ‘neutralise’ SARS-CoV-2.

Neutralisation curves: Y axis percentage inhibition, x axis is concentration of drug; different curves for different variants including ‘ancestral’ line (for example, Delta). Different graphs for each drug.

PK/PD data: pharmacokinetic and a pharmacodynamic model which describes exposure response in vivo.

Quality-adjusted life year: ‘generic’ measure of effectiveness used in cost-utility analysis.

Receptor binding domain: a part of the SARS-CoV-2 virus located on its ‘spike’ protein that allows it to dock to body receptors to gain entry into cells and cause infection.

Therapeutics for people with COVID-19. An economic evaluation: EAG additional analysis post NICE Appraisal Consultation Document

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Date completed	13th January 2023

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135564.

Declared competing interests of the authors

Matt Stevenson provided advice to Astra Zeneca Rare Diseases regarding an unrelated intervention in an unrelated disease area. No other author declares a conflict of interest.

1 Introduction

In November 2022, NICE released an Appraisal Consultation Document (ACD) related to Therapeutics for people with COVID-19.[1] In brief, the recommendations are (full details are provided in the ACD):

- Tocilizumab was recommended within its marketing authorisation provided the company provides it according to an agreed commercial arrangement
- Baricitinib is recommended subject to it receiving a marketing authorisation in Great Britain
- Nirmatrelvir plus ritonavir (henceforth nirmatrelvir/ritonavir) is recommended for adults with COVID-19 provided they do not need supplemental oxygen and have an increased risk for progression to severe COVID-19 and defined in an independent advisory group report commissioned by the Department of Health and Social Care.[2]
- No other treatments ((casirivimab and imdevimab (henceforth casirivimab/imdevimab), remdesivir, baricitinib with remdesivir, molnupiravir, sotrovimab, and tixagevimab and cilgavimab (henceforth tixagevimab/cilgavimab)) were recommended.

Many comments were received by NICE in response to the ACD, some of which have direct implications to the population of the EAG's model and therefore the results generated. This document details changes made to the EAG model. Given the large volume of comments received and the time constraints due to the timing of the second Appraisal Committee Meeting (the 24th of January 2023) not all comments are directly addressed in the document. Some comments also fall outside of the remit of the EAG, such as the fact that only nirmatrelvir/ritonavir was recommended for treating people in the community and this treatment has many contra-indications.

This document should be read in conjunction with the initial EAG report[3] and erratum[4], which provide more details on the work undertaken. Section 2 provides a summary of the key changes made to the EAG model. Section 3 details an addition sensitivity analysis undertaken by the EAG; Section 4 provides the new results generated by the EAG. Section 5 details additional responses by the EAG to consultee comments that did not alter model structure or parameter values.

All analyses in this report have used list prices, with analyses using the PAS for tocilizumab, baricitinib and sotrovimab included in a confidential appendix. Three drugs had list prices which were not publicly available: casirivimab/imdevimab; molnupiravir; and tixagevimab/cilgavimab. No economic analyses are presented for these interventions in this report but will be contained in a confidential appendix.

Results generated by the EAG are provided as incremental cost-effectiveness ratios (ICERs), expressed in terms of cost per quality-adjusted life year (QALY) gained.

2 Changes made to the EAG model

This ERG report is structured around seven changes made to the population of the EAG's model and description of four additional scenario/sensitivity analyses conducted by the EAG. These are described in Sections 2.1 to 2.7, along with an indication of whether the ICER becomes more or less favourable to COVID-19 therapeutics as a result of each change. The impact on the ICERs when the changes made to the model are made simultaneously are provided in Section 3.

2.1 *Change 1: Updated data from COVID-NMA*

As detailed in the main EAG report Covid-NMA[5] was used to provide the efficacy data assumed in the analyses undertaken. Since the initial report, COVID-NMA has been updated which has altered the estimated efficacy of some treatments.

The latest estimates of efficacy are shown in Table 1 for treatments used in patients hospitalised due to COVID-19 and in Table 2 for patients in the community with COVID-19 at high-risk of hospitalisation. Rows where values have changed have been indicated in red.

Table 1: Summarised clinical effectiveness data in patients hospitalised due to COVID-19

Intervention	Estimated efficacy (95% CI)	Mean value from the lognormal distribution	Source of evidence (number of studies informing the estimate)
Time to death HR			
Casirivimab/imdevimab	0.69 (0.50 – 0.93)	0.70	COVID-NMA[5] (1 study)
Tocilizumab	0.76 (0.64 – 0.90)	0.76	COVID-NMA[5] (9 studies)
Remdesivir	0.77 (0.57 – 1.04)	0.78	COVID-NMA[5] (3 studies)
Baricitinib	0.61 (0.47 – 0.78)	0.62	COVID-NMA[5] (2 studies)
Baricitinib/remdesivir	0.65 (0.39 – 1.09)	0.67	COVID-NMA[5] (1 study)
RR for clinical improvement at 28 days			
Casirivimab/imdevimab	1.03 (0.98 – 1.09)	1.03	COVID-NMA[5] (2 studies)
Tocilizumab	1.05 (1.00 – 1.11)	1.05	COVID-NMA[5] (15 studies)
Remdesivir	1.04 (0.99 – 1.10)	1.04	COVID-NMA[5] (4 studies)
Baricitinib	1.02 (1.00 – 1.05)	1.02	COVID-NMA[5] (3 studies)
Baricitinib/remdesivir	1.08 (1.00 – 1.17)	1.08	COVID-NMA[5] (1 study)
Time to discharge HR			
Casirivimab/imdevimab	1.24 (1.05 – 1.47)	1.24	metaEvidence[6] (2 studies)
Tocilizumab	1.05 (0.88 – 1.25)	1.05	metaEvidence[6] (2 studies)

CI – confidence interval, HR – Hazard ratio, RR – Relative Risk

The updated evidence in COVID-NMA has produced a favourable impact for casirivimab/imdevimab with the median HR for time to death reducing from 0.81 to 0.69 and the median RR for clinical improvement at 28 days increasing from 1.02 to 1.03. There were marginal improvements for tocilizumab, with the median HR for time to death reducing from 0.77 to 0.76, and for baricitinib/remdesivir with the median RR for clinical improvement at 28 days increasing from 1.02 to 1.03.

Table 2: Summarised clinical effectiveness data for patients at high-risk of hospitalisation due to COVID-19

Intervention	Estimated efficacy (95% CI)	Mean value from the lognormal distribution	Source of evidence (number of studies informing the estimate)
Hospitalisation or death RR			
Casirivimab/imdevimab	0.28 (0.18 – 0.44)	0.29	COVID-NMA[5] (3 studies)
Molnupiravir	0.80 (0.56 – 1.15)	0.81	COVID-NMA[5] (5 studies)
Nirmatrelvir/ritonavir	0.13 (0.07 – 0.27)	0.14	COVID-NMA[5] (1 study)
Remdesivir	0.28 (0.10 – 0.74)	0.32	COVID-NMA[5] (1 study)
Sotrovimab	0.20 (0.08 – 0.48)	0.22	COVID-NMA[5] (1 study)
Tixagevimab/cilgavimab	0.50 (0.29 – 0.86)*	0.52	metaEvidence[6] (1 study)
All-cause mortality RR at 28 days			
Casirivimab/imdevimab	0.51 (0.09 – 2.95)	0.76	COVID-NMA[5] (4 studies)
Molnupiravir	0.27 (0.09 – 0.82)	0.32	COVID-NMA[5] (7 studies)
Nirmatrelvir/ritonavir	0.04 (0.00 – 0.63)	0.15	COVID-NMA[5] (1 study)
Remdesivir	1.00 (0.02 – 50.23)**	7.36***	COVID-NMA[5] (1 study)
Sotrovimab	0.20 (0.01 – 4.16)	0.65	COVID-NMA[5] (1 study)
Tixagevimab/cilgavimab	1.00 (0.32 – 3.06)	1.18***	COVID-NMA[5] (1 study)

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

* An odds ratio was provided in the source and the authors calculated the RR.

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

*** A value of 1.00 was used in the modelling

The updated evidence in COVID-NMA has produced an unfavourable impact for molnupiravir with the median RR for hospitalisation or death increasing from 0.68 to 0.80 and the RR for all-cause mortality increasing from 0.19 to 0.27.

2.2 Change 2: Capping efficacy values in the low efficacy scenario such that the treatments do not, on balance, harm patients

For patients in hospital due to COVID-19, the EAG has amended the low efficacy scenario in order that the treatments evaluated do not, on balance, harm patients, that is, at the very worst, the treatments would produce identical QALYs to SoC. This means that in the low efficacy scenario, a HR of unity was used for time to death for remdesivir and for baricitinib/remdesivir and a RR of unity for clinical improvement for remdesivir. The mean values from the estimated distributions have been left unchanged. The EAG believed it plausible that other aspects such as time to discharge and clinical improvement could plausibly be worse for treatments as a by-product of preventing death, and only capped these values at unity if the treatment were shown to have no benefit on mortality. As such, the RR for clinical improvement at 28 days for remdesivir was set to unity.

For patients treated in the community at high-risk of COVID-19, the EAG has set the RR for all-cause mortality at 28 days to be unity in the low efficacy scenario for casirivimab/imdevimab, remdesivir, sotrovimab, and tixagevimab/cilgavimab. The RR for-all cause mortality in the mean efficacy scenario was set to unity for remdesivir and tixagevimab/cilgavimab. The EAG has capped the RR for hospitalisation or death for molnupiravir at unity in the low efficacy scenario as it was deemed implausible that molnupiravir would have a positive impact on mortality but would markedly increase the number of hospitalisations.

The capping of HRs or RRs such that treatments do not harm patients will be favourable to treatments which have scenarios where previously treatment did harm patients.

2.3 Change 3: Amending the hospitalisation percentage assumed in the base case for patients at high-risk in the community

In its report, the EAG assumed that 2.79% of patients at high-risk in the community would be hospitalised if they had COVID-19. This was interim data from a study, Patel *et al*.,[7] that has now been published as a pre-print. In the pre-print, 114 of 4044 high-risk untreated patients were hospitalised equating to a value of 2.82% which has now been used in the base case. The EAG has selected this paper as it appears most generalisable to the decision problem, analysing patients in North-West London, diagnosed with COVID-19 between the 1st of December 2021 and the 31st of May 2022. The Patel *et al*. study[7] also included results for those treated with sotrovimab, nirmatrelvir/ritonavir, and molnupiravir which could cause confounding, although baseline characteristics for patients indicated that the proportion of patients with at least 1 of the highest-risk conditions was greatest in the untreated patients, or at least 3 high-risk conditions was reasonably similar for sotrovimab, molnupiravir, and untreated patients and was lower for those receiving nirmatrelvir/ritonavir. As such, no evidence of confounding was observed. Whilst the EAG has selected a base case value of 2.82%, sensitivity analyses are still presented at different hospitalisation percentages to allow the committee to explore the cost-effectiveness of treatments at different values. The EAG has increased the upper level of risk of hospitalisation to 20% to allow the committee to explore extremely high-risk patients if it desired.

The EAG notes that in a *post hoc* analysis analysing Omicron BA.5 patients only 12 of 657 patients who received no treatment were hospitalised (1.8%, 95% CI (0.8% – 2.8%)) possibly suggesting a lower percentage of hospitalisation in this variant compared with 3.2% in Omicron BA.1 and 2.1% in Omicron BA.2, although the authors note that potential reasons for this could also include reduced immune naivety/susceptibility due to vaccination or prior infection. Furthermore, changes to guidance on the 21st of December 2021 on who should be treated may have resulted in an untreated population at lower risk of hospitalisation.

This change will be favourable to treatments that could be provided to patients at high-risk in the community where it is assumed that there is a benefit in preventing hospitalisation. For all analyses for high-risk people in the community, costs will be increased and QALYs will be decreased.

2.4 Change 4: Changes in the costs of hospitalisation in ordinal scales 4 or 5

Consultation comments indicated that there was a better way to calculate the costs of a bed day in hospital in ordinal scales 4 or 5 as the cost per finished cost episode (FCE) was used to approximate the cost per bed day and there can be multiple FCEs per admission. The EAG has reviewed these approaches and agrees that these are an improvement and preferred the approach where the costs of being in ordinal scale 5 was greater than in ordinal scale 4. The EAG calculated values using this

approach (described below) and produced slightly higher costs values than the consultee; the higher costs were used in the model.

The mean length of stay associated with COVID-19 was estimated from NHS Digital, Hospital Episode Statistics for England. Admitted Patient Care statistics, 2020-21[8] using primary diagnosis codes U07.1 and U07.2 which suggested a weighted average of 10.6 days. From the same source, the weighted mean number of FCEs per admission for U07.1 and U07.2 was 2.29. The cost per FCE for ordinal scale 4 was calculated using the National Schedule of NHS costs[9] as the weighted average of HRG codes DZ11R, DZ11S, DZ11T, DZ11U and DZ11V (lobar, atypical or viral pneumonia, without interventions) for non-elective long stay which was a value of £3524. Using the same source, the cost per FCE for ordinal scale 5 was calculated as the weighted average of HRG codes DZ11N, DZ11P and DZ11Q (lobar, atypical or viral pneumonia, with single intervention) for non-elective long stay which was £5411. The use of DZ11 has previously been used as a proxy for COVID-19 costs in a published paper.[10]

The costs for ordinal scale 4 and 5 were calculated as the average cost per FCE (£3524 and £5411 respectively), multiplied by the mean number of FCEs per admissions (2.29) and divided by the mean length of stay (10.6 days); this results in a cost per day of £759.28 in ordinal scale 4 and £1165.70 in ordinal scale 5.

A revised table of cost per day by ordinal scale is shown in Table 3 to provide the Appraisal Committee with the new values in context of other values. The increased costs of ordinal scale 4 and 5 will be favourable to treatments that prevent people entering hospital and for those treatments provided in hospital that have fewer people in ordinal scales 4 and 5. The costs will be increased for all scenarios where patients can be in ordinal scales 4 and 5.

Table 3: The bed day costs used in the economic model by ordinal scale

Ordinal scale	Clinical status	Unit cost	Source
3	hospitalised, no longer requiring ongoing medical care	£248	National Schedule of NHS costs 2020 – 2021[9] Using the weighted average of DZ11R to DZ11V (Lobar, Atypical or Viral Pneumonia, without Interventions) for a regular day or night admission
4	hospitalised, not requiring supplemental oxygen	£759	National Schedule of NHS costs 2020 – 2021[9] and NHS Digital, Hospital Episode Statistics for England. Admitted Patient Care statistics, 2020-21[8] Using the weighted average cost of DZ19R - DZ19V (lobar, atypical or viral pneumonia, without interventions) for non-elective long stay multiplied by the mean number of FCEs and divided by the weighted mean length of stay associated with primary diagnosis codes U07.1 and U07.2.
5	hospitalised, LFO	£1166	National Schedule of NHS costs 2020 – 2021[9] and NHS Digital, Hospital Episode Statistics for England. Admitted Patient Care statistics, 2020-21[8] Using the weighted average cost of DZ19N - DZ19Q (lobar, atypical or viral pneumonia, with single intervention) for non-elective long stay multiplied by the mean number of FCEs and divided by the weighted mean length of stay associated with primary diagnosis codes U07.1 and U07.2.
6	hospitalised, HFO or NIV	£1977	National Schedule of NHS costs 2020 – 2021[9] Using XC07Z (Adult Critical Care, 0 Organs Supported)
7	hospitalised, receiving IVM or ECMO	£2393	National Schedule of NHS costs 2020 – 2021[9] Using the weighted average of XC01Z, XC02Z, XC03Z, XC04Z, XC05Z, and XC06Z (Adult Critical care one or more organs supported)

FCE – finished consultant episodes; HFO: high-flow oxygen; IVM: invasive mechanical ventilation; LFO: low-flow oxygen; NIV: non-invasive ventilation

2.5 Change 5: Amending the average duration of long COVID

The Office for National Statistics released an updated report in December 2022 on the prevalence of ongoing symptoms following COVID-19 in the UK.[11] These (self-reported) data were now used to estimate the average duration of COVID-19 instead of the data contained in an earlier report, dated May 2022.[12] The methodology remains the same as detailed in Section 3.2.9 of the initial EAG report.[3] The updated data reports that 87% of people reporting long COVID were infected at least 12 weeks previously, that 55% were infected at least 1 year previous and 27% were infected at least 2 years previously.

The plot of the lognormal and the Weibull parametric fits, which have the highest and lowest mean times of the distributions that fitted the data well are shown in Figure 1, with the lognormal (with a mean of 113.6 weeks) used in the base-case. For the lognormal distribution, approximately 30% of people still have symptoms at 2 years, 10% at 5 years and 3% at 10 years.

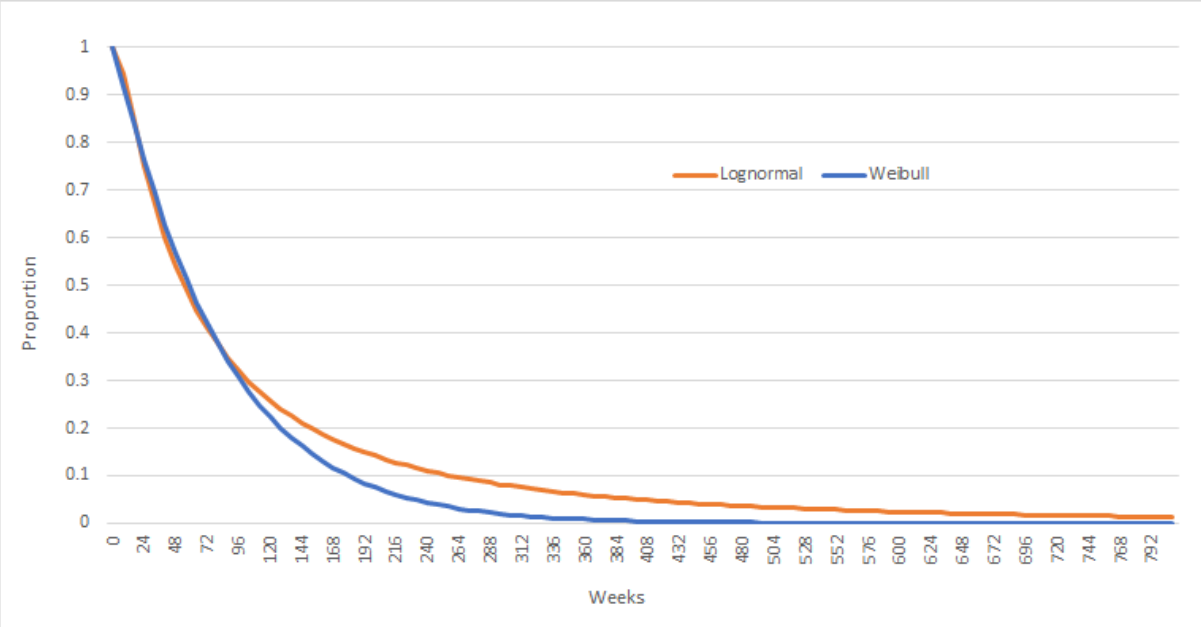

Figure 1: Assumed duration of long Covid

Increasing the assumed duration of long COVID will be unfavourable to treatments provided in hospital that prevent death, as there will be more people alive with long COVID. This factor is also applicable to treatments in the community that prevent death, however, there would also be a benefit for treatments that prevent hospitalisation as the modelling assumes an increased prevalence of long COVID in those hospitalised (100%) compared with patients who are not hospitalised (10%). QALYs will be reduced in all analyses due to this change.

2.6 Change 6: Amending the costs associated with long COVID

During the ACD consultation period, a stakeholder highlighted a report relating to the costs associated with chronic fatigue syndrome / myalgic encephalomyelitis,[13] that could be a better source for the costs of long COVID than that used in the initial EAG report (Vos-Vromans *et al*.[14]). Having reviewed this document, the EAG believes that this is preferable and has now adopted this source. Table 2.4 of this document reports an annual cost of £2095 (in 2014/15 prices) for total health care cost. The ERG has inflated this value to 2020/2021 prices using Jones and Burns[15] to assume a cost of £2267 per annum for those with long COVID. Due to this change, the scenario analysis where the cost per annum of long COVID was assumed to be £2500 has not been re-run.

Increasing the annual costs associated with long COVID will be unfavourable to treatments provided in hospital that prevent death, as there will be more people alive with long COVID. This factor is also applicable to treatments in the community that prevent death, however, there would also be a benefit for treatments that prevent hospitalisation as the modelling assumes an increased prevalence of long COVID in those hospitalised (100%) compared with patients who are not hospitalised (10%). Costs will be increased in all analyses due to this change.

2.7 Change 7: Amendment to the code related to clinical improvement

During the response to the ACD, the authors identified an error where the reciprocal of the RR values for clinical improvement were used instead of the RR values. This has been corrected. The cells affected in the model were in the 'Clinical status' sheet cells D48:F48, E49:F49, F50, D78:F78, E79:F79, F80, D138:F138, E139:F139, F140, D160:F160, E161:F161, F162, D190:F190, E191:F191, F192.

3 Additional scenario analyses using SOLIDARITY and ACTT-1 data for remdesivir in hospitalised patients and TACKLE data for tixagevimab/cilgavimab in patients treated within 5 days from symptom onset in the community

3.1 *Remdesivir scenario analysis*

As The EAG noted comments from consultees that the results from the WHO Solidarity study which reported the results of 8275 hospitalised patients randomly allocated to either remdesivir treatment or control were not included in COVID-NMA. Data were collected from 454 hospitals in 35 countries between the 22nd of March 2022 and the 29th of January 2021 which was before the dominance of the Omicron variant.

The company supplied an exploratory meta-analysis on the efficacy of remdesivir on time to death including the results from SOLIDARITY. For patients requiring supplemental oxygen but not ventilation a HR of 0.85 (95% CI 0.76 to 0.96) was estimated and for patients not requiring supplemental oxygen a HR of 0.77 (95% CI 0.59 to 1.00) was estimated. In line with other estimates and noting the overlap in confidence intervals the EAG used the overall population estimate supplied by the company which was a HR of 0.85 (95% CI 0.76 to 0.95). The mean value used in the EAG analysis is 0.85 with the high and low efficacy scenarios using the 95% confidence interval.

Two separate scenarios were run dependent on the assumption made regarding time to discharge. The first scenario followed the EAG's main analyses assuming a RR for clinical improvement of 1.04 in the mean efficacy scenario (1.00 in the low efficacy scenario and 1.10 in the high efficacy scenario) and a HR for time to discharge of 1.00 for all efficacy scenarios. In the second scenario, a time to discharge of 1.27 was used for the main efficacy scenario (1.10 in the low efficacy scenario and 1.46 in the high efficacy scenario) based on the RR for discharge or National Early Warning Score ≤2 for 24 hours as reported in ACTT-1.[16] As these values incorporated clinical improvement but were assumed to apply to time to discharge only, a RR of unity was assumed for clinical improvement in all 3 efficacy scenarios to reduce the possibility of double counting.

3.2 *Tixagevimab/cilgavimab scenario analysis*

The EAG undertook a scenario analysis for tixagevimab/cilgavimab using efficacy data provided by the company for people treated within 5 days of symptom onset. Within their response to the consultation on the draft guidance, the company states that "*Evusheld is more clinically effective and cost-effective when used within 5 days from symptom onset*" and that "*selecting 5 days as a treatment cut-off for Evusheld aligns with how clinicians would seek to use Evusheld in clinical practice*". The company provided an unpublished set of outcomes for this set of patients from TACKLE[17] which were a RR of hospitalisation or death RR of 0.31 (95% CI 0.15 to 0.64) with a calculated mean value of 0.33,

and RR of all-cause mortality RR at 28 days of 0.33 (95% CI 0.03 to 3.15) with a calculated mean value of 0.67. Following the logic detailed in Section 2.2, the mortality RR for the low efficacy scenario was capped at unity.

4 New results generated by the EAG

In this section, the EAG presents results following the changes described in Sections 2.1 to 2.6 and the sensitivity analysis reported in Section 3. The layout follows that of the original EAG report, although the sensitivity analysis on long COVID costs has been removed due to more robust data having been identified.

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 4. All interventions were estimated to have a cost per QALY gained compared to SoC below £12,000.

Table 4: Mean efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	22,127	4.61	-	-	-	-
Tocilizumab	25,551	5.12	6728	6755	11,844	6728
Remdesivir	27,773	5.08	11,989	3773	8484	Dominated
Baricitinib	30,223	5.46	9519	8915	17,421	13,676
Baricitinib/remdesivir	30,515	5.32	11,744	5897	13,040	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained

QALY – quality-adjusted life years; SoC – standard of care

Discounted QALYs for casirivimab/imdevimab are 5.27

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 5. All interventions were estimated to have a cost per QALY gained compared to SoC below £12,000. The costs associated with tocilizumab are noticeably lower than for other drugs due to the assumed higher rate of discharge of patients as the remaining interventions do not have data and assumed to have the same discharge rate as SoC.

Table 5: High efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	22,127	4.61	-	-	-	-
Tocilizumab	23,452	5.41	1661	14,635	22,745	1661
Remdesivir	33,100	5.57	11,433	8,223	17,727	Ext Dom
Baricitinib	34,364	5.82	10,116	11,957	24,141	Ext Dom
Baricitinib/remdesivir	38,517	6.03	11,559	11,968	26,025	24,302

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained

Ext Dom – Extendedly dominated; QALY – quality-adjusted life years; SoC – standard of care

Discounted QALYs for casirivimab/imdevimab are 5.76

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 6. Remdesivir and baricitinib/remdesivir were dominated by SoC due to providing no additional QALYs at an increased price. The ICER for baricitinib was below £9,000, that for tocilizumab was below £29,000.

Table 6: Low efficacy results for people who require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	22,127	4.61	-	-	-	-
Remdesivir	24,077	4.61	Dominated	-2001	-2002	Dominated
Baricitinib/remdesivir	24,339	4.61	Dominated	-2102	-2102	Dominated
Baricitinib	26,099	5.08	8470	5513	10,203	8470
Tocilizumab	28,009	4.81	28,806	-1687	354	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained

QALY – quality-adjusted life years; SoC – standard of care

Discounted QALYs for casirivimab/imdevimab are 4.76

Figure 2 summarises the NMB values assuming a threshold of £20,000 per QALY whilst Figure 3 summarises the NMB values assuming a threshold of £30,000 per QALY. All NMBs are positive in the mean and high efficacy scenarios; in the low efficacy scenario, all NMBs are negative with the exception of baricitinib at both WTP values and tocilizumab at a WTP of £30,000 per QALY.

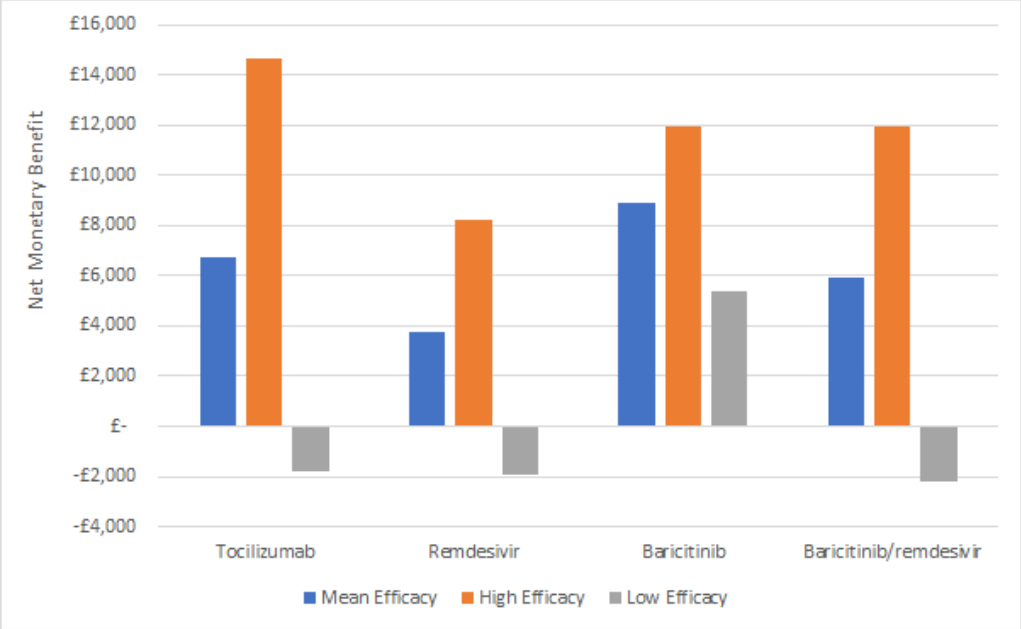

Figure 2: **Base case net monetary benefits for patients admitted to hospital who require supplemental oxygen assuming a threshold of £20,000 per QALY gained**

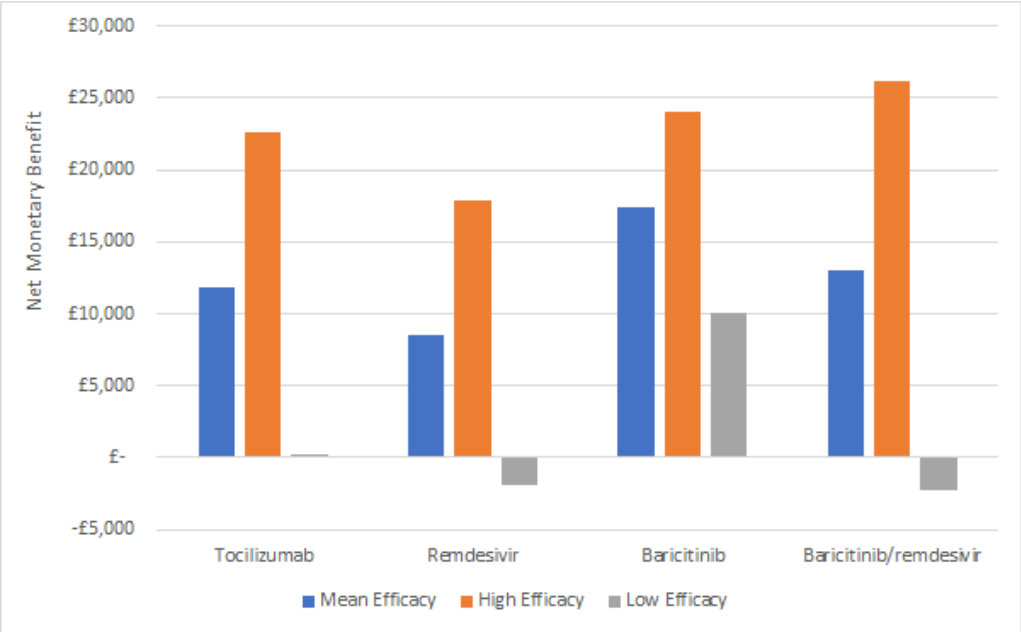

Figure 3: **Base case net monetary benefits for patients admitted to hospital who require supplemental oxygen assuming a threshold of £30,000 per QALY gained**

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 7. All interventions were estimated to have a cost per QALY gained compared to SoC below £12,000.

Table 7: Mean efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	13,316	5.79	-	-	-	-
Baricitinib	16,073	6.29	5499	7271	12,284	5499
Remdesivir	16,487	6.07	11,214	2485	5313	Dominated
Baricitinib/remdesivir	17,509	6.21	9895	4282	8519	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab are 6.18

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 8. All interventions were estimated to have a cost per QALY gained compared to SoC below £9000.

Table 8: High efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	13,316	5.79	-	-	-	-
Baricitinib	17,534	6.49	6019	9799	16,808	6019
Remdesivir	18,182	6.35	8648	6389	12,017	Dominated
Baricitinib/remdesivir	20,308	6.60	8595	9278	17,413	24,628

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab are 6.45

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 9. Remdesivir and baricitinib/remdesivir were estimated to be dominated by SoC due to producing no additional QALYs at an additional cost. Baricitinib had a cost per QALY below £6000.

Table 9: Low efficacy results for people who do not require supplemental oxygen on admission to hospital

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	13,316	5.79	-	-	-	-
Baricitinib	14, 797	6.07	5259	4279	7466	5259
Remdesivir	15,239	5.79	Dominated	-1924	-1924	Dominated
Baricitinib/remdesivir	15,477	5.79	Dominated	-2037	-2037	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab are 5.88

Figure 4 summarises the NMB values assuming a threshold of £20,000 per QALY whilst Figure 5***Error! Reference source not found.*** summarises the NMB values assuming a threshold of £30,000 per QALY. Baricitinib has positive NMBs in all scenarios. Remdesivir and baricitinib/remdesivir has positive NMBs in the mean and high efficacy scenarios but negative NMBs in the low efficacy scenario independent of the WTP assumed.

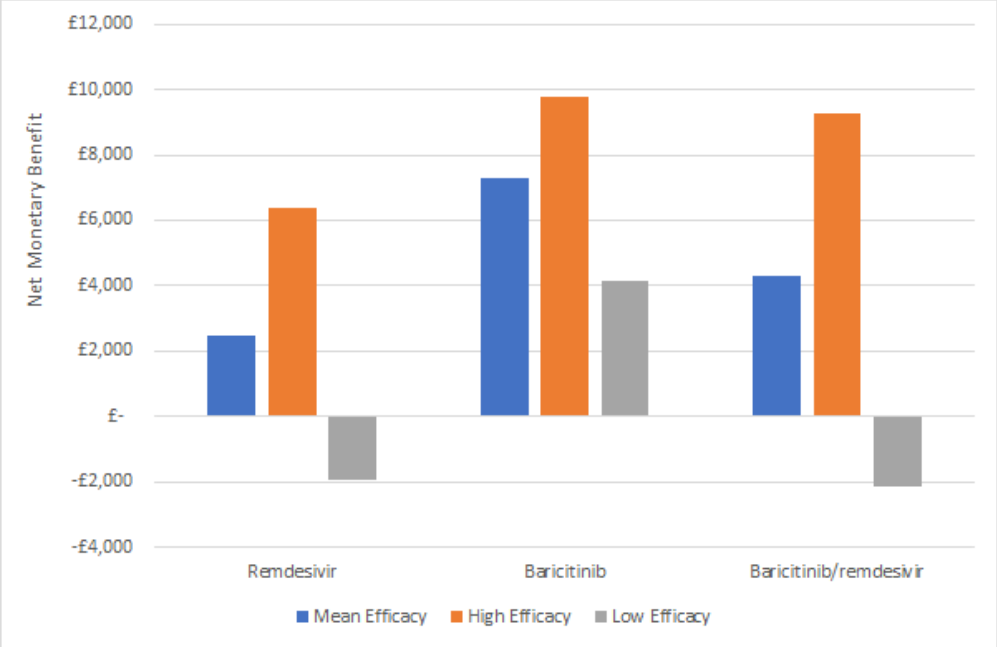

Figure 4: **Base case net monetary benefits for patients admitted to hospital who do not require supplemental oxygen assuming a threshold of £20,000 per QALY gained**

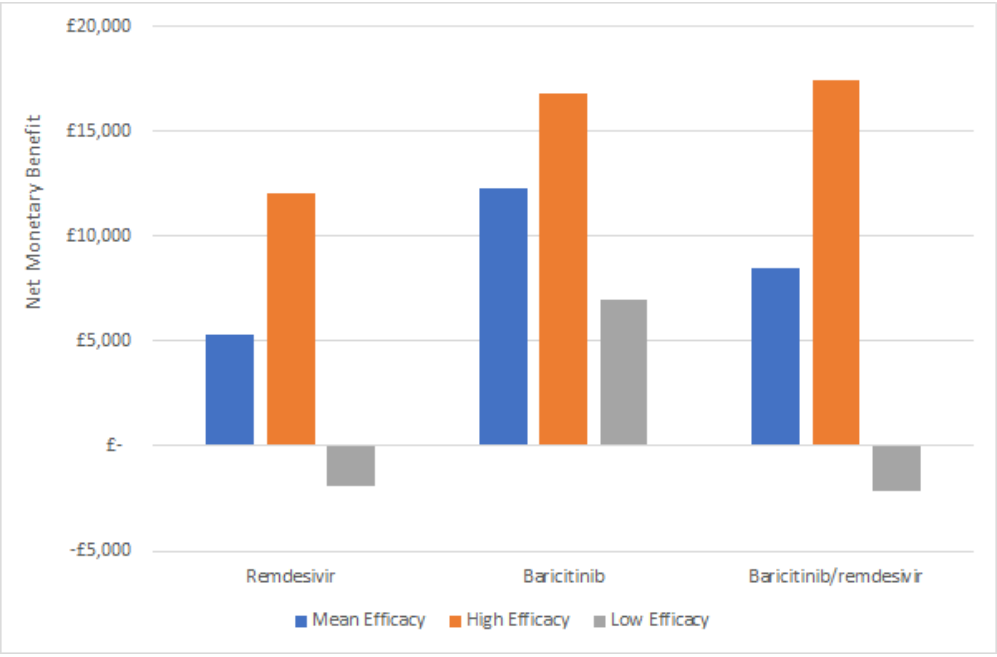

Figure 5: **Base case net monetary benefits for patients admitted to hospital who do not require supplemental oxygen assuming a threshold of £30,000 per QALY gained**

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 10. Nirmatrelvir/ritonavir was estimated to have a cost per QALY compared to SOC of below £7000 with the remaining interventions having an ICER above £30,000.

Table 10: Mean efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	1053	13.41	-	-	-	-
Nirmatrelvir/ritonavir	1805	13.53	6168	1687	2907	6168
Sotrovimab	3580	13.48	34,999	-1083	-361	Dominated
Remdesivir	4390	13.45	90,850	-2602	-2235	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.47, 13.50 and 13.43 respectively

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

The results of the high efficacy analysis for patients at high-risk of hospitalisation are shown in Table 11. Nirmatrelvir/ritonavir was estimated to have a cost per QALY compared to SOC of below £6000, sotrovimab was estimated to have a cost per QALY compared to SOC of below £19,000, and remdesivir was estimated to have a cost per QALY compared to SOC of below £25,000.

Table 11: High efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY Incremental Analyses (£)
SoC	1053	13.41	-	-	-	-
Nirmatrelvir/ritonavir	1817	13.55	5420	2055	3464	5420
Sotrovimab	3613	13.55	18,336	232	1628	Dominated
Remdesivir	4421	13.55	24,431	-611	768	Dominated

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.54, 13.54 and 13.51 respectively

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

The results of the low efficacy analysis for patients at high-risk of hospitalisation are shown in Table 12. Nirmatrelvir/ritonavir was estimated to have a cost per QALY compared to SOC of below £12,000 whilst remdesivir and sotrovimab both had ICERs of over £100,000 compared with SoC.

Table 12: Low efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	NMB compared with SoC[††] (£)	Cost per QALY Incremental Analyses (£)
SoC	1053	13.41	-	-	-	-
Nirmatrelvir/ritonavir	1817	13.48	11,009	623	1317	11,009
Sotrovimab	3686	13.44	116,505	-1673	-1447	Dominated
Remdesivir	4651	13.42	373,256	-3405	-3309	Dominated

[†] Assuming a threshold of £20,000 per QALY gained [††] Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care
Discounted QALYs for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab are 13.44, 13.43 and 13.42 respectively

Figure 6 summarises the NMB values assuming a threshold of £20,000 per QALY whilst Figure 7 summarises the NMB values assuming a threshold of £30,000 per QALY. Nirmatrelvir/ritonavir has a positive NMB in all scenarios; remdesivir has a negative NMB in all scenarios except the high efficacy scenario with an assumed WTP of £30,000; whilst sotrovimab has a positive NMB in the high efficacy scenario but negative NMBs in the mean and low efficacy scenarios independent of the WTP assumed.

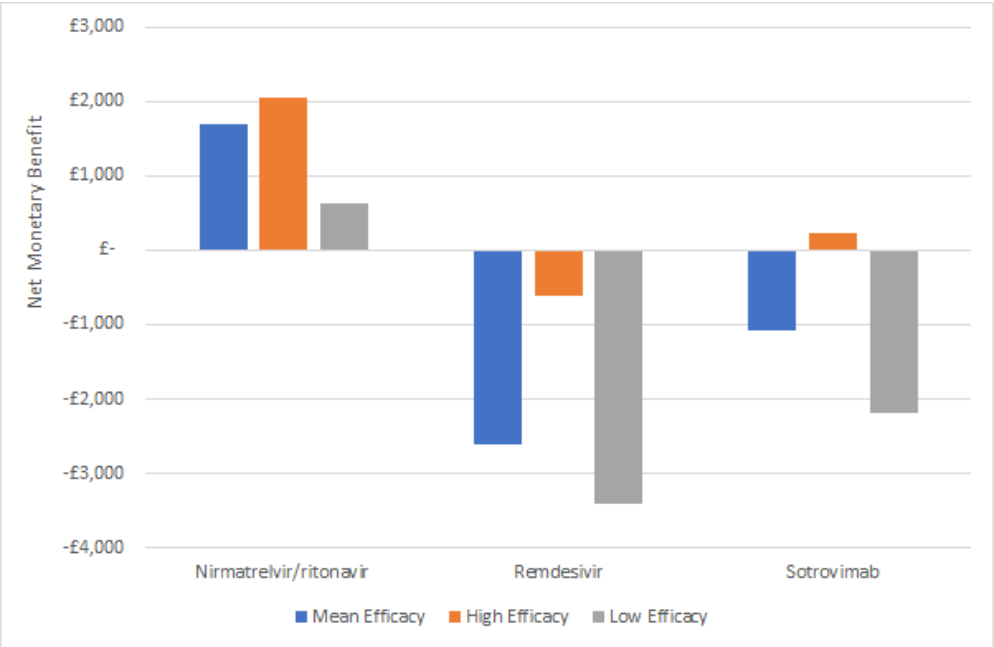

Figure 6: Base case net monetary benefits for patients with COVID-19 in the community and high-risk of hospitalisation assuming a threshold of £20,000 per QALY gained

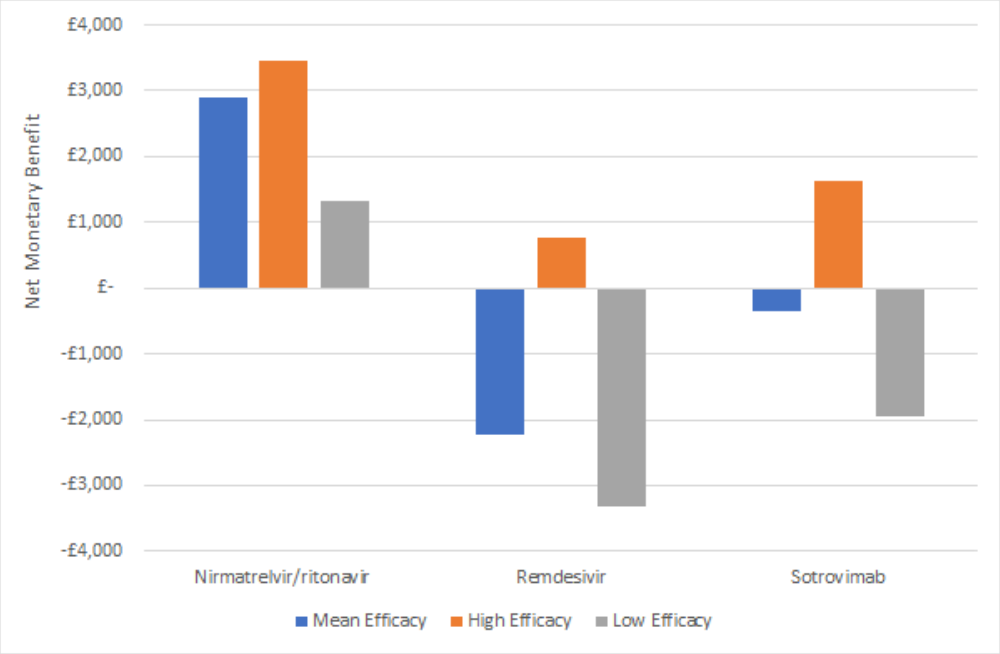

Figure 7: Base case net monetary benefits for patients with COVID-19 in the community and high-risk of hospitalisation assuming a threshold of £30,000 per QALY gained

4.4 Sensitivity Analysis Results

The seven sets of sensitivity analyses described in Section 3.4 were run. The results from these analyses should be compared with the summarised NMBs presented in Figure 2 to Figure 7.

4.4.1 Amending the duration of long COVID

The NMB results when the duration of long COVID is doubled (to 227.6 weeks) and halved (to 56.8 weeks) are shown in Figure 8, Figure 9, Figure 10 for people admitted to hospital requiring supplemental oxygen, those admitted to hospital with no need for supplemental oxygen, and those treated in the community at high-risk of hospitalisation respectively, using a WTP of £20,000 per QALY. Corresponding data using a WTP of £30,000 per QALY are shown in the Appendix (Figure 22, Figure 23, and Figure 24).

For patients in hospital, longer durations of COVID reduced NMBs, as there were more survivors with long COVID when treatment was beneficial. In contrast, NMBs were increased in patients at high-risk in the community as treatments stopped patients being hospitalised and therefore reduced the numbers assumed to have long COVID. There were one instances where the NMB had a different sign compared with the base case when the duration of COVID was changed which was for sotrovimab in the mean efficacy scenario when the duration of long covid was doubled. There was a moderate impact on the ICERs generated for hospitalised patients in the mean scenario typically changing between +/- £2000

per QALY. The impact was greater for remdesivir when used in the community although in this instance the initial ICERs were large.

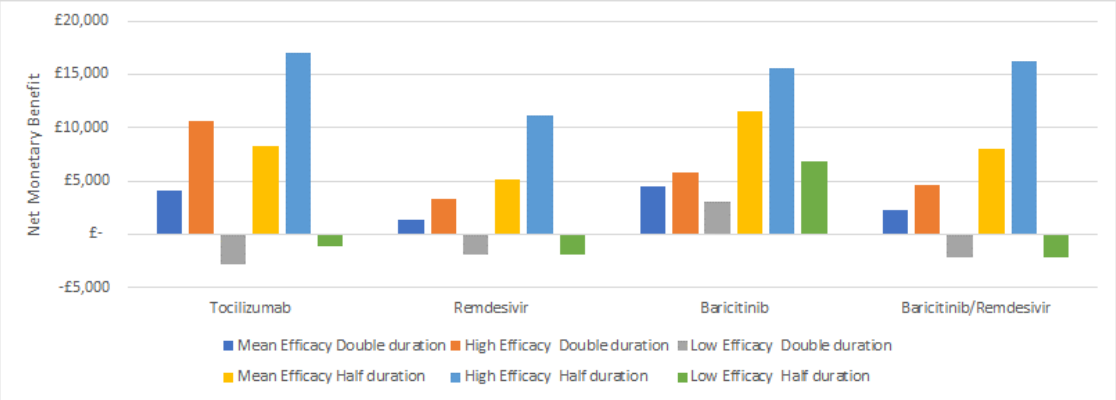

Figure 8: **The NMB results for patients admitted to hospital who require supplemental oxygen when the duration of long COVID is halved and doubled. WTP = £20,000 per QALY**

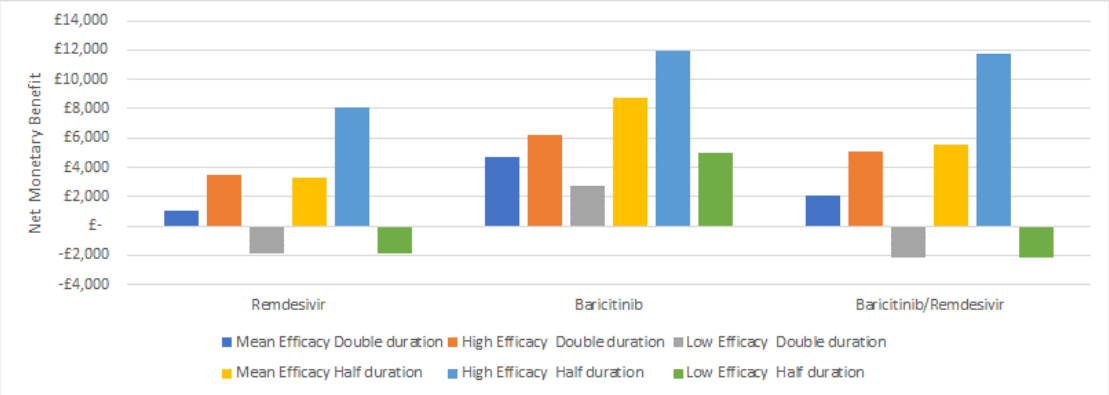

Figure 9: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the duration of long COVID is halved and doubled. WTP = £20,000 per QALY**

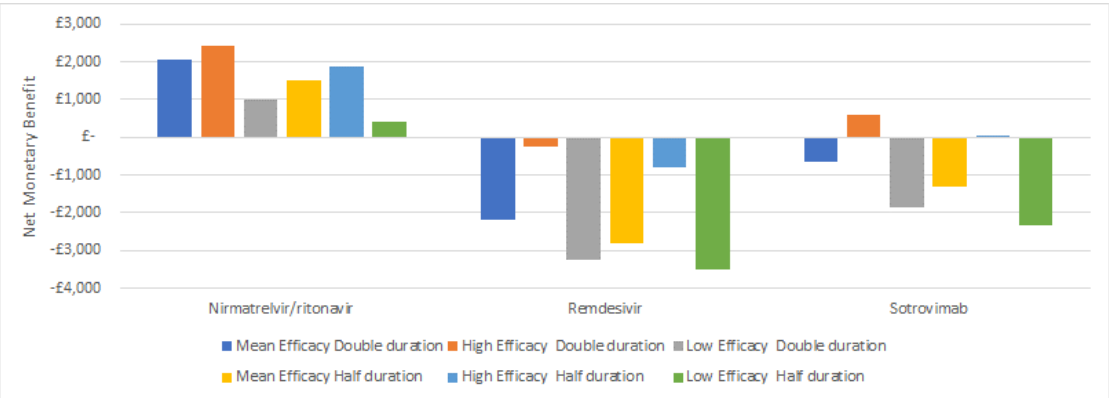

Figure 10: **The NMB results for high-risk patients in the community with COVID-19 who are at high-risk of hospitalisation when the duration of long COVID is halved and doubled. WTP = £20,000 per QALY**

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

The NMB results when the hospitalisation admission percentage for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC was changed from 2.82% to 1%, 5%, 10% and 20% are shown in Figure 11 assuming a WTP of £20,000 per QALY and in the Appendix (Figure 25) assuming a WTP of £30,000 per QALY. The proportion of patients with COVID-19 at high-risk of being hospitalised being admitted to hospital makes a large difference to the NMB with values increasing as the admission proportion increases. All interventions had a positive NMB when the proportion of patients hospitalised was increased to 10.00% and the mean efficacy scenario was used independent of the WTP assumed. Although remdesivir and sotrovimab had negative NMBs when the low efficacy scenario was used even when the admission percentage was increased to 20%. The ICERs versus SoC changed considerably based on the proportion of high-risk patients hospitalised. The ICERs when assuming 1%, 10% and 20% and the mean efficacy were: nirmatrelvir/ritonavir (£24,647, dominant and dominant) remdesivir (£280,819, £16,170 and £1512) and sotrovimab (£111,318, £4870 and dominant).

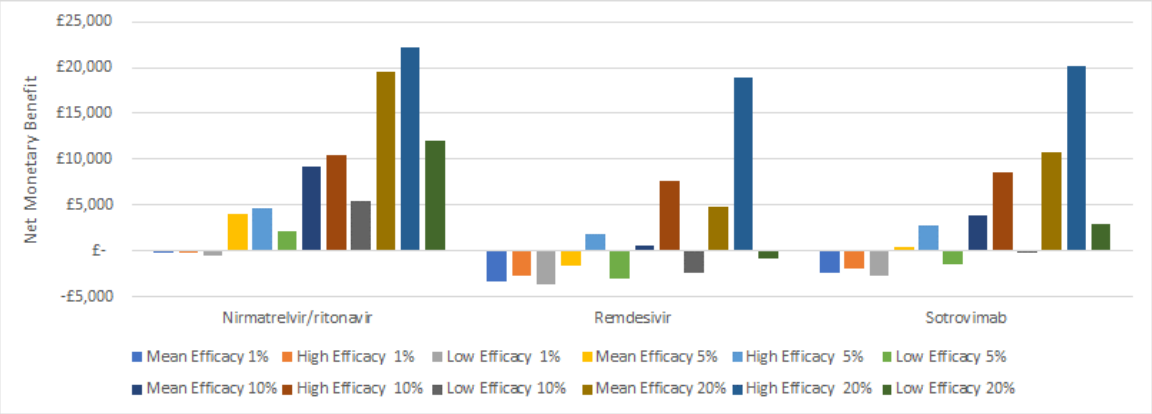

Figure 11: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the hospital admission percentage was changed. Assuming a WTP of £20,000

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

The NMB results when the age assumed for people with COVID-19 in the community at high-risk of hospitalisation treated with SoC was changed from 55 years to 50 years and 60 years are shown in Figure 12, assuming a WTP of £20,000 per QALY, Figure 26 in the Appendix shows results using a WTP of £30,000 per QALY. Where the RR of day 28 mortality is lower than 1 the NMBs decrease as the age of the patients increases because less QALYs are gained when a death is prevented. However, the EAG notes that there is no explicit link between risks of poor outcomes and age, and it is likely that all other things being equal, older patients are at a higher risk and that the results could be misleading. However, there was only a moderate impact on the ICERs generated for hospitalised patients in the mean scenario typically changing between +/- £2000 per QALY.

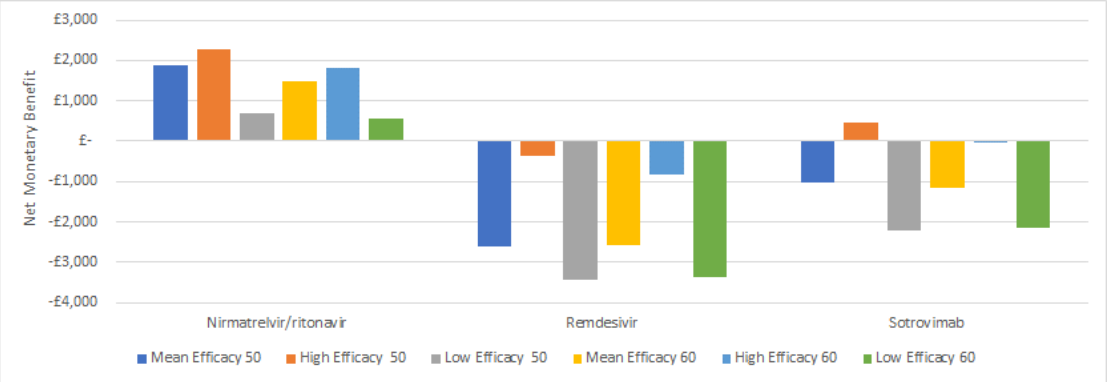

Figure 12: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the age was changed from 55 years to 50 years and 60 years. Assuming a WTP of £20,000 per QALY

4.4.4 Using a HR of unity for all interventions in relation to time to hospital discharge and time to clinical improvement

The NMB results when all interventions and SoC had the same impact on time to hospital discharge and time to clinical improvement are shown in Figure 13 for patients requiring supplemental oxygen and in Figure 14 for patients not requiring supplemental oxygen, assuming a WTP of £20,000 per QALY. Figure 27 and Figure 28 in the Appendix use a WTP of £30,000 per QALY. This sensitivity analysis did not change the patterns or the sign of the NMBs. The only noticeable change in the ICER was that for tocilizumab which increased by about £3000 compared with SoC.

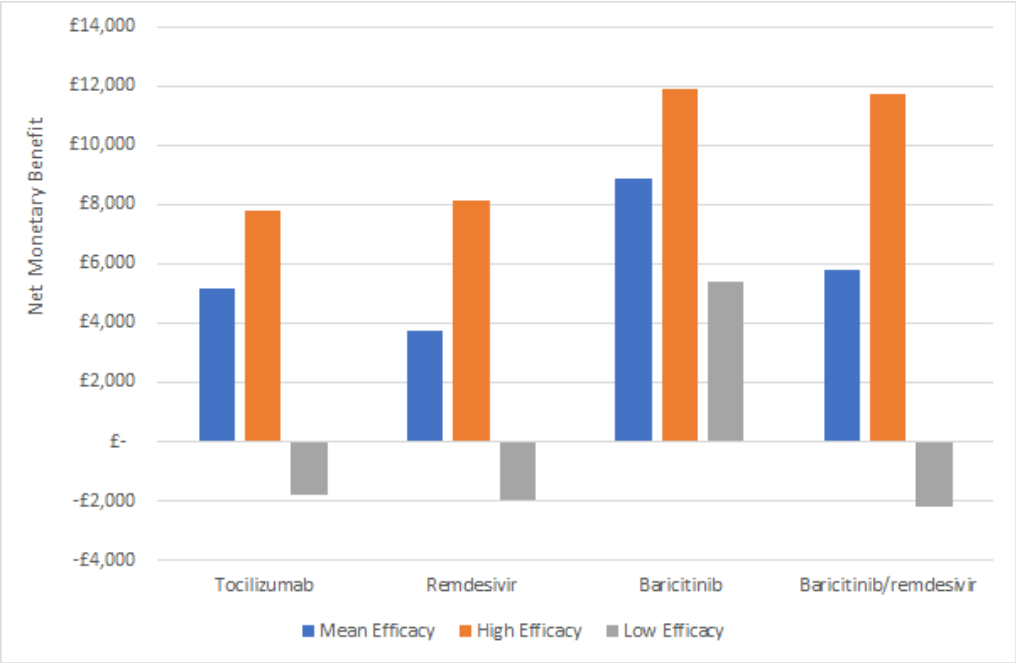

Figure 13: The NMB when a HR of unity was used for all interventions in relation to time to hospital discharge and time to clinical improvement for patients requiring supplemental oxygen. Assuming a WTP of £20,000 per QALY

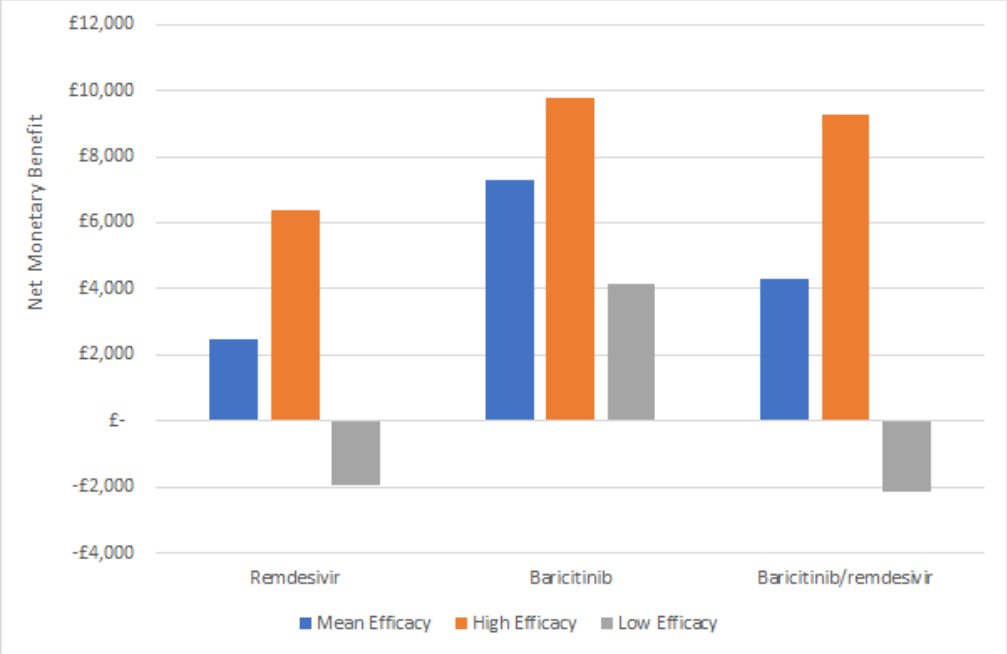

Figure 14: The NMB when a HR of unity was used for all interventions in relation to time to hospital discharge and time to clinical improvement for patients not requiring supplemental oxygen. Assuming a WTP of £20,000 per QALY

4.4.5 Changing the baseline distribution of supplemental oxygen requirements for people with COVID-19 in the community upon hospitalisation

The NMB results when the interventions were assumed to have a less severe distribution following treatment in the community are shown in Figure 15 assuming a WTP of £20,000 per QALY. Figure 29 in the Appendix provides NMBs assuming a WTP of £30,000 per QALY. This sensitivity analysis had a minor impact on the ICERs and did not change whether any NMBs were positive and negative.

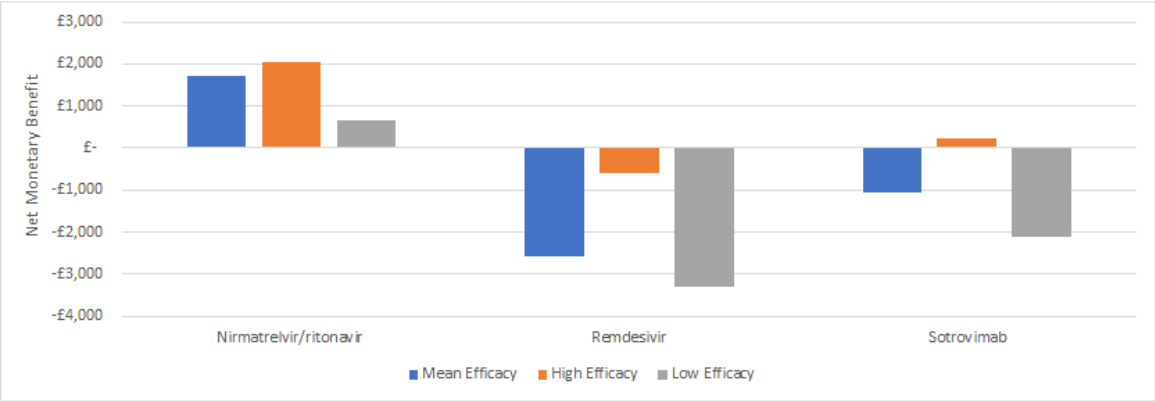

Figure 15: The NMB results when treatment in the community for high-risk patients was associated with less supplemental oxygen on admission to hospital. Assuming a WTP of £20,000 per QALY

4.4.6 Applying a utility decrement of 0.02 per day for people in the community receiving IV treatment

The NMB results when a disutility of 0.02 per day for those receiving IV treatment in the community are shown in Figure 16 assuming a WTP of £20,000 per QALY and in Appendix 3 (Figure 33) assuming a WTP of £30,000. This sensitivity analysis made no discernible change to the NMBs or ICERs.

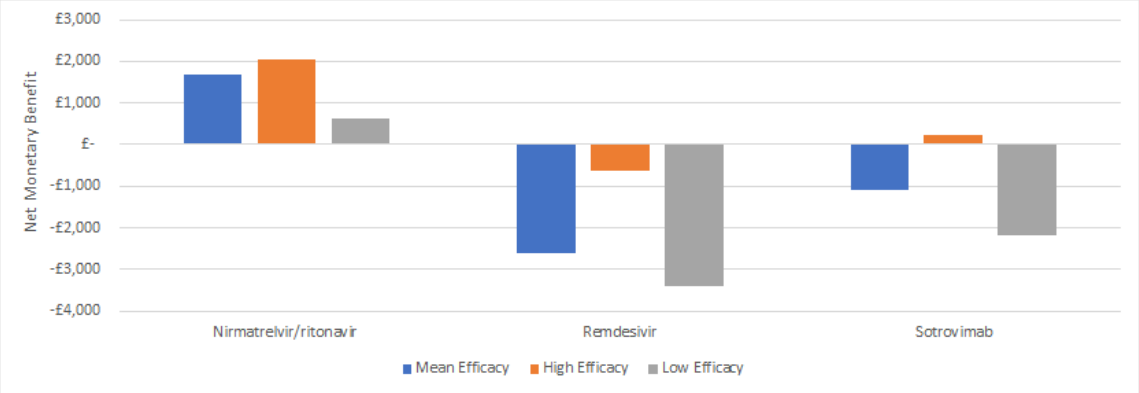

Figure 16: The NMB results when a disutility of 0.02 per day is assumed for patients receiving IV treatment in the community. Assuming a WTP of £20,000 per QALY

4.4.7 Changing the SMR for people with long COVID

The NMB results when the SMR associated with long COVID is changed from 7.7 to 5.0 and 10.0 are shown in Figure 17, Figure 18, and Figure 19 assuming a WTP of £20,000 per QALY. Figure 31, Figure 32, and Figure 33 in the Appendix provide these data assuming a WTP of £30,000 per QALY. The change in the SMR for people with long COVID had little impact on the ICERs for hospital treatments. There was a greater impact for treatments in the community, but this did not change whether an NMB was positive or negative.

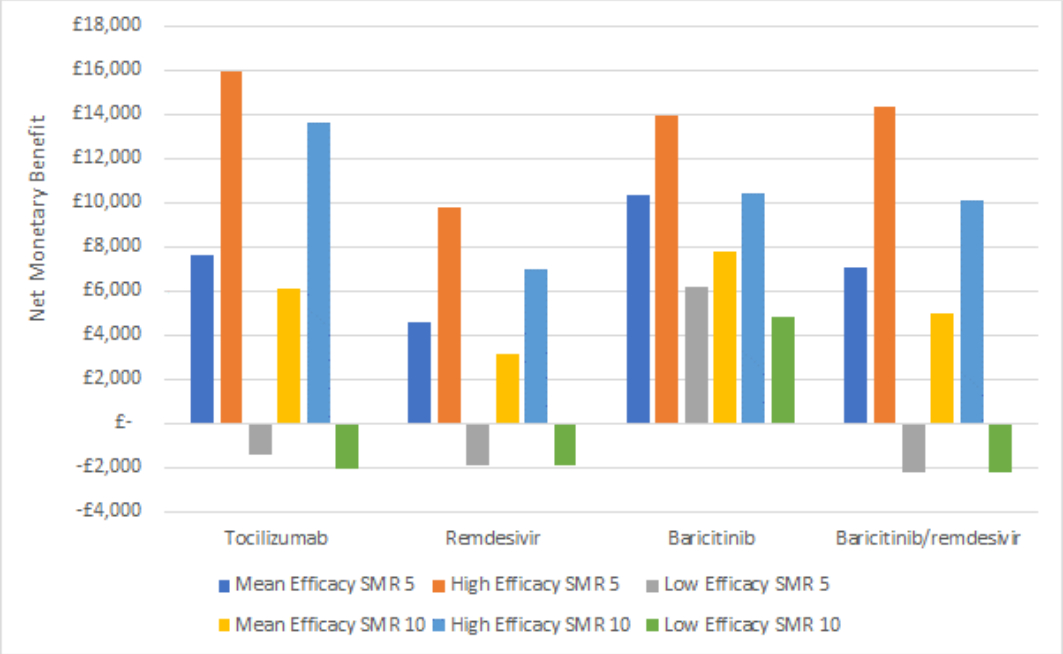

Figure 17: **The NMB results for patients admitted to hospital who require supplemental oxygen when the SMR associated with long COVID is changed. Assuming a WTP of £20,000 per QALY**

Figure 18: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the SMR associated with long COVID is changed. Assuming a WTP of £20,000 per QALY**

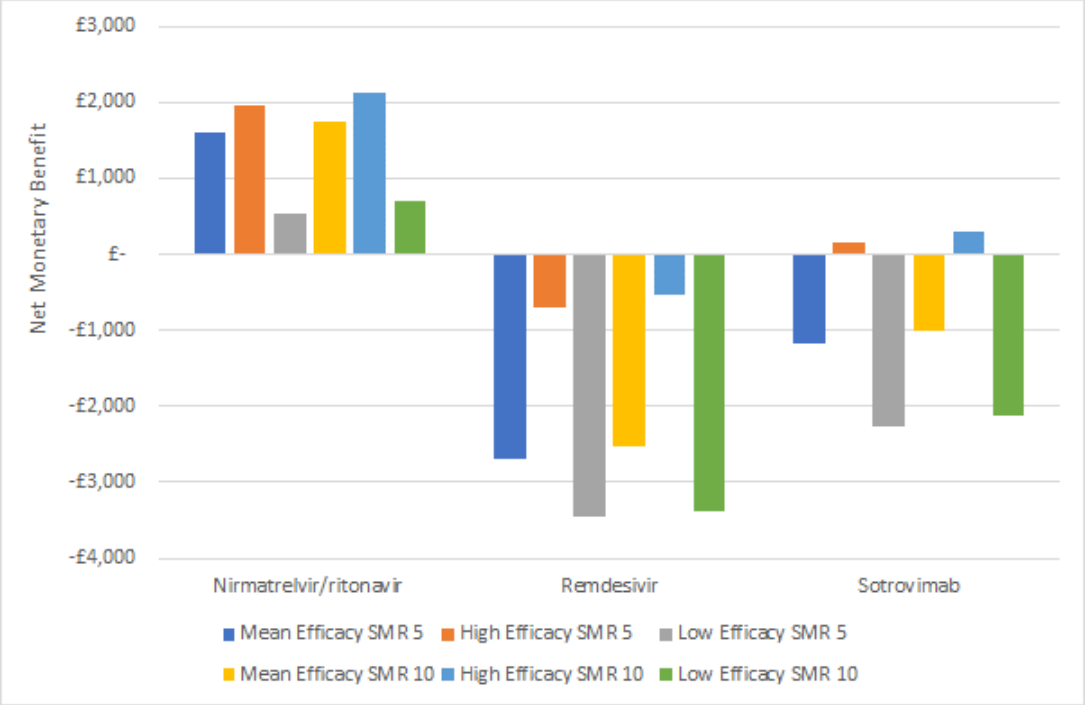

Figure 19: The NMB results for high-risk patients in the community when the SMR associated with long COVID is changed. Assuming a WTP of £20,000 per QALY

4.4.8 Remdesivir scenario analyses using Solidarity and ACTT-1 data

The NMB results when HR of time to death estimated from meta-analysis include data from Solidarity with and without RR of time to discharge from ACTT-1 are shown in Figure 20 for those who require supplemental oxygen and in Figure 21 for those that do not require supplemental oxygen assuming a WTP of £20,000 per QALY. Figure 34 and Figure 35 in the Appendix provide these data assuming a WTP of £30,000 per QALY. At the mean and high efficacy scenario, when data from Solidarity were used remdesivir had a positive NMB regardless of the WTP and oxygen status assumed. In the low efficacy scenario, remdesivir had a positive NMB regardless of the WTP and oxygen status assumed if Solidarity data and the HR for time to discharge from ACTT-1 were used. For patients requiring supplemental oxygen the ICER was £25,903 in the low efficacy scenario when only Solidarity data were used; the corresponding ICER was £34,550 for those not requiring supplementary oxygen.

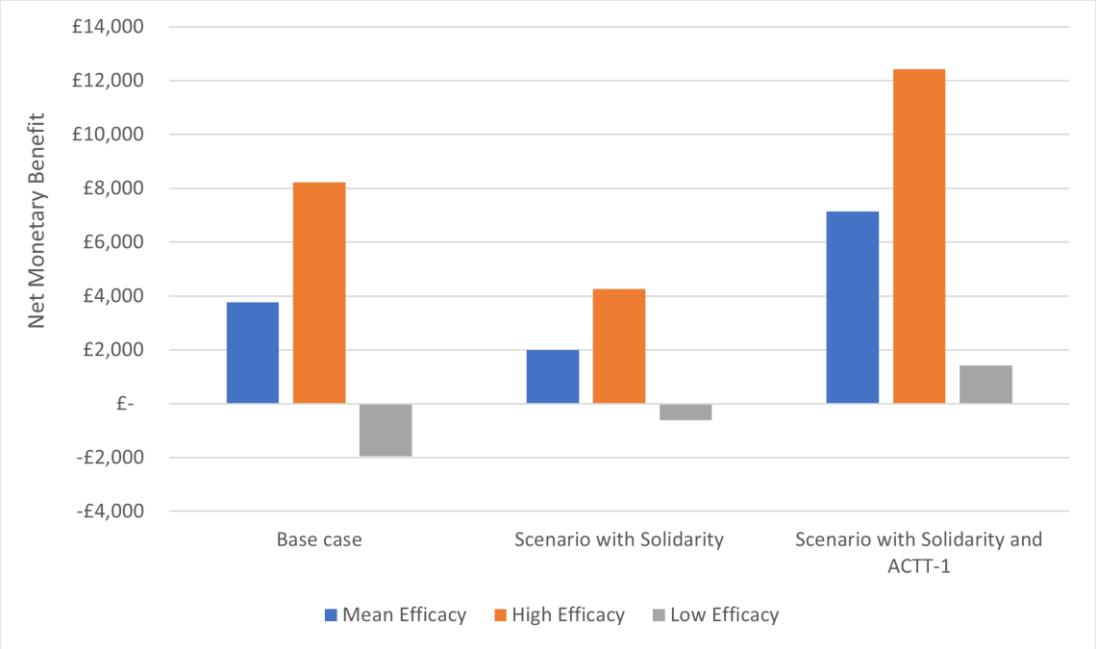

Figure 20: **The NMB for patients admitted to hospital who require supplemental oxygen when Solidarity data on time to death is used assuming a WTP of £20,000 per QALY**

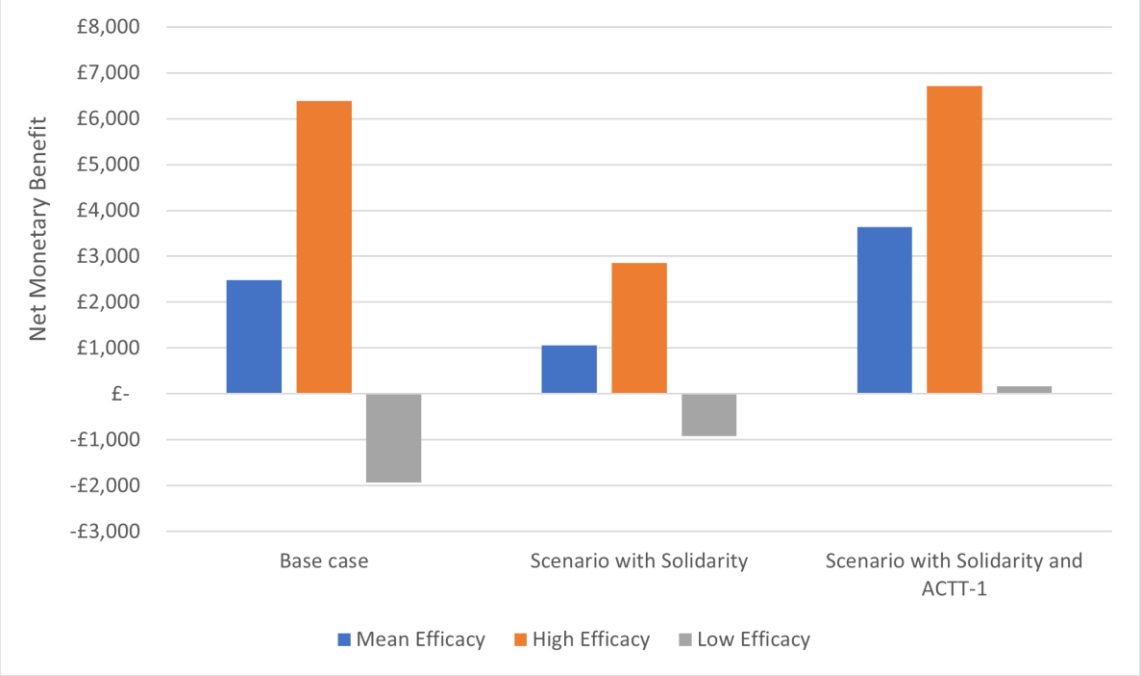

Figure 21: **The NMB for patients admitted to hospital who do not require supplemental oxygen when Solidarity data on time to death is used assuming a WTP of £20,000 per QALY**

4.4.9 Tixagevimab/cilgavimab scenario analyses using TACKLE data provided by the company for patients treated within 5 days from symptom onset

The use of 5-day outcome measures for tixagevimab/cilgavimab increased total discounted QALYs from: 13.42 to 13.43 in the low efficacy scenario; from 13.43 to 13.47 in the mean efficacy scenario; and from 13.51 to 13.55 in the high efficacy scenario.

5 Additional responses to selected comments made by consultees following the ACD

The EAG has provided responses to selected comments made by the consultees. Many comments did not warrant a response by the EAG, however, time constraints meant that not all comments have been answered. The EAG is happy to respond to any omitted comments thought to be important by the committee within the Appraisal Committee Meeting.

5.1 *Response 1: The validity of the mean, low and high efficacy scenarios in decision making*

Due to the uncertainty in efficacy of treatments associated with changing variants, vaccination status, prior infection and standard of care (SOC) the EAG provided the committee with three efficacy scenarios for each treatment: mean efficacy, high efficacy, and low efficacy. The mean efficacy would be the efficacy expected if the conditions were exactly the same as during the studies contained in COVID-NMA[5] and metaEvidence[6]. However, the high and low efficacy scenarios were for reasons of transparency and not knowing the 'true' efficacy were set to the lower and upper 95% limits of the confidence intervals of reported efficacy, respectively. The EAG has acknowledged a limitation that the confidence interval is influenced by the number of observed events and the sample size, such that two identical treatments could have markedly different confident intervals purely due to the size of the pivotal study. The EAG does not have a preferred base case as the impact of changing variants, vaccination status, prior infection and SOC are likely to affect the efficacy observed in RCTs. Real-world and in vitro evidence are discussed in Section 5.3. The EAG has maintained the three scenarios, subject to capping as detailed in Section 2.2, to inform the Appraisal Committee of the likely changes in ICERs assuming different efficacy values.

The EAG highlights that the three efficacy analyses are not intended to be a substitute for probabilistic sensitivity analyses (PSA). PSA was not run due to two reasons 1) time constraints due to the need to use Excel's SOLVER functionality in the community analyses and 2) the relative unimportance of PSA when there was such considerable uncertainty in the true efficacy values due to changing conditions. The EAG notes, however, that in the mean efficacy scenario, the mean value was used rather than the median to acknowledge the non-linearity of the distribution.

5.2 *Response 2: The limitations of COVID NMA and meta-Evidence*

The two living systematic reviews have limitations as detailed by the EAG in Section 2.1 its original report. However, the time required to undertake a full systematic review were beyond the time scales of this accelerated multiple technology assessment. The EAG has therefore continued to rely on these sources but has provided the Appraisal Committee with three efficacy scenarios (see Section 5.1) should they wish to consider alternative efficacy estimates. Two additional scenario analysis have also been run. One using data from the Solidarity study[18] to provide estimates of the efficacy of remdesivir in high-risk patients in the community and one using the TACKLE study[17] to estimate the efficacy of tixagevimab/cilgavimab if used within 5 days of symptom onset.

5.3 *Response 3: The exclusion of real-world evidence and in vitro studies*

The EAG has not formally critiqued real-world evidence or in vitro studies. Real-world data may be confounded, and/or not be representative of current conditions and the interpretation of generalising in vitro data to clinical practice is outside of the expertise of the EAG. In addition, time constraints prevented in-depth exploration. The EAG believes that the three scenarios provided to the Appraisal Committee (and discussed in Section 5.1) should cover any efficacy assumption that the Appraisal Committee may wish to consider incorporating real-world evidence or in vitro studies.

5.4 *Response 4: Potentially unintuitively higher percentage of deaths in hospital following active treatment in the community than when receiving no treatment*

In its model it was assumed, for simplicity that all deaths related to COVID-19 in high-risk people occurred in the hospital. This was because the EAG did not have information related to the proportion of deaths that occurred prior to hospital admission. The EAG needed to ensure that the assumed ratio of deaths was maintained in the model which could result in a higher percentage of deaths after admission in the treatment arm. For example, if an intervention reduced hospitalisation by 90% and reduced death by 80% then assuming 1000 people in the SoC were hospitalised and that 100 died, the numbers for the intervention would be 100 people hospitalised and 20 deaths, meaning that 1 in 10 people died in hospital in the SOC arm, compared to 1 in 5 in the treatment arm. These results may not be unintuitive if the treatment did not work in some people or may be a by-product of the EAG's assumption that all deaths occur in hospital. Whatever the reason, the EAG believes that this does not introduce noticeable bias (if any) into the analysis and ensures that the assumed efficacy in relation to hospitalisation and mortality are preserved.

5.5 *Response 5: The assumed costs of providing treatment within the community may be too high*

In its model the EAG uses costs provided by the COVID Medicines Delivery Units to NICE; these costs included elements for: staffing, administrative support, dispensing, clinical consumables, couriering medicines, travel, stationary, and hiring rooms, but excluded medical review to assess drug interactions and any changing in permanent staffing structures. Commentators suggested that these costs (of £410 per person receiving oral antivirals and £820 per person receiving intravenous infusions) were too high and that these costs would decrease as time progress, particularly so if antivirals were provided in primary care. One commentator suggested values of £75 based on a 1-hour medical review from a band 8a pharmacist or £117 based on the average cost per resident of the multi-professional medication review intervention.

The EAG has received no further information on the costs of administration of treatment in the community and has maintained the values in the original report – however, should the committee believe that an alternative value is more appropriate, then this can be adjusted for within the net monetary benefit (NMB) approach used by the EAG or by changing the incremental costs within the ICER. For example, if the Appraisal Committee decided that the true costs of providing oral treatment was £110, then the NMB of the treatment would be increased by £300; alternatively, incremental costs could be reduced by £300 and a new ICER calculated by the Appraisal Committee.

5.6 *Response 6: That the costs of administering nirmatrelvir/ritonavir in the community may be underestimated due to the complications associated with contra-indications and drug-drug interactions*

Commentators suggested that the costs of administering nirmatrelvir/ritonavir in the community should be higher than for other oral antivirals due to the greater number of drug-drug interactions. The EAG has not changed the relative administration costs, but highlights that should the Appraisal Committee wish to add additional costs for administering nirmatrelvir/ritonavir in the community then the methodology described in Section 5.5 would apply.

5.7 *Response 7: Accessing more recent data on the prevalence of long COVID*

Whilst there was an updated document related to the prevalence of long COVID (July 2022[19] rather than May 2022[12]) these data did not substantial alter the EAG's conclusions and the assumption that 10% of people have long COVID in the community was maintained.

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7 Appendix – NMB results assuming £30,000 per QALY

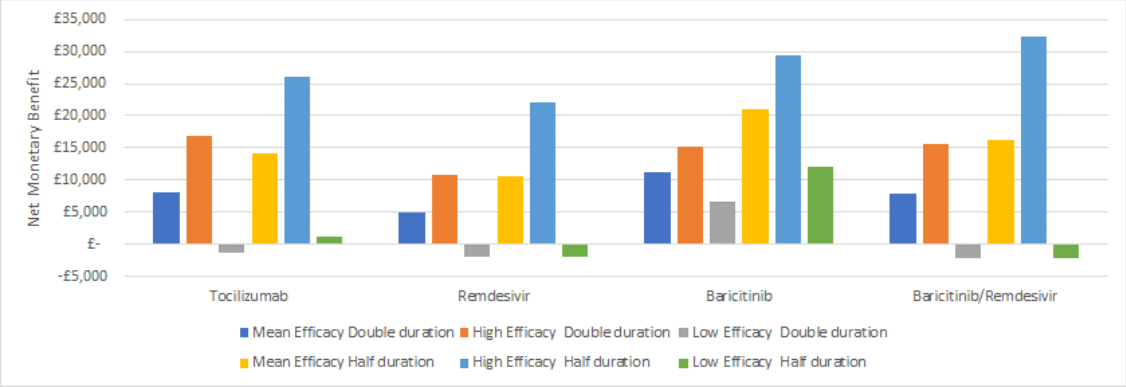

Figure 22: **The NMB results for patients admitted to hospital who require supplemental oxygen when the duration of long COVID is halved and doubled. Assuming a WTP of £30,000**

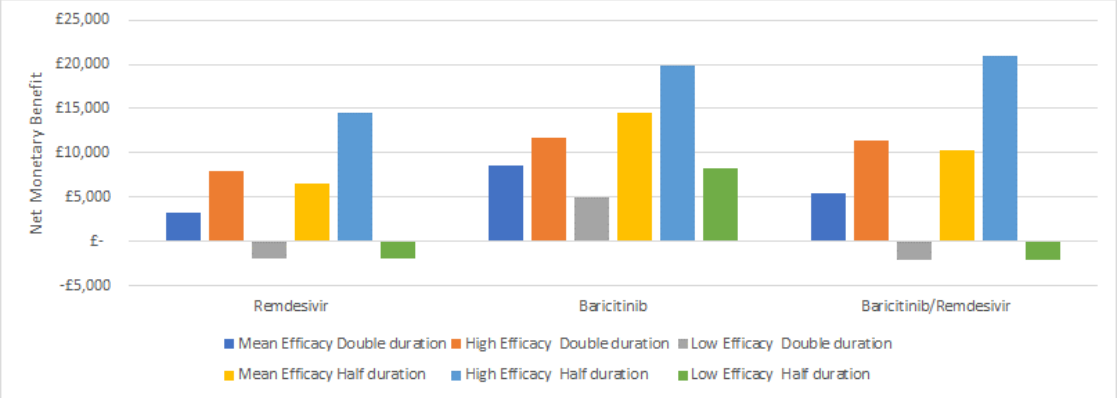

Figure 23: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the duration of long COVID is halved and doubled. Assuming a WTP of £30,000**

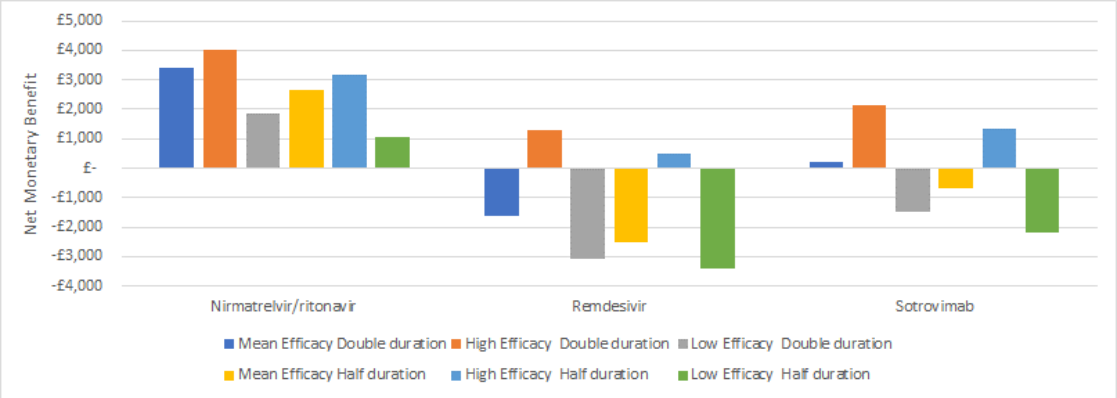

Figure 24: **The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the duration of long COVID is halved and doubled. Assuming a WTP of £30,000**

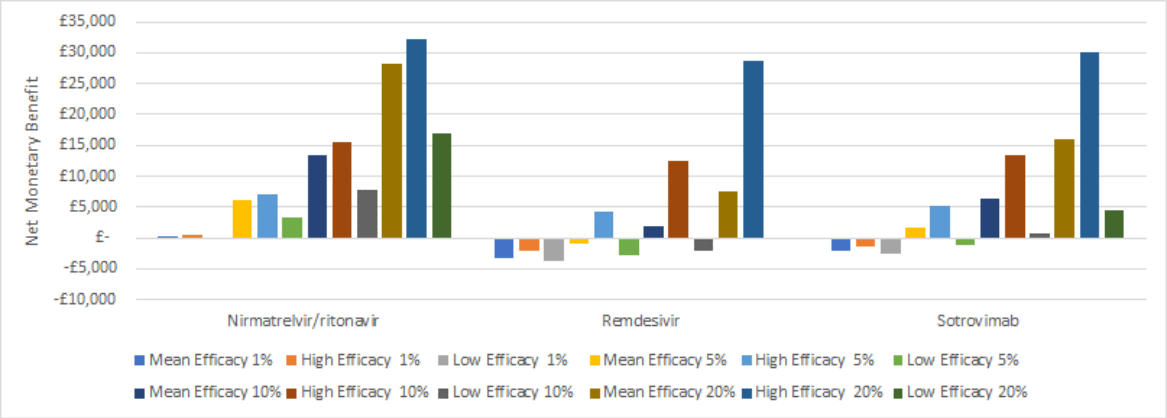

Figure 25: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the hospital admission percentage was changed. Assuming a WTP of £30,000

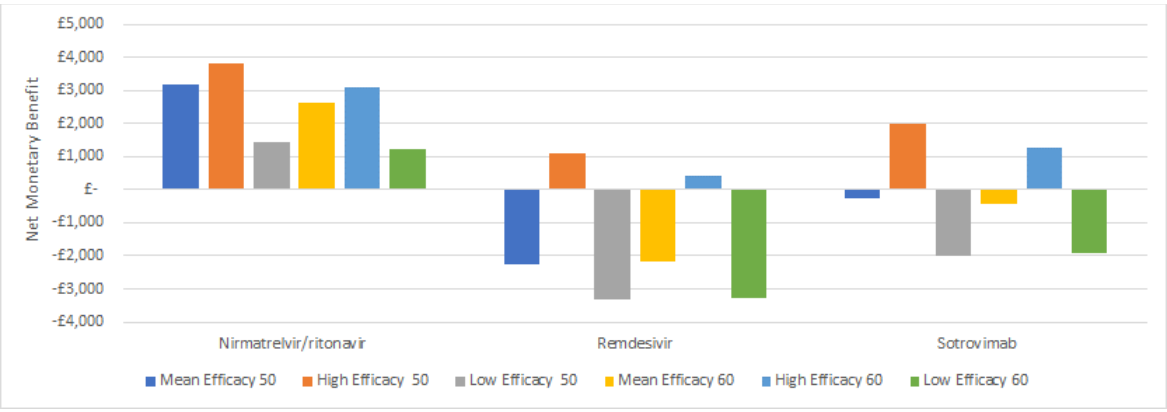

Figure 26: The NMB results for patients in the community with COVID-19 who are at high-risk of hospitalisation when the age was changed from 55 years to 50 years and 60 years. Assuming a WTP of £30,000 per QALY

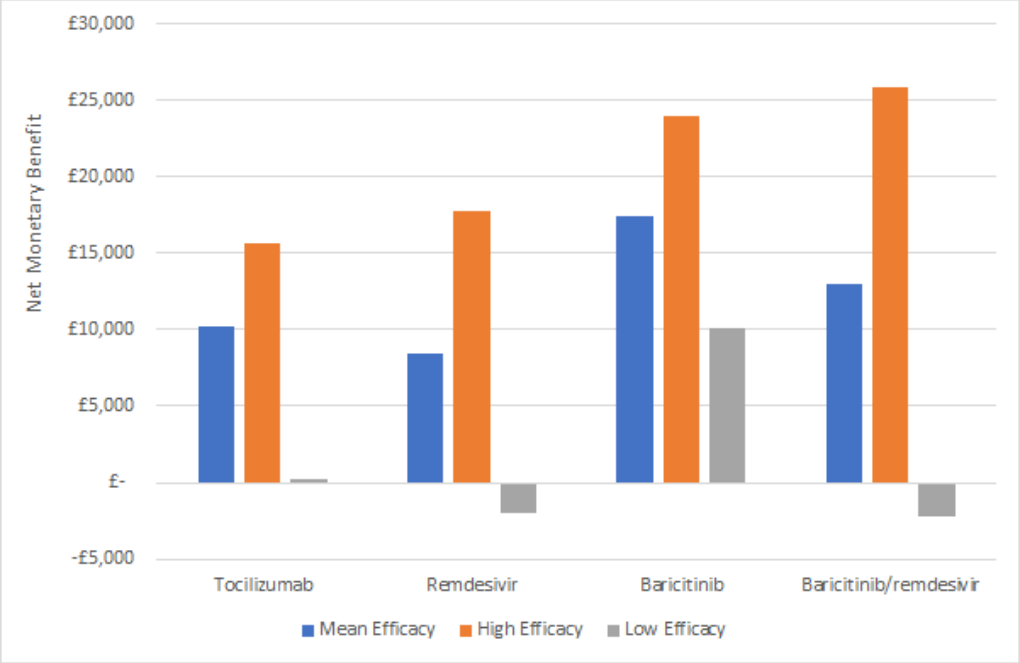

Figure 27: **The NMB when a HR of unity was used for all interventions in relation to time to hospital discharge and time to clinical improvement for patients requiring supplemental oxygen. Assuming a WTP of £30,000 per QALY**

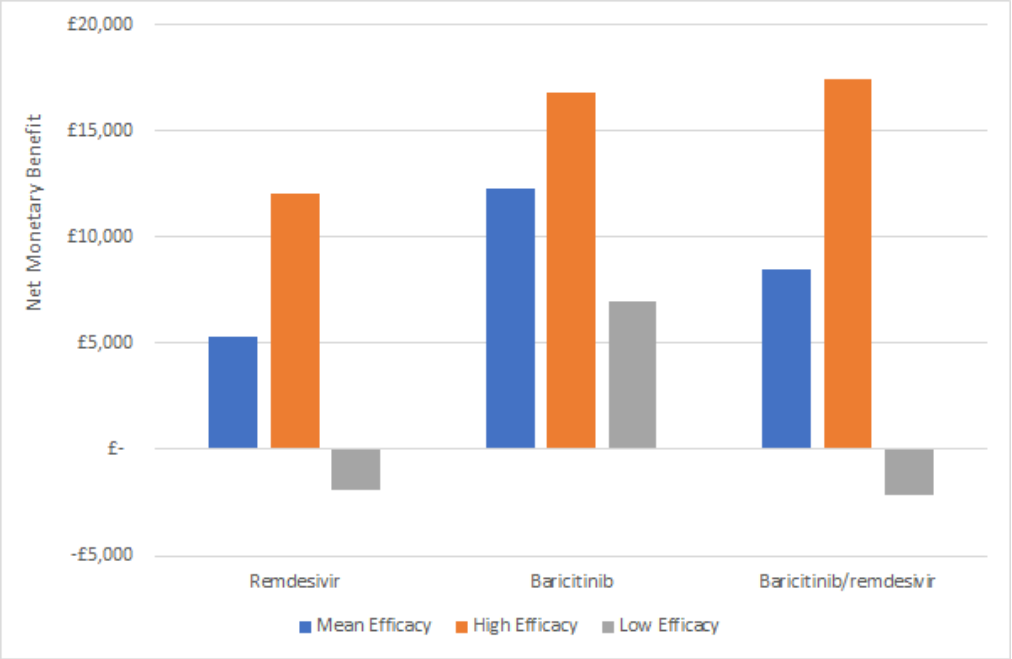

Figure 28: **The NMB when a HR of unity was used for all interventions in relation to time to hospital discharge and time to clinical improvement for patients not requiring supplemental oxygen. Assuming a WTP of £30,000 per QALY**

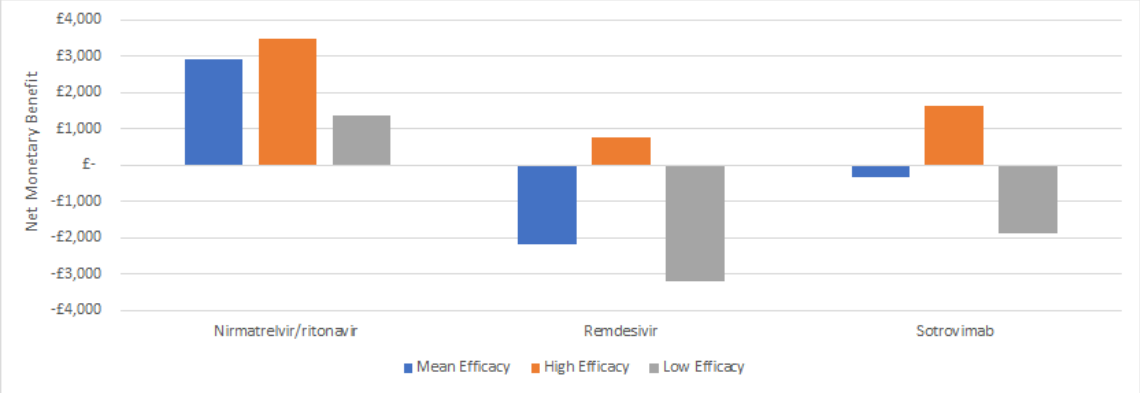

Figure 29: **The NMB results when treatment in the community for high-risk patients was associated with less supplemental oxygen on admission to hospital. Assuming a WTP of £30,000 per QALY**

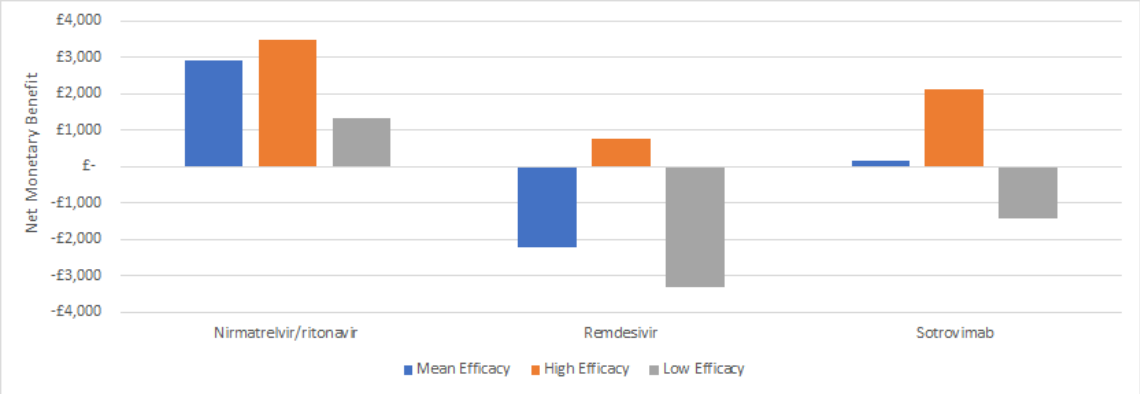

Figure 30: **The NMB results when a disutility of 0.02 per day is assumed for patients receiving IV treatment in the community. Assuming a WTP of £30,000 per QALY**

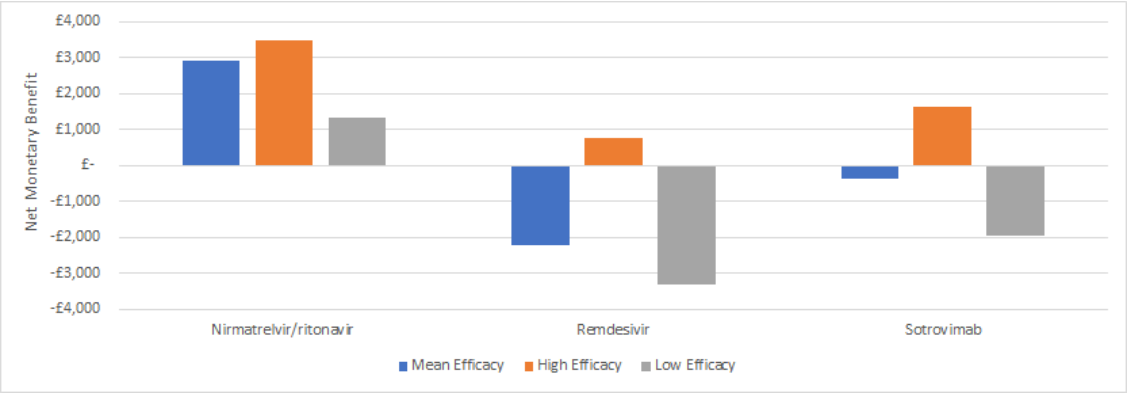

Figure 31: **The NMB results for patients admitted to hospital who require supplemental oxygen when the SMR associated with long COVID is changed. Assuming a WTP of £30,000 per QALY**

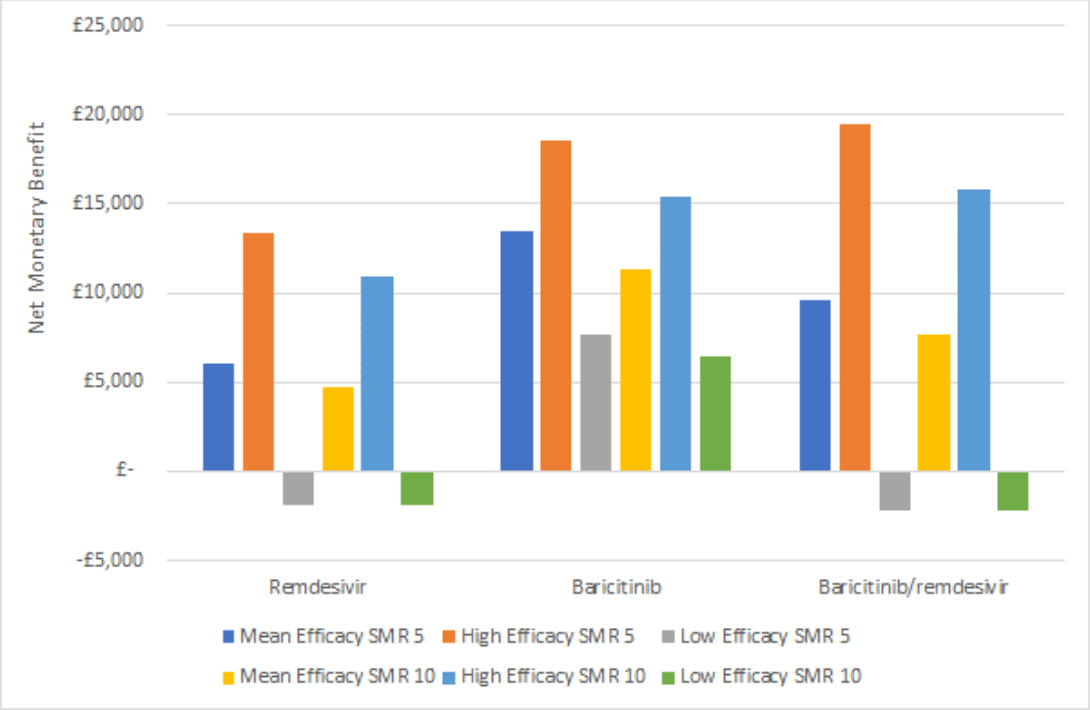

Figure 32: **The NMB results for patients admitted to hospital who do not require supplemental oxygen when the SMR associated with long COVID is changed. Assuming a WTP of £30,000 per QALY**

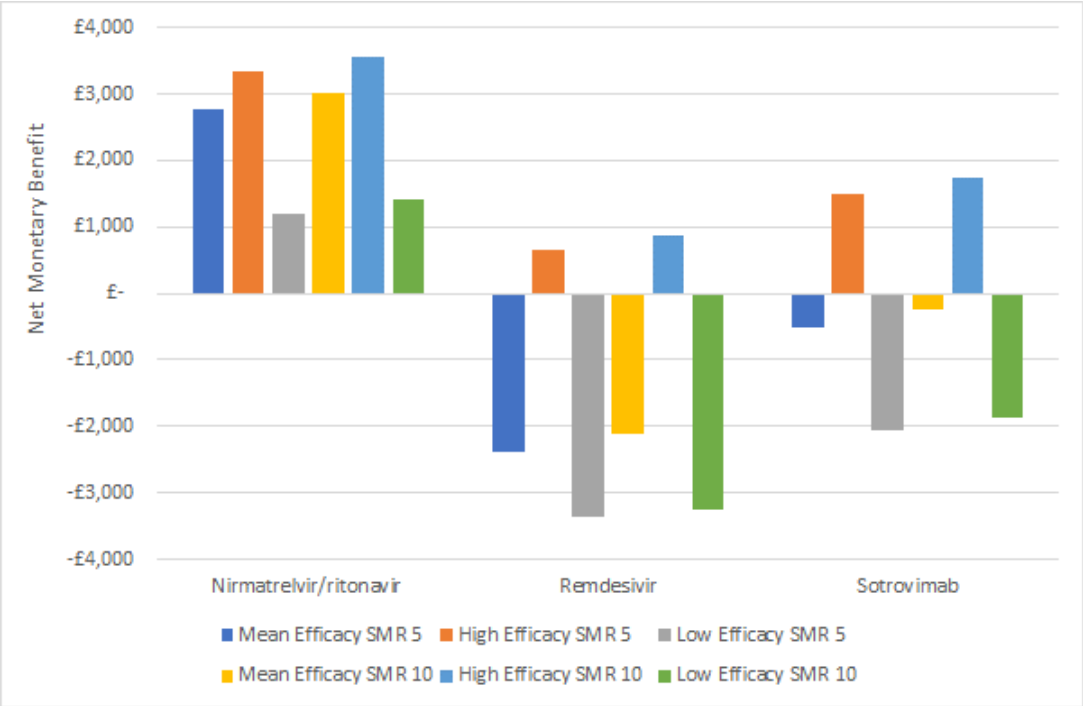

Figure 33: **The NMB results for high-risk patients in the community when the SMR associated with long COVID is changed. Assuming a WTP of £30,000 per QALY**

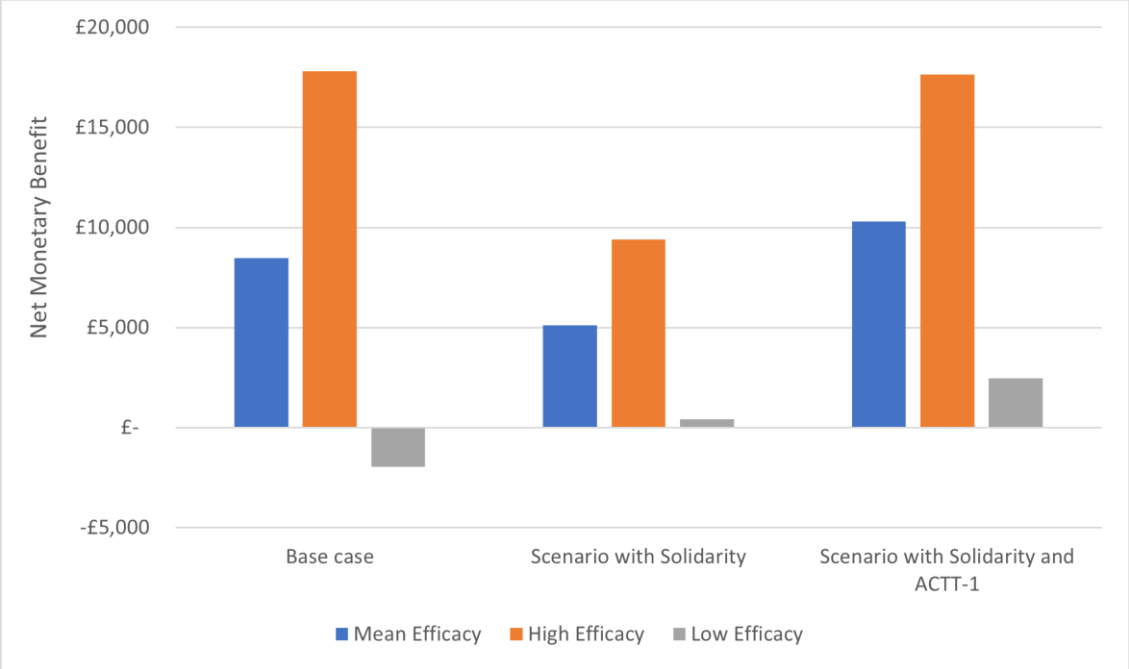

Figure 34: The NMB for patients admitted to hospital who require supplemental oxygen when Solidarity data on time to death is used assuming a WTP of £30,000 per QALY

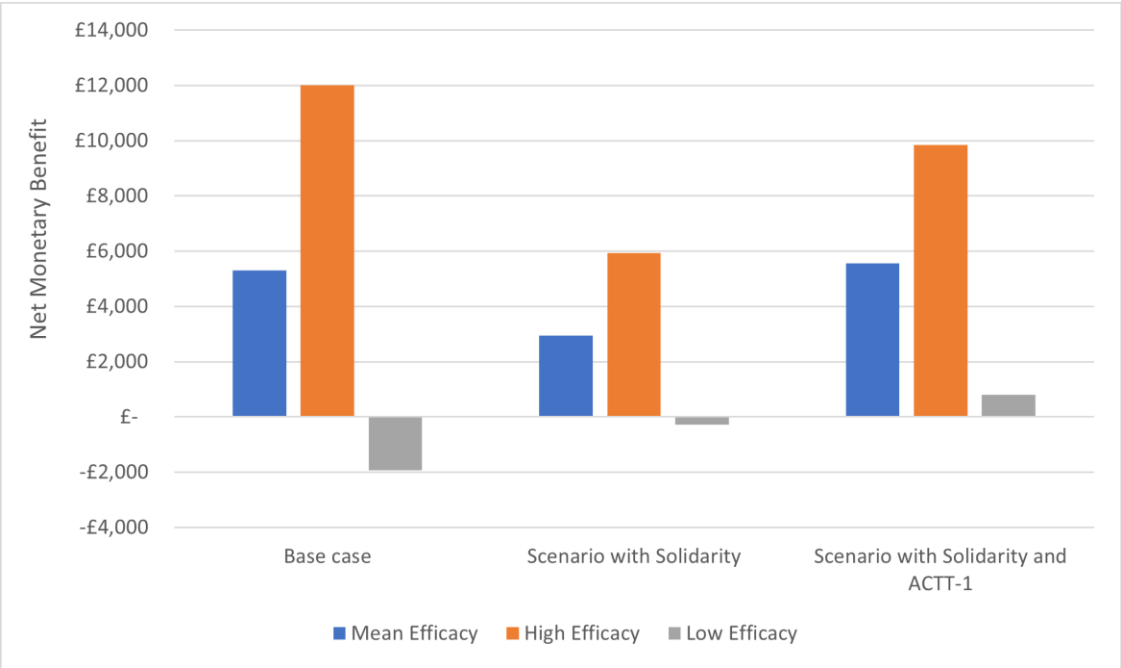

Figure 35: The NMB for patients admitted to hospital who do not require supplemental oxygen when Solidarity data on time to death is used assuming a WTP of £30,000 per QALY