National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Therapeutics for people with COVID-19 [ID4038]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

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Appropriateness	Eli Lilly and Company Limited	Yes, this is an appropriate topic to refer to NICE for multiple technology appraisal.	Thank you for your comment. No action needed.
	Gilead Sciences	We believe it is appropriate to refer this topic for appraisal, but that this topic has a number of unique features which may challenge NICE's methods and processes, and therefore that efforts should be made to ensure the methods and processes applied are flexible enough to manage the characteristics of this appraisal. Specifically, COVID-19 presents a rapidly changing landscape with emergence of different variants, changing vaccination landscape, rapid growth of clinical and real-world evidence, as well as evolving clinical commissioning guidelines. Therefore, Gilead believes it will be appropriate for NICE to consider a more collaborative approach with companies by, for example, facilitating access to relevant non-company sponsored data, including additional technical engagement steps to the standard process, and providing greater clarity around the scope of the evaluation.	Thank you for your comment. This work will be of importance when managing COVID-19 becomes a routine part of NHS work, plausibly towards the end of 2022. As a technology appraisal takes 6 to 9 months to produce draft recommendation it is appropriate to begin the scoping exercise.

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		The interventions being assessed in this MTA underwent clinical trials during different stages of the pandemic, meaning they were assessed against different COVID variants and in populations with differing levels of vaccination and differing levels of vaccine-driven immunity (given it wanes with time). It is impossible to foresee the future effectiveness of interventions that target the virus directly (both the anti-viral class and the neutralising antibody class) – indeed interventions that currently are not effective against Omicron could be highly effective against future variants. Therefore, Gilead believes NICE should review cost effectiveness using the assumption that future clinical effectiveness matches that seen in the key clinical trials. As each new variant arises, and vaccine/booster is rolled out, the NHS will then need to make an assessment as to which interventions retain clinical effectiveness and should thus be utilised at that time.	The scope has been updated to acknowledge the impact of variant-specific treatment efficacy. The assessment group are taking a pragmatic approach to solve data limitations. Potential methods to overcome data limitations, include implementing sensitivity analysis and scenario analysis. Discrete time points for analysis could also be implemented.
	GlaxoSmithKline	Yes	Thank you for your comment. No action needed.
	Humanigen, Inc.	Yes.	Thank you for your comment. No action needed.
	Merck Sharp & Dohme (UK) Limited	MSD would like to thank NICE for the opportunity to participate in this Scoping process. MSD would like to express its concern regarding undertaking a Multiple Technology Appraisal (MTA) of COVID-19 therapeutics at this time. We are concerned that the data necessary to make robust recommendations are not yet available. We are particularly concerned that any recommendations will	Thank you for your comment. This work will be of importance when managing COVID-19 becomes a routine part of NHS work, plausibly

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		not remain relevant given that MTAs routinely take many months to complete. Any NICE recommendations may have global influence. We are therefore concerned that such influential recommendations only be made following appropriate assessment, rather than risk future evidence based recommendations in the UK and globally by making recommendations too soon, with too incomplete evidence. MSD considers the proposed timing for this appraisal, which is aimed at exploring the clinical effectiveness and cost-effectiveness of COVID-19 related therapeutics, to be inappropriate. We are still in the pandemic phase and it remains uncertain how the trajectory of the disease and therefore infection rates will evolve over time. Pivotal RCTs and additional studies generating relevant data (see PANORAMIC trial) are ongoing [i]. Similarly, data on the effectiveness over time of vaccines, antivirals and monoclonal antibodies against different variants is unknown. The impact of herd immunity and vaccination rates in the community, on novel variants, is unknown and the impact of those that are vaccinated but do not mount an immune response on transmission and severity of disease is not clear. As our understanding of this pandemic evolves it becomes clear that the current evidence is simply insufficient to support a robust NICE appraisal. Guidance issued by NICE needs to remain relevant. At this stage any NICE final recommendations based on the current evidence base, is likely to become obsolete shortly after publication. It is possible the recommendation will be obsolete before the process is completed. MSD is currently unclear as to the phase of virus transmission being modelled (pandemic, epidemic or endemic). This requires more clarity since it has implications for the assessment of clinical effectiveness and cost-effectiveness of therapies. The COVID-19 pandemic is rapidly evolving in the UK and globally (with the emergence of new variants and therefore new clinical evidence). The usual HTA methods, relying on currently available data, cannot be used at this time	towards the end of 2022. As a technology appraisal takes 6 to 9 months to produce draft recommendation it is appropriate to begin the scoping exercise. The model will be flexible and as new data are made available an option to include them in the model will be made. Clinical effectiveness evidence will be based on publicly available living network analyses, ensuring the data are as up to date as possible. However, the model design and functionality will need to be built in advance to ensure comments on its appropriateness could be made. Guidance on the use of the treatments will be for use in an endemic situation, but the

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		to conduct a robust assessment, given how quickly the situation and therefore the resultant data are changing. The only available data focus on the pandemic phase of COVID-19. There is no clear consensus at this stage as to when an endemic phase will be reached, its frequency, severity and transmissibility of variants or any risk factors that may influence these in part. Considerations for future pandemic preparedness in the likelihood of new COVID-19 variants and the need to retain access to molnupiravir to mitigate against risk of future coronavirus-like pandemics. Standardisation around the management of new variants and selective pressure considerations alongside the measurement of efficacy of current antivirals and monoclonal antibodies (mAbs) is lacking, which prevents a robust HTA process. To understand the pathogenesis of SARS-CoV2 infection in more detail more genomic data are currently being collected that will better guide the use of antivirals and what the public health programmes should look like. The RAPID C-19 multi-agency initiative was developed to ensure rapid access to innovative, safe, effective and promising COVID-19 therapeutics, due to the public health urgency. This process is based on current evidence base which is insufficient for a full HTA assessment. More input from the COVID-19/SAGE Task Force to understand the appropriate roll out of antiviral agents that have received a conditional marketing authorisation (CMA) in the UK is needed. Therefore, wider data sets are needed to fully understand how to implement the current antiviral drugs in the endemic phase alongside the nationally deployed COVID-19 vaccines. Further understanding is required around the data generation activities in the UK (e.g. PANORAMIC clinical trial)[i] to understand how these could be leveraged into the decision-making process. Further consideration should be given to companies accessing these data at an aggregate level to leverage in a future HTA process if this warranted at a later stage.	recommendation would need to be mindful of use of treatments in a pandemic situation. The assessment group is taking a pragmatic approach to solve data limitations. Potential methods to overcome data limitations, include implementing sensitivity analysis and scenario analysis. Discrete time points for analysis could also be implemented.

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		MSD's perspective is that the level of maturity of the data necessary for a robust decision-making purposes is not yet available across comparators listed in the draft scope. Early initiation of this process risks reaching obsolete recommendations. Key data uncertainties would mean that a set of assumptions will need to be employed for decision making purposes that may disadvantage technologies. Data relevant for each of the comparators in an endemic phase is currently lacking. The comparability and exchangeability of these products is currently unknown, and this is apparent when new evidence emerges with regards to the effectiveness of antivirals and mAbs for new variants over time and the impact of these on the national vaccination programmes. At the same time, all of these therapies constitute the current standard of care in the UK NHS. Trial population differences, outcomes collected, different stages at which the clinical studies were conducted during the pandemic (including variant circulation) severely impact any indirect treatment comparisons that may be necessary for decision making purposes. Further, differences in tolerability cannot by definition be robustly synthesised with the exception of qualitative comparisons and this may disadvantage all technologies during the assessment process. Treatment options under different circumstances/different patient characteristics is currently unknown: co-admin/monotherapy/responders non-responders/ worsening disease/community treatments/hospital treatments In relation to further data generation, we are aware that the PANORAMIC study is currently recruiting and that it may provide more evidence for a more robust HTA assessment; not waiting for that study to read out would require sufficient resource dedication from NICE (potentially directing these from the rest of the Technology Appraisal Guidance [TAG] programme) and may risk recommendations that may not be relevant once the HTA process concludes. More clarity is required as to what constituted Established Clinical standard of care (SoC) at this stage across hospitalised and non-hospitalised patients. This has serious implication for decision making purposes.	Any clinical effectiveness evidence is based on publicly available living network analyses, ensuring the data are as up to date as possible. The risk of progressing to severe COVID-19 is based on the characteristics from key clinical trials and feed into the risk calculations used in the model. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care, which is routinely

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		NICE requires comparison against SoC, however, to our knowledge all of these treatments listed currently constitute the SoC. The methodological question therefore remains as to how the HTA process could be conducted at this instance. MSD disagrees with NICE's proposal to leverage the MTA process to assess the clinical effectiveness and cost-effectiveness of innovative COVID-19 related therapeutics at this stage. An MTA process may experience prolonged timelines at this stage given the extent of data gaps and should therefore not be currently initiated. MSD's position is that it is simply too soon to conduct an MTA. In the interim, the RAPID C-19 Initiative has acted as the basis for temporary market access of novel COVID-19 therapeutics in the UK NHS. The MTA process goes beyond the RAPID C-19 initiative and therefore, it is important to determine that RAPID C-19 policies will not be undermined leading to confusion. The MTA process is not designed for parallel assessment of multiple technologies which do not necessarily have interchangeable marketing authorisations or trial populations as in the case of COVID-19 therapeutics. In particular, all of the proposed technologies are the SoC at this stage, the treatment pathway is rapidly evolving with both new data on the available therapies, new therapies and the new variants that impact the effectiveness of vaccines and mAb as well as the evolving vaccination rates that affect community disease rates and outcomes likely until we are fully in an endemic phase, and finally, our inability to compare therapies due to lack of real-world evidence (RWE) and the fact that indications/trial populations are not comparable. The MTA process is inflexible and unable to capture wider considerations for COVID-19 therapeutics such as supply chain and distribution models that are necessary for therapies rolled out in the community setting. The PANORAMIC study would provide the supportive evidence to adequately address the cost-effectiveness of community targeted therapies.	funded by the NHS with no strong rationale to appraise it. As managing COVID-19 becomes a routine part of NHS work, plausibly towards the end of 2022, both the clinical and cost-effectiveness of treatments will need to be explored to guide future commissioning and funding decisions. The appraisal focuses on 2 populations: people with mild symptomatic COVID-19 at risk of progressing to severe COVID-19 and people with severe COVID-19. The treatments are being evaluated within their marketing authorisations and compared with each other where appropriate.

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		The resource intensity of MTAs means that they may prove highly burdensome for NICE, the Assessment Group (AG) and all other stakeholders involved in the process, whilst companies may also find challenging to support the process by addressing ongoing HTA requests. Initiating an MTA at this stage would mean that its timeline is likely to be prolonged and its recommendations may become obsolete. Assessment delays may introduce public scepticism around these technologies in the general population. Finally, any assessment at this stage could potentially disadvantage technologies, resulting in wider societal and health system consequences at this critical stage. *MSD is fully supportive of the VPAS principle 3.17 which states that "all new active substances in their first indication, and extensions to their Marketing Authorisation to add a significant new therapeutic indication, will undergo an appropriate NICE appraisal", unless a "clear rationale not to do so exists".* MSD strongly urges NICE to reconsider and delay the appraisal of COVID-19 related therapeutics to a later date when the necessary evidence is available for a robust appraisal to take place. Given the national procurement at this stage which is facilitated by the RAPID C-19, it is neither relevant nor necessary to conduct a HTA in this space. A potentially negative HTA decision based on the rigid MTA process and current data uncertainties could disadvantage patients, the health system and society overall. In the interim, Rapid Evidence Summaries alongside RAPID C-19 provide sufficient level of information for decision making purposes. *MSD has been privileged to support the UK Government and the NHS in a time of crisis. MSD believes it is inappropriate timing to initiate an MTA. While MSD would intend to be a stakeholder, we do not yet have the data or evidence necessary to support a robust assessment of value in the endemic setting. MSD urges NICE to reconsider the timing and the routing of this*	Any clinical effectiveness evidence is based on publicly available living network analyses, ensuring the data is as up to date as possible. As managing COVID-19 becomes a routine part of NHS work, plausibly towards the end of 2022, both the clinical and cost-effectiveness of treatments will need to be explored to guide future commissioning and funding decisions.

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		appraisal to allow for a robust future assessment to take place. MSD advocates for an open dialogue between companies and NICE to identify the optimal process for HTA routing for a formal clinical and cost-effectiveness evidence review.	
	Pfizer UK	Yes. There is an unmet need for therapies targeting COVID 19 infections. Treatments to reduce hospitalisations as well as manage severe clinical manifestations in hospital.	Thank you for your comment. No action needed.
	Roche	Whilst Roche is supportive of NICE's technology appraisal processes, for severe/hospitalised patients an MTA does not seem appropriate at this stage. Reducing the scope to products whose efficacy is less likely to be affected by virus mutations and to a population that is large, expected to increase and has early/less severe COVID-19, could be considered if enough evidence is available. In the above settings, advancing the understanding of a clear Population, Intervention, Comparison, Outcomes and Study (PICOS) design could be a first step that would allow more detailed comments. Guidance on how to capture additional elements not routinely included in an appraisal, like the impact of "long COVID" (with a clear definition), career disutilities and wider societal benefit should also be considered, as these are important factors in COVID-19 that should not be dismissed without an explanation. For severe COVID-19 in particular, there are a number of unresolved complex considerations that would currently limit the feasibility of an assessment. Among which we mention: ● The lack of clarity and the impact emerging variants of SARS-CoV-2 can have on several clinical and economic endpoints ● For severe patients, treatments may currently be used in an off-label capacity and/or before marketing authorisation.	Thank you for your comment. The scope has been updated to acknowledge the impact of variant-specific treatment efficacy. The PICO table has been updated following the scoping workshop to ensure a clear understanding of the proposed appraisal. Although post-COVID-19 syndrome will be an important consideration, it won't be the focus. The focus will be on the clinical- and cost-effectiveness of therapeutics to treat

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		● The amount of data being published weekly that could potentially make an assessment quickly outdated (1) ● New agents introduced at fast pace and older agents repurposed for use in severe COVID-19 (> 100 drug combinations) ● Timelines for the potential availability of relevant biosimilars ● Product supply considerations. Reasons specifically related to Roche's products: ● Tocilizumab biosimilar availability working assumptions are that they are anticipated from Q4 2022 (subject to uncertainty) which potentially coincides with the time frame associated with this appraisal. ● The combination of Casirivimab and imdevimab does not retain neutralising activity against the Omicron variant (2), which currently accounts for the vast majority of UK cases. (1) While, as of today, 424 RCTs have been reported on COVID-19 treatments and 17 on COVID-19 prevention, currently there are 3,396 randomised trials ongoing on COVID-19 (3014 on treatments, 382 on prevention), excluding vaccines trials Source: https://covid-nma.com/. https://www.roche.com/dam/jcr:dfe6dcb4-d787-45d6-9b1d-ffc17d667e4c/2021216_Roche%20statement%20on%20Ronapreve%20Omicron.pdf	COVID-19. These treatments might have an impact on the incidence or severity of post-COVID-19 and this will be an exploratory outcome, if there is clinical data to support this. Carer disutilities will be considered as per the methods guide, if there was evidence to support this. Wider societal benefits will not be included in the appraisal. The NICE health technology appraisal manual states that *"…in exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."*

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			The aim of an appraisal of treatments for COVID-19 is to inform the management of COVID-19 as it becomes a routine part of NHS work, rather than an exceptional circumstance. The NICE health technology appraisal manual states that *"Productivity costs should be excluded from the reference case."* The treatments will be evaluated within their marketing authorisations and compared with each other where appropriate. Any clinical effectiveness evidence will be based on publicly available living network analyses, ensuring the data are as up to date as possible.

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			The introduction of any biosimilars would also be considered in any appraisal, if the timings are appropriate. If they are not, a rapid update to the guidance following the loss of market exclusivity will be made. Product supply considerations will be considered as part of implementing any positive guidance.
	Swedish Orphan Biovitrum (Sobi) Ltd	Although Sobi are supportive of the NICE technology appraisal programme, we would urge caution around conducting a Multiple Technology Appraisal (MTA) in this area. There is great heterogeneity across the proposed COVID-19 (C19) therapeutic interventions and the populations they treat across the clinical pathway. We would anticipate significant technical and methodological challenges in conducting an MTA due to this inherent heterogeneity in the types of therapeutics, their licensed/anticipated licensed indications and the populations they are intended to treat. The pandemic is also everchanging with new variants, increased vaccination rates, and unpredictability in the "waves" of infection which means that any guidance might potentially become outdated soon after publication. An MTA represents a significant investment in time and resource and any appraisal would need to add durable value.	Thank you for your comment. The scope has been updated to acknowledge the impact of variant-specific treatment efficacy. The assessment group is taking a pragmatic approach to solve data limitations. Potential methods to overcome data limitations, include

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			implementing sensitivity analysis and scenario analysis. Discrete time points for analysis could also be implemented.
	British Infection Association	There is no document called ‘draft remit’ so we presume you mean the paragraph entitled “draft remit/appraisal objective”. This could expand to state ‘and additional agents felt to be appropriate during the consultation process’ as changes may occur during the consultation.	Thank you for your comment. The remit has been updated to reflect the relevant interventions at the time of scope finalisation.
	Long COVID SOS	We believe that it is appropriate to refer this topic to NICE for appraisal. We welcome that Long Covid has been mentioned within the scope.	Thank you for your comment. No action needed.
	NHS England and NHS Improvement	NHS England & NHS Improvement (NHSE&I) feel that it is appropriate to refer this topic to NICE for appraisal via the MTA route. We are in the unusual situation that these therapies have been made available to the NHS through DHSC funded supply arrangements and via trials, prior to the detailed NICE appraisal process, due to the pandemic and the wish to provide patients with access to COVID treatments supported by published trial evidence. As the acute situation is appearing to ease, subject to further variants emerging, we feel that it is important to consider these interventions at an individual and a public health level, taking into account both clinical and cost-effectiveness to guide future commissioning / funding decisions.	Thank you for your comment. No action needed.
	Dr Lucy Lamb	Yes it is appropriate	Thank you for your comment. No action needed.
	University of Bristol	Yes	Thank you for your comment. No action needed.

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Wording	Eli Lilly and Company Limited	Yes, the remit broadly reflects the clinical and cost effectiveness for the therapeutic technologies to treat COVID-19.	Thank you for your comment. No action needed.
	Gilead Sciences	The wording is appropriate.	Thank you for your comment. No action needed.
	Humanigen, Inc.	Would NNT be a helpful measure? Please note publication in the peer-reviewed Journal Medical Economics https://doi.org/10.1080/13696998.2022.2030148 and a UK-focused manuscript published on medRxiv and currently undergoing peer review https://doi.org/10.1101/2022.02.11.22270859	Thank you for your comment. It is expected that numbers needed to treat (NNT) will be implicit in the modelling results.
	Merck Sharp & Dohme (UK) Limited	We suggest the following changes with regards to molnupiravir to reflect the Conditional Marketing Authorisation granted from the UK MHRA. Lagevrio® (Molnupiravir) is indicated for treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness (see sections 4.2 and 5.1 for information on posology and limits of clinical trial population)[ii].	Thank you for your comment. The marketing authorisation for molnupiravir has been updated as suggested.
	Pfizer UK	No. The remit mentions "…within their proposed marketing authorisations ...". However, some of the treatments included are current being used off label.	Thank you for your comment. The remit has been updated to reflect the relevant interventions at the time of scope finalisation.The scope does not include treatments, such as sarilumab, which are not expected to have a marketing authorisation

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			for treating COVID-19, specifically.
	Roche	For severe patients, treatments may currently be used in an off-label capacity and/or before marketing authorisation. For this population, an appraisal of treatments based on the data underpinning marketing authorisation may not be reflective of current practice.	Thank you for your comment. The remit has been updated to reflect the relevant interventions at the time of scope finalisation.. NICE can only make recommendations in line with marketing authorisations. Any limitations with the data will be considered by the committee.
	Sobi Ltd	We consider the wording of the remit to be too broad as the listed C19 interventions are used at different points across the clinical pathway and there are individual variation and nuances in the licensed/anticipated licensed indications. This serves to highlight the potential issues of conducting an MTA in an area where significant variation exists in how and when pharmacological interventions are used in the clinical pathway.	Thank you for your comment. Although there are significant variation and nuances in interventions the appraisal will focus on 2 populations: people with mild symptomatic COVID-19 at risk of progressing to severe COVID-19 and people with severe COVID-19. The treatments will be evaluated within their marketing authorisations and compared with each

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			other where appropriate.
	Faculty of Pharmaceutical Medicine	The clinical indications of treatments currently licenced for COVID-19 are diverse from mild disease to treatment of severe disease. These may well increase in diversity to include pre- and/or post-exposure prophylaxis, depending on the time frame for the appraisal and progression through licensing. The range of therapeutics covered by the draft remit is also diverse, covering 3 different ATC codes ATC J06, J05 and L04). This means that the comparisons between different medicines for use in different situations will need to be carefully considered. As such the remit should reflect this complexity.	Thank you for your comment. The population has been updated to focus on 2 populations: people with mild symptomatic COVID-19 at risk of progressing to severe COVID-19 and people with severe COVID-19. The treatments will be evaluated within their marketing authorisations and compared with each other where appropriate.
	British Infection Association	There is no document called 'draft remit' so we presume you mean the paragraph entitled "draft remit/appraisal objective". This should perhaps be expanded to state 'and additional agents felt to be appropriate during the consultation process'. This paragraph needs expanding to explain why the scope is relevant eg. Questions regarding the benefit of some agents.	Thank you for your comment. The remit has been updated to reflect the relevant interventions at the time of scope finalisation The remit defined in the scope is from the Department of Health and Social Care, and states the interventions and expected disease area. No other detail is

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			added to the remit of the scope. The treatments included in the scope are expected to have marketing authorisations for treating COVID-19 within the next year.
	Long COVID SOS	Yes	Thank you for your comment. No action needed.
	Long Covid Research Initiative	The workshop characterizes Covid 19 as "predominantly an acute respiratory illness". This is in conflict with much of the scientific literature which sees Covid 19 as an endothelial disease, and which is increasingly understood in many cases to be chronic. As a result of this mischaracterization, there is very little consideration in the draft scoping document of Long Covid. This seems to be a major oversight given the numbers of people in question. There are 1.3 million people living with Long Covid in the UK according to the ONS, prior to the impact of Omicron. Many of these people are living in appalling states of health. Treatment options are extremely limited. Workshops like this one could make a vital difference to giving the therapeutic help that these people desperately and urgently need - many of whom have been suffering now for almost 2 years. Our comment would be to strongly suggest that the agenda is updated to include substantial time to consider Covid 19 in its chronic manifestation, in addition to its acute manifestation. Given the urgency of the matter, in our view this is not something that should be left for a later date.	Thank you for your comment. If this appraisal proceeds, although post-COVID-19 syndrome will be an important consideration, it won't be the focus. The focus will be on the clinical- and cost-effectiveness of therapeutics to treat COVID-19. The treatments will be evaluated within their marketing authorisations. Currently, the marketing authorisations do not cover treatment for post-COVID-19 syndrome. However, as

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			these treatments might have an impact on the incidence or severity of long COVID and this will be an exploratory outcome, if there is clinical data to support this. The characterisation of COVID-19 as a predominantly acute respiratory illness aligns with the severe acute respiratory syndrome coronavirus 2 which causes COVID-19. Although endothelial disease is a consideration the characterisation of the disease will remain broad, in line with government bodies and the world health organisation.
	NHS England and NHS Improvement	Yes	Thank you for your comment. No action needed.
	Dr Lucy Lamb	The wording reflects the issues	Thank you for your comment. No action needed.

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	University of Bristol	The appraisal is referred to as “therapeutics for people with COVID-19”. A distinction should be drawn between SARS-Cov-2 infection, which may be asymptomatic (and therefore should not be classed as the disease COVID) and symptomatic COVID. This distinction is a routine one in infectious disease (i.e. people were not said to “have polio” when they were one of the very high majority of asymptomatic infections, they were said to have been infected with the virus). There may be cases where in very high risk individuals therapeutic approaches are appropriate when they carry asymptomatic infection, and it is important the wording is clear about this.	Thank you for your comment. This clarification has been made in the text.
Timing Issues	Eli Lilly and Company Limited	There is a relative urgency due to high numbers of cases to new variants such as Omicron which increases likelihood of hospitalisation in spite of lower absolute risk vs the Delta variant.	Thank you for your comment. No action needed.
	Gilead Sciences	The company is of the opinion that it is appropriate for NICE to progress this appraisal once the NHS has moved out of a pandemic situation to treating COVID-19 as part of its usual work-flow.	Thank you for your comment. This work will be of importance when managing COVID-19 becomes a routine part of NHS work, plausibly towards the end of 2022. As a technology appraisal takes 6 to 9 months to produce draft recommendation it is appropriate to begin the scoping exercise.
	GlaxoSmithKline	MTA appraisal is required to establish the advantages and disadvantages of treatment options	Thank you for your comment. No action needed.
	Humanigen, Inc.	Extremely – the rapid predominance of the omicron variant, the BA.2 sub-variant and ability of these variants to evade neutralizing monoclonal antibodies, coupled with the diminution of vaccine efficacy over time unless boosters are administered and the increased risk of certain populations	Thank you for your comment. The scope has been updated to acknowledge the impact

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		means the urgency is apparent and acute. Focusing on preventing hospital admission using neutralizing monoclonals and/or oral anti-virals, will not future-proof this guidance from the uncertainty of future variants. There should also be a focus on variant-agnostic approaches.	of variant-specific treatment efficacy.
	Merck Sharp & Dohme (UK) Limited	We strongly urge NICE to reschedule the proposed HTA until a later date, once more evidence is available for all technologies to allow NICE to issue a final guidance that would have continued relevance for the NHS. This should take place once we have certainty that the endemic disease phase has been reached. In the current, unique context an MTA (or other HTA process at this stage) is neither needed nor necessary since the RAPID C-19 framework allows patients to access these therapeutics, which have already procured by the DHSC.	Thank you for your comment. This work will be of importance when managing COVID-19 becomes a routine part of NHS work, plausibly towards the end of 2022. As a technology appraisal takes 6 to 9 months to produce draft recommendation it is appropriate to begin the scoping exercise.
	Pfizer UK	With patients already accessing these medicines through RAPID C19 and advance purchase agreements, appraisal timelines should ensure continuity of access.	Thank you for your comment. No action needed.
	Roche	As stated in the “Appropriateness” section above, timing is an important factor for this potential appraisal. An appraisal not restricted to the correct treatments, settings and populations could be out of date as soon as it is produced and not be beneficial to patients, the NHS and NICE.	Thank you for your comment. This work will be of importance when managing COVID-19 becomes a routine part of NHS work, plausibly towards the end of 2022. As a technology appraisal takes 6 to 9 months to produce draft recommendation it is

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			appropriate to begin the scoping exercise.
	British Infection Association	Time lines need to be realistic and balance both the rapidly changing evidence in this area and the need for busy clinicians to engage	Thank you for your comment. This will be considered. The multiple technology appraisal will give stakeholders the opportunity to comment on the appraisal.
	Long COVID SOS	From the perspective of potential preventing the development of Long Covid, as well as the possibility that these drugs may help in the treatment of Long Covid where viral persistence or a disordered immune response is suspected, we would say that this is a matter of urgency considering the estimates of those already affected by the ONS.	Thank you for your comment. If this appraisal proceeds, although post-COVID-19 syndrome will be an important consideration, it won't be the focus. The focus will be on the clinical- and cost-effectiveness of therapeutics to treat COVID-19. These treatments might have an impact on the incidence or severity of post-COVID-19 syndrome and this will be an exploratory outcome, if there is clinical data to support this.

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	NHS England and NHS Improvement	The majority of the interventions to be appraised are already in use within the NHS, in line with published interim clinical commissioning policies. There is, therefore, some urgency to determine the clinical and cost-effectiveness of these interventions to inform front line clinical decision making and future commissioning and funding decisions.	Thank you for your comment. No action needed.
	Dr Lucy Lamb	Urgent as a number of treatments available and it will aid the clinician on the ground	Thank you for your comment. No action needed.
	University of Bristol	Timing depends upon the particular technology under appraisal, and how evidence may be changing for that. In the case of therapeutics for people with SARS-CoV-2 infection changes in viral type appear to be leading to rapid changes in effectiveness of monoclonal antibodies, with a possibility that results from RCTs carried out at one time may not apply when the virus has changed. This is a key issue with an appraisal in this area.	Thank you for your comment. The scope has been updated to acknowledge the impact of variant-specific treatment efficacy. Any clinical effectiveness evidence will be based on publicly available living network analyses, ensuring the data are as up to date as possible.
Additional comments on the draft remit	Humanigen, Inc.	It is clear, with the omicron variant and sub-variants of concern, such as BA.2, that there is loss of efficacy for neutralizing monoclonals. There remains uncertainty with regard to future variants and the timing, frequency and appropriateness of repeated booster vaccinations. Therefore, variant-agnostic therapeutics will be a critical tool in the NHS armamentarium. Immunomodulating antibodies have a key role in this regard.	Thank you for your comment. The scope has been updated to acknowledge the impact of variant-specific treatment efficacy. Any clinical effectiveness evidence will be based on publicly available living network analyses,

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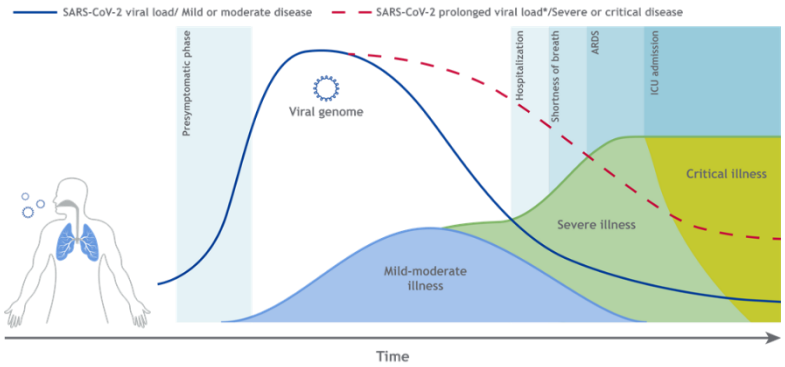
			ensuring the data are as up to date as possible.
	Merck Sharp & Dohme (UK) Limited	As notes above, the draft remit should explicitly state whether a pandemic or epidemic phase of COVID-19 is to be modelled.	Thank you for your comment. Guidance on the use of the treatments will be for use in an endemic, but the recommendation would need to be mindful of use of treatments in a pandemic situation.
	British Infection Association	There is no document called 'draft remit' so we are unsure which document you are seeking comments on.	Thank you for your comment. The draft remit is the brief for the appraisal. Your comments made above reflect this, but apologies that this was not made clearer.
	Long Covid SOS	It is welcome to see post covid syndrome mentioned and also be included as an outcome measure.	Thank you for your comment. No action needed.
	Dr Lucy Lamb	The CAS Alerts from Jan 22 need to be included in related national policy to discuss. I have commented on the scope.	Thank you for your comment. This will be added to the text.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eli Lilly and Company Limited	This section provides considerable background information.	Thank you for your comment. No action needed.
	Gilead Sciences	As noted in the draft scope, COVID-19 is an acute respiratory illness caused by infection with SARS-CoV-2, which progresses through different stages, moving from an acute viral infection with high viral load that then subsides (as depicted in figure 1) followed by an exacerbated immune response with increased levels of systemic inflammatory markers. Figure 1: Viral load in COVID-19  Footnotes: Prolonged viral load in senior patients (immunosenescence), patients with comorbidities (cancer, cardiovascular disease, chronic kidney disease) and patients with specific genetic traits (interferon-I deficiency). Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Sources: Cevik et al., 2020; Wu et al., 2020.1,2	Thank you for your comment. The scope has been updated to clarify that anti-virals can be beneficial during the severe stage of the disease course. The distinction between subgroups of treatment classes has also been updated in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		Although anti-virals are beneficial during the viral shedding stage because they inhibit viral replication, they remain applicable from the early stages of disease course all the way to severe disease, as there can be ongoing viral replication during the “inflammatory” phase of the disease course. The applicability of treatment with remdesivir from early to severe disease is evidenced by the inclusion of multiple populations in the MHRA GB label for remdesivir. Remdesivir is indicated for the treatment of coronavirus disease 2019 (COVID-19) in: • adults and adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) • adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 This broad positioning of remdesivir is reflected in the context of the regulatory label and the three recently updated NHS clinical commissioning policies for COVID-19, covering the treatment of both hospitalised (high risk patients not yet requiring supplemental oxygen to patients requiring low flow oxygen supplementation) and non-hospitalised high risk (usually milder) patients3–5. As such, remdesivir can be viewed as a backbone treatment for patients in hospital. In contrast, other drug classes play different roles in the disease course and therefore are useful in different settings. Although treatments can be broadly split into anti-viral and anti-inflammatory, there are subgroups within these groups that relate to different populations (as described in the Population section of this form). Broadly speaking, subgroups include: • Antivirals targeting the virus to stop viral replication	

Section	Consultee/ Commentator	Comments [sic]	Action
		• Neutralising monoclonal antibodies that target the outer virus receptors to neutralise the virus and prevent entry into cells • Anti-inflammatories (including monoclonal antibodies working as anti-inflammatories)	
	Humanigen, Inc.	The background does not seem to acknowledge that the severe inflammatory response can be stopped or blunted if an appropriate treatment is administered early enough. Many current treatments only have evidence for use in the later stage, full blown hyper-immune response where patients may have already progressed to ICU admission, mechanical ventilation and/or multi-organ failure. Efforts should be made to provide for timely interventions to prevent the progression of the immune response by earlier treatment directed at initiator cytokines, such as GM-CSF. This can be achieved through simple, evidence-based biomarker-driven patient selection using CRP, as per the UK ISARIC scoring system.	Thank you for your comment. The scope states that if the disease is not adequately controlled with anti-viral treatments an excessive immune response can lead to more severe complications. The scope has been updated to clarify that neutralising monoclonal antibodies can also be beneficial throughout this stage.
	Merck Sharp & Dohme (UK) Limited	MSD confirm that the background section is accurate.	Thank you for your comment. No action needed.
	Pfizer UK	The background information should include a statement acknowledging the impact of vaccines in reducing symptomatic disease and hospitalisations. However, COVID 19 therapies are crucial for the treatment of breakthrough infections and vaccine resistant COVID 19 variants.	Thank you for your comment. The scope has been updated to consider the impact of vaccines.

Section	Consultee/ Commentator	Comments [sic]	Action
		The potential for treatment induced escape variants is also not discussed.	
	Roche UK	"A combination of casirivimab and imdevimab is recommended for people who have no detectable COVID-19 antibodies." This information is taken from an NHS commissioning policy and is not reflective of the marketing authorisation. As such it contradicts the draft remit of the appraisal and it highlights how in severe COVID-19 settings an appraisal with the product marketing authorisation would not reflect clinical practice. Clinical benefit on mortality in study 2066 and RECOVERY was demonstrated in those patients that were 'seronegative' at baseline when compared to those seropositive at baseline. Neither of these studies are currently detailed in the SmPC as the conditional marketing authorisation was granted against data provided by study 2067 (ambulatory care) and 2069 (post-exposure prophylaxis and prevention). Various analyses have demonstrated that the combination of casirivimab and imdevimab has no activity against the Omicron variant of SARS-CoV-2. Variants of interests should be mentioned in the document and the scope of the MTA should be restricted.	Thank you for your comment. This paragraph of the scope describes the current guidance from the COVID-19 rapid guidelines. The NHS commissioning policy notes that people can be considered eligible for casirivimab and imdevimab if they have a positive PCR test**.** The scope has been updated to acknowledge the impact of variant-specific treatment efficacy. However, it is not within the remit of the appraisal to support any guidance based on changes in the evidence base that may be reflected in regulatory decision making.
	Faculty of Pharmaceutical Medicine	The background does not cover the full range of potential therapeutic uses, such as pre- and post-exposure prophylaxis.	Thank you for your comment. The remit of

Section	Consultee/ Commentator	Comments [sic]	Action
			the appraisal does not include pre- and post-exposure prophylaxis. The populations included in the appraisal are people with symptomatic COVID-19.
	British Infection Association	The background information may have been accurate during a pre-vaccine era but needs updating to a post-vaccine era. Which conditions listed demonstrate evidence of increased mortality in these groups in a post-vaccine situation? The interim commissioning policies in the document background have now been superseded.	Thank you for your comment. The scope has been updated to consider the impact of vaccines. The interim commissioning policies have been updated.
	Long Covid SOS	It should be explicitly stated whether any of these technologies have evidence from clinical studies on the prevention of Long Covid currently	Thank you for your comment. Although post-COVID-19 syndrome will be an important consideration, it won't be the focus of the appraisal. The focus will be on the clinical- and cost-effectiveness of therapeutics to treat acute COVID-19. NICE can only make recommendations within the marketing authorisation of a treatment. The sponsor

Section	Consultee/ Commentator	Comments [sic]	Action
			of each drug is responsible for the intended marketing authorisation.
	Metabolic Support UK	The background information is accurate and complete to the best of our knowledge.	Thank you for your comment. No action needed.
	NHS England and NHS Improvement	The following interim clinical commissioning policies (CCPs) have been published: Antivirals or neutralising monoclonal antibodies (nMABs) for non-hospitalised patients with COVID-19 (available via the CAS Alert at: CAS-ViewAlert (mhra.gov.uk)) Antivirals and neutralising monoclonal antibodies (nMABs) in the treatment of COVID-19 in hospitalised patients (available via the CAS Alert at: CAS-ViewAlert (mhra.gov.uk)) The above two policies will be live from 10th February. Interleukin-6 inhibitors (tocilizumab or sarilumab) for adult patients hospitalised due to COVID-19 (available via the CAS Alert at: CAS-ViewAlert (mhra.gov.uk)). Interim clinical commissioning policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older) (available at: Briefing template (england.nhs.uk)) – this is currently being updated. Please note that further guidance (either policies and / or CAS alerts) has been published on other COVID-related treatments including corticosteroids, oral budesonide, azithromycin etc. A full list of publications agreed via UK	Thank you for your comment. The interim clinical commissioning policies have been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		wide collaboration can be found here: CAS - Coronavirus (COVID-19) Alerts (mhra.gov.uk)	
	Dr Lucy Lamb	See above new CAS Alerts	Thank you for your comment. The interim clinical commissioning policies have been updated.
	University of Bristol	See above comment on terminological issues.	Thank you for your comment. This clarification has been made in the text.
The technology/ intervention	Eli Lilly and Company Limited	Please consider revising the wording as proposed: Baricitinib (Olumiant, Eli Lilly and Company) is an orally available immunomodulator. It is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. These enzymes mediate pathways involved in the inflammatory processes underlying COVID-19. "By blocking the actions of the enzymes it can reduce joint and skin inflammation" we believe this should be deleted as this inhibition also plays a role in other chronic disease such as atopic dermatitis (AD) and Rheumatoid Arthritis (RA). Not factually correct as this signalling pathway has a role in both chronic inflammatory diseases such as RA/AD, and in acute inflammatory processes.	Thank you for your comment. This clarification has been made in the scope.
	Gilead Sciences	The description of remdesivir should be updated to reflect the current licence and therefore applicable patient group for treatment with remdesivir, which is for the treatment of coronavirus disease 2019 (COVID-19) in: • adults and adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or	Thank you for your comment. This clarification has been made in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		high-flow oxygen or other non-invasive ventilation at start of treatment) • adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 Use of remdesivir in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 includes both the hospital and community settings. Within the hospital setting, as stated in NICE's conditional recommendation, remdesivir is used in patients receiving low flow oxygen. Remdesivir is currently established clinical practice, and represents a backbone to the treatment regimen, across a broad spectrum of COVID-19 disease for these patients as set out in 3 existing Clinical Commissioning Policies: 1. Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older) focuses on the use of remdesivir for hospitalised COVID-19 patients requiring supplemental oxygen.5 2. Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies in the treatment of COVID-19 in hospitalised patients (Version 5) focuses on the use of remdesivir (alongside other options) for patients with hospital onset COVID-19 at high risk of progressing to severe COVID-19 disease but not yet requiring supplemental oxygen.3 3. Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies for non-hospitalised patients with COVID-19 focuses on the use of remdesivir (alongside other options) in non-hospitalised patients with COVID-19 at high risk of progressing to severe COVID-19 disease.4	

Section	Consultee/ Commentator	Comments [sic]	Action
		Remdesivir has also been considered standard of care in the clinical trials of other treatments being studied for use in hospitals, for example: • The US National Institute of Allergy & Infectious Diseases ACTT and ACTIV platform trials:ACTT-2: evaluated the combination of baricitinib and remdesivir compared to remdesivir alone 6 • ACTT-3: evaluated the combination of interferon beta-1a and remdesivir compared to remdesivir alone 7 • ACTT-4: evaluated the combination of baricitinib and remdesivir compared to dexamethasone and remdesivir. 8 • ACTIV-3: evaluating the combination of ACTIV-3 investigational treatments and remdesivir compared to remdesivir plus placebo 9 • ACTIV-5 (BET-A): evaluated the combination of remdesivir and Risankizumab compared to remdesivir plus placebo8,10 • ACTIV-5 (BET-B): recruiting to evaluate the combination of lenzilumab and remdesivir compared to remdesivir plus placebo8,11 • ACTIV-5 (BET-C): recruiting to evaluate the combination of danicopan and remdesivir compared to remdesivir plus placebo in patients younger than or older and equal to 70 years old12 • ITAC trial (NIAID, NIH and INSIGHT): evaluating the combination of hyperimmune immunoglobin to SARS-CoV-2 (hIVIG) and remdesivir compared to remdesivir plus placebo.13 • Casirivimab and Imdevimab for Treatment of Hospitalized Patients With COVID-19 Receiving Low Flow or No Supplemental Oxygen14 In addition, the scoping document needs to be updated to clearly differentiate the different classes of monoclonal antibodies; namely: • Neutralising monoclonal antibodies (nMAbs) that bind to the virus spike proteins preventing binding to cell receptors and infection of the cell	This clarification has been made in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Monoclonal antibodies that target inflammatory pathways and thus function by reducing the COVID-19 inflammatory phase	
	GlaxoSmithKline	Sotrovimab 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. Sotrovimab has a conditional marketing authorisation in the UK (GB) for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe covid infection. Sotrovimab is to be used as described in the NHSE Interim clinical commissioning policy, as a first line option in patients where SARS-CoV-2 infection is confirmed by either: • Polymerase chain reaction (PCR) testing OR • Lateral flow test (registered via gov.uk or NHS 119) AND • Symptomatic with COVID-19 and showing no signs of clinical recovery AND • The patient is a member of a 'highest' risk group AND • clinical judgement deems that an nMAB is the preferred option AND • Treatment is delivered within 5 days of symptom onset	Thank you for your comment. No action needed.
	Humanigen, Inc.	There may be confusion as lenzilumab neutralizes GM-CSF, an inflammatory response initiator cytokine, rather than attaching to the spike protein of the virus. Placing it in the class of neutralizing monoclonals would be confusing to treating healthcare professionals as its mode of action is as an immunomodulatory antibody which neutralizes the GM-CSF ligand.	Thank you for your comment. The clarification between monoclonal antibodies

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		Additionally, greater or lesser benefit in certain sub-populations could be considered. Lenzilumab offers a 'future-proof' treatment against current and inevitable future variants. We believe that COVID-19 will become a serious endemic disease and will continue to impact society, healthcare systems and patients. Lenzilumab has demonstrated efficacy, with significant benefit over and above existing standard of care and, importantly, with a safety profile comparable to placebo.	has been made in the scope.
	Merck Sharp & Dohme (UK) Limited	MSD confirm that the information included for Lagevrio® (molnupiravir) is accurate. The MHRA has granted the following indication for Molnupiravir: *"Lagevrio® is indicated for treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness (see sections 4.2 and 5.1 for information on posology and limits of clinical trial population)".* Based on the current conditional licence, MSD confirms that the expected positioning for this technology is in the community or for patients with COVID who are in hospital for reasons other than COVID and do not require high levels of respiratory support. The revised positioning circulated by NICE is accurate. MSD suggest adding information around posology and administration for molnupiravir twice daily every 12 hours at 800 mg (200mg hard capsules) for a maximum of 5 days of treatment duration. Treatment should be administered as soon as possible after a diagnosis of COVID-19 has been	Thank you for your comment. The posology of a treatment is not usually added to a scope. The posology of the treatment will be

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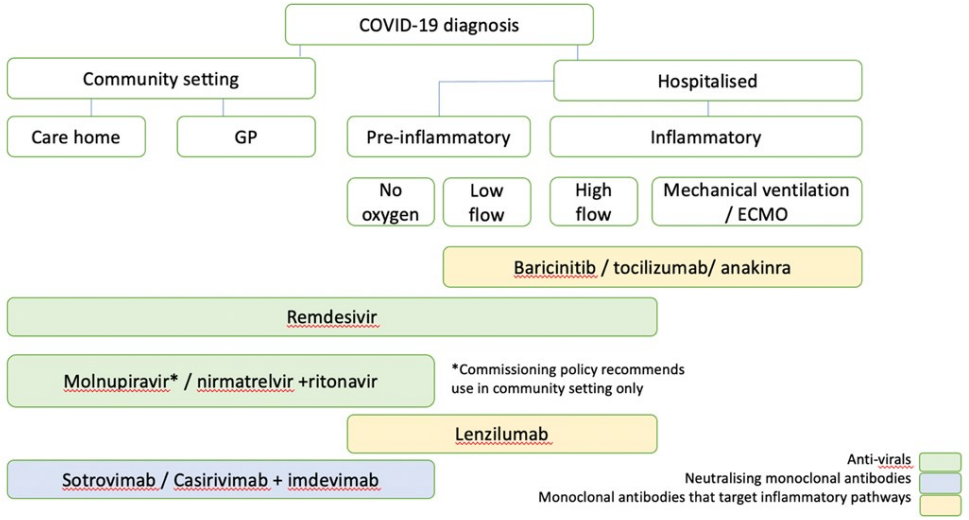
		made and within 5 days of symptom onset (see section 5.1)[Error! Bookmark not defined.]. NICE may also consider including a further statement that antivirals have the potential to retain activity against different variants, however, *in vitro* studies will need to be conducted to confirm in each occasion [iii].	explored in the appraisal. The scope will be kept broad. Any future evidence that this is the case, will be incorporated into the economic model.
	Pfizer UK	Yes	Thank you for your comment. No action needed.
	Roche	Tocilizumab now has a marketing authorisation for COVID-19, as specified in Comment 4 below. The exact wording of this indication is as follows: "RoActemra (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."	Thank you for your comment. The wording of the marketing authorisation has been updated.
	Sobi Ltd	Anakinra specifically blocks interleukin-1α (IL1α) and interleukin-1β (IL-1β). Correction to text – Anakinra "has been studied in clinical trials, alone, in people hospitalised with COVID-19." Anakinra has been studied in people alongside standard of care, not alone, as reflected in the pivotal SAVE-MORE study.	Thank you for your comment. This clarification has been made in the scope.
	Faculty of Pharmaceutical Medicine	The description does not distinguish the different classes of medicines adequately. The description does not include information on pre- and post-exposure prophylaxis trials to date, nor regulatory approvals for these indications.	Thank you for your comment. Clarification to the different classes of treatments has been made. The remit of the

Section	Consultee/ Commentator	Comments [sic]	Action
			appraisal does not include pre- and post-exposure prophylaxis. The populations included in the appraisal are people with symptomatic COVID-19.
	British Infection Association	There are additional technologies not listed- other NMABs. Why and how were these selected? This is not detailed in the background.	The remit has been updated to reflect the relevant interventions at the time of scope finalisation.
	Metabolic Support UK	These technologies are not well known within the Inherited Metabolic Disorder patient community, therefore we are unable to comment.	Thank you for your comment. No action needed.
	NHS England and NHS Improvement	We note that the proposed scope includes only licensed treatments. We would welcome the inclusion of medicines being use off-label under UK-wide clinical commissioning policies and / or the NICE COVID-19 rapid guideline (e.g. sarilumab, remdesivir in non-hospitalised children aged 12-17 years).	Thank you for your comment. NICE can only make recommendations within the marketing authorisation of a treatment.
	University of Bristol	These are accurate, though the issue of changing effectiveness of some therapeutics with change in viral type should be highlighted, and the implications of that drawn out. PF-07321332 is normally referred to as nirmatrelvir.	Thank you for your comment. The scope has been updated to acknowledge the impact

Section	Consultee/ Commentator	Comments [sic]	Action
		The descriptions are accurate, but more thought should be given to how they are grouped, e.g. monoclonals against the virus are used in different ways to monoclonals aimed at human receptors, e.g. and classification of the technologies should be clear and logical.	of variant-specific treatment efficacy. PF-07321332 has been replaced with nirmatrelvir in the scope. The clarification between different treatment classes has been made in the scope.
Population	Eli Lilly and Company Limited	The population defined in the draft scope does not entirely reflect clinical practice. Therefore, please consider defining severity similar to the definition recently used from the WHO Rapid Recommendations i.e. non-severe, severe and critical (Agarwal et al, 2020). References: Agarwal A, Rochwerg B, Lamontagne F, Siemieniuk R A, Agoritsas T, Askie L et al. A living WHO guideline on drugs for covid-19 BMJ 2020; 370 :m3379 doi:10.1136/bmj.m3379	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19.
	Gilead Sciences	The populations described are broadly appropriate, but we would suggest that the definitions need to be more specific to improve clarity as to the patients included and to aid determination of the stage of the disease in the patient. The treatment setting combined with the level of supplemental oxygen requirement will enable assessment of all of the interventions as per their marketing authorisations.	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic

Section	Consultee/ Commentator	Comments [sic]	Action
		Therefore, we suggest setting out the populations as follows: 1. People with COVID-19 who have not been hospitalised (this would encompass a high-risk symptomatic population) 2. People with COVID-19 who are in hospital and do not require supplemental oxygen (this would encompass a high-risk symptomatic population) 3. People with COVID-19 who are in hospital and require low flow supplemental oxygen for the management of their COVID-19 disease 4. People with COVID-19 who are in hospital and require high flow oxygen 5. People with COVID-19 who are in hospital and require mechanical ventilation / ECMO The term “people with COVID-19 who are in hospital” encompasses: (1) those admitted for COVID-19; (2) those admitted for another indication and then found to also be infected with SARS-CoV-2 (may not have symptomatic disease yet); and (3) Those admitted for another indication and then diagnosed with symptomatic hospital onset COVID 19 disease (nosocomial infections). As the COVID-19 management has evolved, differing definitions have arisen for “severe COVID-19”. At the beginning of the pandemic, severity was defined as per the NICE rapid guideline, and encompassed low-flow, high-flow, non-invasive, IMV and ECMO. According to this definition, disease can be classified as severe when oxygen saturation levels are below 92% in those aged 18 and over in room air at rest, and 91% in children and young people (17 years and under) with COVID-19, amongst some other symptoms15. If NICE is using this definition of severe disease, then it is important to consider the different patient populations within that severe category, and the different treatment options they may receive based on the	COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19. The criteria to identify severe COVID-19 will be based on the criteria used in the COVID-19 rapid guideline: Managing COVID-19. The treatments will be evaluated within their

Section	Consultee/ Commentator	Comments [sic]	Action
		disease progression. The various treatment options for each population are described in figure 2 below, which builds on NICE's treatment pathway presented in the scoping workshop. Please see the appendix which aligns ordinal scales used in key trials across stages of disease. Figure 2: Populations and comparators by class and setting  Figure 2 builds on NICE's pathway to highlight the interventions which are mutually exclusive within each population (as described above) and might be compared with one another. For example, in the community setting and for patients in hospital who do not require oxygen, remdesivir might be compared with other anti-virals, highlighted in green, but remdesivir is the only anti-viral licensed in patients who require supplemental oxygen, and therefore can only be compared with standard of care for those populations. Conversely, a monoclonal antibody that targets inflammatory pathways could be used in	marketing authorisations and compared with each other where appropriate.

Section	Consultee/ Commentator	Comments [sic]	Action
		combination with remdesivir. Therefore, these therapies should not be directly compared with each other. The above populations align to those utilised by the NHS in their Interim Clinical Commissioning Policies. Based upon the remdesivir conditional marketing authorisation, remdesivir should be considered as a therapeutic intervention for populations 1, 2, 3 and 4 as set out above.	
	GlaxoSmithKline	Sotrovimab has been commissioned to be used in both community and nosocomial infections, but it should be noted that currently randomised controlled trial data is only available for people infected in the community.	Thank you for your comment. No action needed.
	Humanigen, Inc.	Paediatrics (0-2, 2-12, 12-18 years old groups); BAME. High-risk populations should also be considered, such as immuno-compromised, the elderly, diabetes, hypertension, chronic renal disease, obesity, etc.. However, we should also strongly consider available laboratory tests to guide treatment decisions, such as CRP, D-dimer, ferritin, creatinine, LDH, troponin, etc..	Thank you for your comment. The risk of progressing to severe COVID-19 will be based on the characteristics from key clinical trials and would feed into the risk calculations used in the model. The use of laboratory test to guide treatment decisions will be considered if these were stated in any marketing authorisation or used in NHS clinical practice.

Section	Consultee/ Commentator	Comments [sic]	Action
	Merck Sharp & Dohme (UK) Limited	MSD is concerned by the proposal to assess the community and hospitalised populations together in a single HTA. MSD strongly urges NICE to consider these settings separately and not in a single MTA, in line with the different clinical management across these two populations. Further clarity on the definition of hospitalisation should be added and whether admission is due to severe COVID-19 infection. More clarity is required as to what constitutes a high risk population since definitions within studies differ. Finally, special considerations should be introduced for patient groups at high risk for developing severe disease and patients with polypharmacy who require COVID-19 treatment that is unlikely to interact with other concomitant medications.	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19. The criteria to identify severe COVID-19 will be based on the criteria used in the COVID-19 rapid guideline: Managing COVID-19. The treatments will be evaluated within their marketing authorisations and compared with each other where appropriate.
	Pfizer UK	Yes. The population is defined correctly but cost effectiveness analysis should consider that some of the therapies have an impact of outcomes for both non hospitalised and hospitalised patients. Appropriateness of different therapies is depended on level of disease severity which should be reflected in the population stratification.	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with

Section	Consultee/ Commentator	Comments [sic]	Action
			mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19.
	Sobi Ltd	Sobi believes that the segmentation of the population should be more nuanced than a binary choice between those not hospitalised and those hospitalised. For example, within the hospitalised population there are subgroups which are clinically relevant as standalone populations and in which patients face different prognoses and treatment options. Sobi would advocate for further segmenting the hospitalised group into populations based on symptoms and oxygen support. For example: Symptomatic, No oxygen > Symptomatic, Pneumonia, No oxygen > Pneumonia, oxygen by NIV or high-flow > Mechanical ventilation.	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19.
	Faculty of Pharmaceutical Medicine	Specific populations to be considered: Pregnant women Those who could benefit from pre-exposure prophylaxis e.g. patients requiring ongoing cancer treatment, for whom a COVID infection would interrupt life-impacting care Those who could benefit from post-exposure prophylaxis Key workers at risk of exposure (e.g. healthcare workers)	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19. The remit of the appraisal does not

Section	Consultee/ Commentator	Comments [sic]	Action
			include pre- and post-exposure prophylaxis, or people who are at a higher risk of exposure. The populations included in the appraisal are people with symptomatic COVID-19.
	British Infection Association	The population needs to be considered as vaccinated, previously infected or naïve to infection or vaccinated/exposed but unlikely/not expected to develop an immune response. The effects in these differing populations may be considerably different. Seropositive and seronegative is sometimes used as a surrogate for response to vaccination or prior infection but has limitations. If felt to be of utility this could be used with rapid serology tests e.g. point of care tests for antibodies where appropriate could be considered if confirmed to be suitable and available. The efficacy of some interventions will vary significantly according to viral variant and may cause issues in the meta-analysis. That could be defined in the PICO, a priori subgroups or as a significant covariate.	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19. The scope has been updated to acknowledge the impact of variant-specific treatment efficacy.
	Long Covid SOS	Use and effectiveness of these treatments should also be determined in children. Evidence is starting to gather about Long Covid sufferers not having an antibody response to their infection, so the use of these drugs in a non-hospitalised setting should also be considered for those patients in the community. https://www.nature.com/articles/s41467-021- 27797-1 People	Thank you for your comment. The treatments will be evaluated within their

Section	Consultee/ Commentator	Comments [sic]	Action
		with Long Covid currently, who catch Covid-19 again, should be treated as an 'at-risk' group until further evidence is gathered.	marketing authorisations.
	Metabolic Support UK	The population has been defined appropriately. However due to the complexities, morbidities and mortalities related to rare diseases, we recommend the rare disease community is considered separately.	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19. The risk of progressing to severe COVID-19 will be based on the characteristics from key clinical trials and would feed into the risk calculations used in the model. Stakeholders will have the opportunity to comment on this throughout the appraisal.
	NHS England and NHS Improvement	The draft scope focuses on people with COVID-19 who have been hospitalised and those that have not. NHSE&I feels that this may not take into account the severity of infection sufficiently as a proportion of people treated in hospital will have 'incidental'	Thank for your comment. Following the discussion held in the scoping workshop the population has been

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		COVID (e.g. admitted for a non-COVID-19 related issue and subsequently tested positive). In line with the updated policies, such patients will be managed in line with the 'Antivirals and neutralising monoclonal antibodies in the treatment of COVID-19 in hospitalised patients' interim CCP as hospital-onset COVID-19, which broadly reflects (but does not exactly mirror) treatments available in the community. Defining populations based on time from symptom onset and severity of infection may be helpful. There are likely to be various groups within the population which may need to be considered, including age groups, those with pre-existing conditions (high risk; highest risk), ethnicity and vaccination status. The interim CCPs for antivirals and nMABs include a criterion where a patient cohort is considered at highest risk from COVID-19. The CCPs also require individuals to be symptomatic of COVID-19 infection. There are differing eligibility criteria for access to some therapies, for example via PANORAMIC, compared with use in line with the community policy; sensitivity analyses may be helpful. Consideration should be given to generic eligibility criteria related to risk of severe COVID/death (e.g. age, comorbidities etc), and whether specific groups (e.g. ethnicity) represents an additional risk factor (not accounted for by the generic risk factors) that should be accommodated in addition to the generic eligibility criteria.	updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19. The remit has also been updated to consider people with symptomatic COVID-19. The scope has been updated to acknowledge the impact of variant-specific treatment efficacy. The treatments will be evaluated within their marketing authorisations. The risk of progressing to severe COVID-19 will be based on the characteristics from key clinical trials and would feed into the risk calculations used in the model. Equality

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			considerations will be taken into account in the appraisal.
	Dr Lucy Lamb	Does not specify children.	Thank you for your comment. The treatments will be evaluated within their marketing authorisations.
	University of Bristol	No – see comment above about terminology re: SARS-Cov-2 infection and COVID-19.	Thank you for your comment. This clarification has been made to the scope.
	NICE Managing COVID-19 Therapeutic subpanel	Alongside the two groups noted in the scope (patients in hospital and in the community), there may be variation in clinical and cost-effectiveness by other patient characteristics (eg. Covid-19 variant, severity status, risk of progression to severe disease, vaccination status, serostatus).	Thank for your comment. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19. The remit has also been updated to consider people with symptomatic COVID-19.

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Comparators	Eli Lilly and Company Limited	The comparators listed provide a comprehensive reference for treatment of COVID-19. However, baricitinib should only be compared to treatments considered at the same point in the treatment pathway i.e., Tocilizumab.	Thank you for your comment. The treatments will be evaluated within their marketing authorisations and compared with each other where appropriate.
	Gilead Sciences	Gilead notes that, in contrast with other MTAs, the Comparators section does not include any wording specifying that the interventions will be compared with each other. If this is what is planned, some wording to make this explicit would be helpful for stakeholders as it would render redundant many of the issues associated with comparing interventions in different populations and with different therapeutic targets. Gilead believes it would be appropriate to split patients by both setting (hospitalised with severe disease vs. not hospitalised with high risk of progression to severe disease) and within those groups, further defined by requirement for oxygen (inpatient only) and severity. Patients with COVID-19 are commonly categorised according to disease severity, and it is important to note that the NHS England policy uses a measure of severity to define patients and treatment options. NICE should consider the publications arising from the RECOVERY trial as an indication of treatments that constitute standard of care. In these, remdesivir is utilised in as part of standard of care. NICE may also wish to consider PANORAMIC and the available NHS England Commissioning Policies for defining patients that are at high risk. <u>People with COVID-19 who have not been hospitalised</u> As per figure 2, in the outpatient setting, anti-virals could be compared with each other, but not with other classes of medicine.	Thank you for your comment. The treatments will be evaluated within their marketing authorisations and compared with each other where appropriate. Following the discussion held in the scoping workshop the population has been updated to people with mild symptomatic COVID-19 at risk of progression to severe COVID-19 and people with severe COVID-19.

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		<u>People with COVID-19 who are in hospital and do not require supplemental oxygen</u> Equally, as per figure 2, for patients who are in hospital and have COVID-19, but do not require supplemental oxygen, remdesivir may be compared with nirmatrelvir + ritonavir and in combination with other treatment options. <u>People with COVID-19 who are in hospital and require supplemental oxygen</u> As described in the treatment sequence above, there are no direct comparators for remdesivir when used in patients requiring supplemental oxygen, and therefore in this population comparison should be with standard of care minus remdesivir. This positioning of remdesivir is evidenced by the fact it forms part of the control arm of numerous trials for other interventions, including lenzilumab, which further speaks to the complementary mechanisms of action of these classes of medicine. In the UK, there are interim NICE clinical management guidelines in place for the treatment of COVID-19, last updated October 2021, which indicate standard of care. Additionally, remdesivir is currently established clinical practice for these patients as set out in 3 existing Clinical Commissioning Policies: 1. *Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older) focuses on the use of remdesivir for hospitalised COVID-19 patients requiring supplemental oxygen.5* 2. *Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies in the treatment of COVID-19 in hospitalised patients (Version 5) focuses on the use of remdesivir (alongside other options) for patients with hospital onset COVID-19 at high risk of progressing to severe COVID-19 disease but not yet requiring supplemental oxygen.3*	The criteria to identify severe COVID-19 will be based on the criteria used in the COVID-19 rapid guideline: Managing COVID-19.

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		3. *Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies for non-hospitalised patients with COVID-19 focuses on the use of remdesivir (alongside other options) in non-hospitalised patients with COVID-19 at high risk of progressing to severe COVID-19 disease.4* These guidelines use the WHO definition of severity described above to classify patients and the 4C mortality risk assessment.	
	Humanigen, Inc.	Recent evidence from the Veterans Administration in the US suggests steroid use in patients who are hypoxic on room air ($Sp0_2$ <94%) or on low-flow supplemental oxygen have worse outcomes when placed on steroids. Tocilizumab data favours use in patients with a baseline CRP>75mg/L. However, the patient populations in some of the tocilizumab trials have significantly higher median CRP levels. These include CORI-MUNO (120mg/L), EMPACTA (136mg/L), RECOVERY (143 mg/L), REMAP-CAP (136mg/L) and COVACTA (155 mg/L). The guidelines should focus on the totality of evidence. There have been multiple negative studies in COVID, but the focus remains only on the positive studies.	Thank you for your comment. In the appraisal, the totality of the evidence will be considered. There will also be more formal opportunities to share any evidence if you feel it has not been captured in the assessment group report.
	Merck Sharp & Dohme (UK) Limited	NICE must provide more clarity as to what established clinical management is for patients who test positive with mild-moderate COVID-19 infection and therefore do not require hospitalisation during the early onset of disease. This is also needed for those that require hospitalisation. It must be clear if different standard of care is established based on any risk factors for more severe disease. MSD asserts that the innovative treatments already in use should be considered standard of care. It is thoroughly inappropriate to consider these not to be standard of care because response to the pandemic required non-typical routes for access to patients. We recognise NICE wants to assess	Thank for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it.

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		value for novel products but this assessment must be reflective of the real world, which is substantially different to the world of 2020 in terms of treatment options for patients.	
	Pfizer UK	• Comparators should be the initial standard of care excluding therapies that are being appraised as some of these are current being used off label or through early access routes such as RAPID C19 • There is a need to differentiate different levels of supplemental oxygen management as there can be a large difference of health care resource use (HCRU) and costs involved.	Thank for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it. In the appraisal, the different levels of supplemental oxygen support will be differentiated. There would also be opportunities to consult on the assessment group's model.
	Roche	In severe/hospitalised patients, where in our opinion an MTA is currently not appropriate, a matrix of populations by treatment and a current treatment algorithm should be a starting point to be able to comment on comparators. In these settings, since not all treatments are being used in all populations it is impossible to comment on the appropriateness of the comparators mentioned. Even within the "hospitalised people" treatments are used under different conditions (e.g. "Remdesivir is recommended for people who need	Thank for your comment. The treatments will be evaluated within their marketing authorisations and compared with each

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		low-flow supplemental oxygen" while "tocilizumab and sarilumab are recommended for people that have completed a course of corticosteroids and need supplemental oxygen"). As new agents are being introduced and older agents repurposed for use in COVID-19, preliminary work by Roche found globally over >100 different drug combinations, with new studies published every week. More clarity on UK "*established clinical management*" would be highly beneficial.	other where appropriate. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it.
	Sobi Ltd	Although the comparators are appropriate, it is worth noting that the standard of care / established clinical management varies dependent on the point of the clinical pathway the patient sits and this should be reflected in any technology appraisal.	Thank for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care at a particular point in the treatment pathway, which is routinely funded by the NHS with no strong rationale to appraise it.
	British Infection Association	Established clinical management with or without corticosteroids and appropriate respiratory support. Why are steroids treated differently? The comparator for both groups should be 'established clinical management' or more usually standard of care. This term should include steroids where indicated and respiratory support when indicated.	Thank for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS

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			as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it. Corticosteroids are very cheap drugs, and so there is not a strong rationale for the NHS to appraised them. Established respiratory management is also optimised currently, although this may develop as treatment continues.
	NHS England and NHS Improvement	The comparators would need to reflect established clinical management for less severe infection and that for severe infection, respectively, if the population is re-defined.	Thank you for your comment. No action needed.
	University of Bristol	Not my area of expertise.	Thank you for your comment. No action needed.
	NICE Managing COVID-19 Therapeutic subpanel	Existing best practice may change rapidly as more evidence becomes available and other interventions are introduced. Comparators and best practice will be setting and patient group specific.	Thank for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS

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			as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it. If established clinical management changes throughout the course of the appraisal, this will be reflected in the appraisal.
Outcomes	Eli Lilly and Company Limited	The outcomes measures presented capture the most important health-related benefits of baricitinib.	Thank you for your comment. No action needed.
	Gilead Sciences	The outcomes should be split by those patient groups as set out earlier in our response. For patients in hospital NICE should consider expanding the list of outcomes to include relevant outcomes such as: • Length of stay in hospital • Time to recovery • Severity of illness/symptoms or symptoms related to worsening of the underlying condition (based on ordinal score) • Mechanical/non-invasive ventilation • Ventilator-free days (CATCO has this) For patients who are not in hospital, an additional outcome that may be important in capturing the benefit of treatments is “admission to hospital”. This is relevant, as the current outcomes list does not capture need for hospitalisation (other than length of stay, which implies hospitalisation must occur).	Thank you for your comment. Hospitalisation (requirement and duration) has been added to the list of outcomes. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.

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		Further, we request that NICE defines post-COVID syndrome, as there is no universally accepted definition.	Post-COVID-19 syndrome will be defined in the same way as the rapid COVID-19 guidelines: any signs or 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.
	GlaxoSmithKline	The following outcomes should be included; • The percentage of patients who were hospitalized for more than 24 hours or who died from any cause through day 29 after randomization • Mean change in FLU-PRO Plus total score (AUC through Day 7). In addition, as these medicines are treating a pandemic disease, wider societal benefits should be considered in the appraisal, namely: • Prevention of significant healthcare system overload/capacity issues including QALYs lost in patients with other diseases not being treated or due to delayed diagnosis. • Work productivity loss	Thank you for your comment. Hospitalisation (requirement and duration) has been added to the list of outcomes. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data. Wider societal benefits would not be included in any proposed appraisal.

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			The NICE health technology evaluation manual states that *"…in exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* The aim of an evaluation of treatments for COVID-19 is to inform the management of COVID-19 as it becomes a routine part of NHS work, rather than an exceptional circumstance. The NICE health technology evaluation manual states that *"Productivity costs should be excluded from the reference case."*
	Humanigen, Inc.	• Survival without ventilation (also referred to as ventilator-free survival) • Incidence of IMV/death	Thank you for your comment.

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		• Ventilator-free days • Duration of ICU • Mortality • Time to recovery • Longer-term sequelae of IMV and other interventions	Hospitalisation (requirement and duration) has been added to the list of outcomes. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.
	Merck Sharp & Dohme (UK) Limited	The MOVe-Out RCT (NCT04575597) assessed the following objectives (and collected the following endpoints respectively)[iv v]: Primary: • Evaluate the efficacy of MK-4482 compared to placebo as assessed by the percentage of participants who are hospitalized and/or die from randomization through Day 29 (hospitalisation or death) • To evaluate the safety and tolerability of MK-4482 compared to placebo (adverse events, adverse events leading to discontinuation). Secondary: • evaluate the efficacy of MK-4482 compared to placebo as assessed by time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomization through Day 29 (COVID-19 signs/symptoms). • evaluate the efficacy of MK-4482 compared to placebo as assessed by the odds of a more favourable response on the WHO 11-point	Thank you for your comment. Hospitalisation (requirement and duration) has been added to the list of outcomes. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.

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		ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29 (WHO 11-point scale score). Tertiary/Exploratory: • Pharmacokinetics of parent nucleoside • antiviral activity of MK-4482 compared to placebo as assessed by the change from baseline in SARS-CoV-2 RNA titer in nasopharyngeal and/or oropharyngeal swabs separately at various timepoints. • evaluate the effect of MK-4482 on viral RNA mutation rate and detection of treatment-emergent sequence variants as assessed by comparison of gene sequencing in virus isolated at baseline and post-baseline in samples with evaluable SARS-CoV-2 RNA. Additional endpoints that may be of interest for decision making purposes and reflect a wider societal value should also be added. Some suggestions below from the PANORAMIC RCT protocol include[i]: - Time to recovery- 1st instance a patient reports feeling fully recovered - Symptom recurrence - Daily rating of feeling well - Household infection rate - Symptoms and wellbeing rate at 3 and 6 m (crucial for long term modelling) - Healthcare service utilisation - Time back to work MSD agrees with the inclusion of health-related quality of life as part of the assessment process. However, we would like to take the opportunity to note some of the difficulties with regards to HRQoL collection, especially in the hospitalised setting. NICE should follow a pragmatic approach and accept	Thank you for your comment. This has been noted. This will be considered in the appraisal.

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		alternative options that may deviate from the optimal Reference case if necessary as part of the HTA process. MSD suggests outcomes relating to health, quality of life and costs in the care home setting are of particular importance with COVID-19 treatments and request inclusion of appropriate outcomes. The usual perspective of NICE assessments are NHS and PSS, and the PSS element is critical in understanding the impact of both COVID-19 and its treatments therefore specific outcomes relevant to care home setting need to be considered and included. This may relate to an expanded definition of 'household infection rate', QoL measures for those isolating in a care home setting. We recognise that NICE does not include productivity costs in its usual base case. However, it is imperative that impact on the health care and social care workforce of both COVID-19 and treatments for COVID-19 are included in the economic modelling. Without this the true cost to the NHS or PSS will not be captured. This is perhaps less relevant to the NHS in an endemic setting – however endemic, epidemic or pandemic need to be robustly defined to enable this to be understood and therefore measured appropriately.	The remit of the appraisal does not include pre- and post-exposure prophylaxis. The populations to be included the appraisal are people with symptomatic COVID-19. Wider societal benefits would not be included in the appraisal. The NICE health technology evaluation manual states that *"…in exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* The aim of an evaluation of treatments

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			for COVID-19 is to inform the management of COVID-19 as it becomes a routine part of NHS work, rather than an exceptional circumstance. The NICE health technology evaluation manual states that *"Productivity costs should be excluded from the reference case."*
	Pfizer UK	Additional value elements for some of the treatments need to be included. Of note: • The impact of secondary infections (transmission value) should be accounted for along with impact of duration of infection. • In addition to length of hospitalisation, averted hospitalisations, averted ICU admissions and length of stay in ICU should also be considered. • There are broader elements that also need consideration. 1. The insurance value of a therapy in mitigating the impact of an increase in incidence of infections that could result from a new variant that escapes vaccine induced immune responses. 2. Enablement value were a therapy enables a wide range of surgical and medical procedures, such as chemotherapy to take place by avoiding pressure on bed capacity and procedure cancellations. Similar value element have been considered when considering new antimicrobials in the context of antimicrobial resistance: Microsoft Word - FINAL AMR Report 2-10-18.docx (eepru.org.uk),	Thank you for your comment. Hospitalisation (requirement and duration) has been added to the list of outcomes. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.

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		https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/evaluation-framework.pdf • The robustness of a treatment against variants (spectrum value) of concern should also be accounted for. For example, in the event of a new COVID-19 variants with immune escape from vaccines, some therapies under consideration retain their efficacy to address pressures from the new variant. Evidence for this has been recently published: Rai, DK 2022 available here, Greasley SE et al 2022 available here, Rosales, R et al 2022 available here, Vangeel et al, 2021 available here. • Potential use as of some of the treatments as prophylactics should be considered for example as an infection control measure in a hospital or in households of vulnerable individuals. Other aspects for consideration would be the impact of therapies on duration of isolation post COVID-19 infection, symptoms alleviation, concomitant treatment safety and the impact of Long Covid should also be accounted for.	The scope has been updated to acknowledge the impact of variant-specific treatment efficacy. The remit of the appraisal does not include pre- and post-exposure prophylaxis. The populations included in the appraisal are people with symptomatic COVID-19. These treatments might have an impact on the incidence or severity of post-COVID-19 and this will be an exploratory outcome, if there is clinical data to support this.

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	Roche	For completeness, regarding the outcomes mentioned in the draft scope, some thoughts are reported below. Requirement for respiratory support ● For completeness, requirements for respiratory support should include duration, type of respiratory support (non-invasive, vs. invasive and ECMO etc.) and progression to more invasive respiratory support should be added (3) Length of hospitalisation should include hospitalisations avoided Time to return to normal activities ● The time to return to usual activities is often dictated by governments and quarantine rules, as such it might not appropriately reflect the burden to the patient if this means return to work or school. The impact on the patients would be measured by symptoms, as such time to symptom improvement / resolution of symptoms might be a more appropriate measure (which might be covered by time to recovery) Symptoms of post COVID-19 syndrome (as described as 'long COVID) are currently poorly defined and more research is needed to define them. As many of the initial clinical studies in COVID-19 were conducted early in the pandemic, before 'long COVID' was recognised as a potential long-term sequelae of COVID-19, the majority of studies conducted at this time focused on endpoints such as reduction in mortality, reduction in need for mechanical ventilation or time to hospital discharge. As such, outcomes and measures related to 'long COVID' were not collected or assessed and therefore it is not feasible to assess many of the initial studies or early adopted treatments for their potential impact on 'long COVID.'	Thank you for your comment. Hospitalisation (requirement and duration) has been added to the list of outcomes. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data. These treatments might have an impact on the incidence or severity of post-COVID-19 and this will be an exploratory outcome, if there is clinical data to support this.

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		Re-infection and onward transmissions can be considered, although probably not always well captured in the clinical trials. A feasibility assessment also found > 100 unique outcomes/definitions reported and a lack of universal definition of severity (ie. mild, moderate, etc.). (3) used for example as endpoint here: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00676-0/fulltext)	
	Sobi Ltd	All the outcomes listed are appropriate.	Thank you for your comment. No action needed.
	British Infection Association	The outcome 'hospitalisation' is not included and would be applicable for the pre-hospital interventions. Consider the addition of those complications relating to severe COVID infection e.g. discharge with LTOT, development of thromboembolic disease	Thank you for your comment. Hospitalisation (requirement and duration) has been added to the list of outcomes. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.
	Metabolic Support UK	The outcome measures are appropriate, however, the psycho-social aspects within the health-related quality of life (for patients and carers) should be explicitly reviewed. Consideration should also be given to the disruptions and burden caused by short term and long term treatments.	Thank you for your comment. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.

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	NHS England and NHS Improvement	We would hope that NICE would make judgements about the relationship between short-term outcomes (e.g. severity of disease /admission to hospital) and likelihood and severity of long COVID-19; and build that into outcomes if the evidence allows.	Thank you for your comment. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.
	Dr Lucy Lamb	The outcomes seem reasonable	Thank you for your comment. No action needed.
	University of Bristol	The disruption to daily life for both patients and those treating them engendered by implementing the treatments widely should be considered, and if possible quantified. Patient preferences should be considered.	Thank you for your comment. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.
Economic analysis	Eli Lilly and Company Limited	The economic analysis proposed seems sufficient however the time horizon may be different depending on treatment. The COV-BARRIER study had a maximum duration on treatment for up to 14 days, however the results from the trial showed that (source data on file from CSR from COV-BARRIER) median days of exposure was 8.1 days. This should be considered in the economic analysis.	Thank you for your comment. No action needed.
	Gilead Sciences	NICE should consider the recommendations from the HTx (2021) Best-practice guidance for the health technology assessment of diagnostics and treatments for COVID-19. 16	Thank you for your comment. The assessment group will choose the outcomes to be included, based on

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			composite endpoints and the available data.
	GlaxoSmithKline	Given the need to account for long-term outcomes such as 'symptoms of post-COVID-19 syndrome' a lifetime time horizon is most appropriate.	Thank you for your comment. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.
	Humanigen, Inc.	In-patient time horizon, plus longer-term for convalescent patient post-hospital discharge. There are very limited data for follow-up of COVID patients. As we don't yet have 5-year data, we may need to use assumptions from other populations (e.g., ARDS) or clinician opinion. There are also very little data on the post-discharge patient pathway. For example, there is expected to be additional respiratory sequelae for patients who have undergone IMV and published data on the burden of illness relative to neurological and psychiatric sequelae. It would be useful to have some guidance. As mortality is a significant driver of ICERs, some guidance on assumptions related to increased mortality post-discharge for patients who required IMV during their hospitalisation would also be useful.	Thank you for your comment. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data. These treatments might have an impact on the incidence or severity of post-COVID-19 and this will be an exploratory outcome, if there is clinical data to support this.
	Merck Sharp & Dohme (UK) Limited	MSD ask that NICE offer more clarity on the phase of COVID-19 that is to be modelled for the purposes of this appraisal (pandemic, epidemic or endemic).	Thank you for your comment.

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		This will allow companies to better undestand any additional aspects of value that may not be fully reflected within the HTA assessement framework and the most suitable appropiriate modelling methodology. Asuming that the endemic phase of COVID-19 is in scope, MSD have no further comment with regards to the standard cost utility analysis (CUA) framework proposed by NICE (whilst we still remain extremely hesitant of this due to data limitations). Nonetheless, we note that the standard HTA assesment framework used by NICE has not been developed with the flexibility to capture some wider societal benefits. Whilst these may not be in the scope of the proposed appraisal, they are nonetheless relevant for HTA decision making purposes even under endepic COVID-19 scenario modelling, for example productivity impacts in the NHS and PSS workforce due to COVID-19 should be included. As example we include the following non-exhaustive list below: • True reflection societal costs, especially within care homes to truly capture the Personal Social Services perspective. • Reduced risk of onward community transmission • Options to reduce risk of hospitalisation for those that cannot receive a COVID-19 vaccine and test positive for the infection • Potential preference for community-based treatments to avoid/resolve NHS hospital capacity issues or inability of travelling to clinic • Phycological burden to wider family for those testing positive at high risk of hospitalisation • Emergence of future variants for which antivirals may continue to retain efficacy versus more specific mAbs	Any guidance will be on the use of the treatments in an endemic. However, the recommendations will be mindful regarding use in pandemics. Wider societal benefits would not be included in the appraisal. The NICE health technology evaluation manual states that *"…in exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* The aim of an

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		• Public health planning for any future significant outbreaks due to new COVID-19 variants of infection • Scenario planning for the management of localised outbreaks MSD believe that the above elements need to be factored into the assessment of COVID-19 therapuetics and therefore urges NICE to consider these. The NICE reference case stipulates that Health effects should be expressed in QALYs and that EQ-5D is the preferred measure of health related quality of life in adults. Our understanding of EQ-5D data from literature are extremely limited and may also not be directly generalisable to these patients. Additionally, prospective collection of the EQ-5D may be hindered in the hospitalised setting. Therefore, NICE should exercise pragmatism where possible and accept alternative sources of evidence that may deviate from the NICE Reference Case. Finally, with regards to the economic analyses, NICE should also clarify the source of prices to be used in absence of list prices for these comparators.	evaluation of treatments for COVID-19 is to inform the management of COVID-19 as it becomes a routine part of NHS work, rather than an exceptional circumstance. The NICE health technology evaluation manual states that *"Productivity costs should be excluded from the reference case."* Thank you for your comment. The NICE health technology evaluation manual states that *"NICE will not publish final guidance on a technology until UK regulatory approval has been granted and the technology's price is known or can be determined."*
	Pfizer UK	Considering the wider societal impact COVID 19 has had on productivity/GDP, the analysis should include a wider societal perspective.	Wider societal benefits would not be included in

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		Current proposal to restrict perspective to just the NHS would grossly undervalue these therapies. In addition, Insurance, enablement and spectrum value as explained above should also be included.	the appraisal. The NICE health technology evaluation manual states that *"…in exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* The aim of an evaluation of treatments for COVID-19 is to inform the management of COVID-19 as it becomes a routine part of NHS work, rather than an exceptional circumstance. The NICE health technology evaluation manual states that *"Productivity costs should be excluded from the reference case."*

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	Roche	Perspective of the analysis ● A broader health care system perspective should be considered in an economic evaluation, as this is an important impact: COVID has an impact on hospital capacity and other treatments being delayed etc. ● In addition, this caused burn out of hospital staff, as such professional caregiver disutility should be taken into account Time horizon ● An appropriate time horizon for cost effectiveness estimates should probably be ~5-10 years to include long COVID, which at the moment is not feasible.	Thank you for your comment. Wider societal benefits would not be included in the appraisal. The NICE health technology evaluation manual states that *"…in exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* The aim of an evaluation of treatments for COVID-19 is to inform the management of COVID-19 as it becomes a routine part of NHS work, rather than an exceptional circumstance. The NICE health technology evaluation manual states that *"Productivity*

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			costs should be excluded from the reference case." These treatments might have an impact on the incidence or severity of post-COVID-19 and this will be an exploratory outcome, if there is clinical data to support this.
	Sobi Ltd	No comments – no different to reference case.	Thank you for your comment. No action needed.
	British Infection Association	The cost needs to ensure the cost of delivery is included. Cost analysis should include secondary cost impacts such as the healthcare costs of contacting a patient who may be eligible for treatment but is not. The cost of the treatments comparison should include the costs of administration in the calculation (e.g. an intravenous agent over 3 days would have high administration costs compared to an oral agent with higher likely conversion to hospital admission and the costs of such events).	Thank you for your comment. The resource cost of delivering treatments will be included in the economic modelling.
	NHS England and NHS Improvement	NHSE&I is keen to work with NICE on the costs of NHS service delivery / administration in support of the planned economic assessment.	Thank you for your comment. No action needed.
	University of Bristol	See above re: disruption to daily life.	Thank you for your comment.

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Equality and Diversity	Eli Lilly and Company Limited	None identified.	Thank you for your comment. No action needed.
	Gilead Sciences	Equalities considerations will be central to this appraisal given that Public Health England has reported the impact of COVID-19 on exacerbating existing health inequalities17. Some of the disparities found were around age and sex, ethnicity, comorbidities, such as those with diabetes, hypertension, cancer and chronic lung disease, and immunosuppression18. For the purposes of the appraisal the following equalities considerations should be made by NICE. <u>Patients with a weakened immune system</u> Immunosuppression, or being immunocompromised, are considered risk factors for more severe COVID-19. Patients with a weakened immune system may be at a greater risk of severe illness from COVID-19 due to impaired immune defences. Many conditions and treatments can cause an individual to be immunocompromised. This high-risk population includes patients with primary immunodeficiency which is caused by genetic defects and patients with secondary immunodeficiency which can be caused by prolonged use of glucocorticoids or other immune weakening medications. 19 <u>Vaccination status:</u> In addition, there is evidence to suggest that uptake of vaccination is substantially lower in specific groups of people including people from lower socioeconomic groups and ethnic communities, which could further heighten their risk of infection and/or disease progression compared to the general population. 20,21 The dramatic impact of COVID-19 on these communities	Thank you for your comment. Equality considerations will be taken into account in the appraisal. The impact of vaccinations has been included in the scope. Equality considerations will be taken into account regarding vaccination status, where possible.

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		has both replicated and exacerbated existing health inequalities.17 Providing the option of treatment with remdesivir, particularly early in their hospital-based management, could help to address some of these inequalities by providing an effective treatment option for more susceptible patients who will not engage with vaccination, or potentially monoclonal antibody therapies. Unless subgroups relating to these factors are introduced in the scope, there could be equality issues arising.	
	Humanigen, Inc.	Given the disproportionate impact of COVID on unvaccinated populations, the BAME community, the elderly, disabled, immuno-compromised, cancer patients and other at-risk populations, we need to ensure adequate attention paid to the needs of these particular groups of patients.	Thank you for your comment. Equality considerations will be taken into account in the appraisal.
	Merck Sharp & Dohme (UK) Limited	None identified in the remit or scope at this stage. However, MSD would like to note that the MTA process in an area with rapidly evolving clincial evidence may disadvantage technologies resulting that are still collecting the evidence base required to meet NICE's assessments, with a potentially negative implication for access. If recommendations result from premature assessment of data there is a real risk populations with protected characteristics could be disproprotionately disadvantaged. We note also that while the remit and scope do not currently suggest any equality issues, COVID-19 has been higly discrimnatory towards older people, people from BAME communities and those with physical and/or learning disabilities. Therefore, the assessment of any COVID-19 treatments	Thank you for your comment. Equality considerations will be taken into account in the appraisal.

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		needs to take into account this disproproptiaonate impact of COVID-19 and any differential treatment effect observed in these populations needs to be properly and discretely considered. MSD urges NICE to consider rescheduling this appraisal.	
	Pfizer UK	Covid-19 has been shown to impact different societal groups differently. Our clinical trials have been designed to include patients from a diverse background reflecting the patients who will be treated. This also has important implications for the broader levelling up agenda with the possibility that Paxlovid may be required outside a hospital setting in areas of deprivation with associated mixed-race demographics.	Thank you for your comment. Equality considerations will be taken into account in the appraisal.
	Sobi Ltd	No equality issues to comment on.	Thank you for your comment. No action needed.
	Faculty of Pharmaceutical Medicine	As noted above, pregnant women are at risk of being full considered. Patients with other medical conditions who require protection from COVID in order to access the treatment they need are at risk of being discriminated against with the current approach.	Thank you for your comment. Equality considerations will be taken into account in the appraisal.
	British Infection Association	The scope needs to include equality impact assessments at all times. In particular it needs to highlight access for those who are deaf (so for whom telephone assessments may be challenging) and lack capacity (again telephone assessments may be more complex). The costings should include ensuring appropriate systems are available nationally for accommodation of such aspects. Ethnicity is also known to be an important predictor of some outcomes, a specific analysis of impact of ethnicity on treatment effects may be helpful.	Thank you for your comment. Equality considerations will be taken into account in the appraisal.

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	NHS England and NHS Improvement	NHSE&I is committed to addressing health inequalities experienced by certain groups. Previous work has highlighted, for example, substantial variation in vaccine coverage in certain groups including those from different ethnic groups; those from poorer areas; those with a learning disability and those with a serious mental illness. [Ref: OpenSAFELYhttps://bjgp.org/content/72/714/e51] NHSE&I asks for consideration of these demographic and clinical subgroups in developing of the MTA and can facilitate access to OpenSAFELY if necessary.	Thank you for your comment. Equality considerations will be taken into account in the appraisal.
	University of Bristol	Equality mentioned but no detailed plans for ensuring such given.	Thank you for your comment. Equality considerations will be taken into account in the appraisal.
Other considerations	Gilead Sciences	<u>Additional complexity</u> As stated above, there is considerable complexity in this appraisal due to the unique and evolving nature of the condition, and of the features of the patient population. Therefore, NICE should not seek to assess the impact of the interventions in the event of further disease mutations, or changing patient profile, as this would introduce uncertainty that cannot be mitigated. Instead, NICE should assess treatments as per their trial data, and available real-world evidence, irrespective of the variant circulating at the time of the studies or the vaccination status of the populations. The point about vaccination status is particularly important as vaccination efficacy wanes with time and a new variant can lead to a vaccine escape mutant rendering vaccination status irrelevant. Equally, new variants can result in an intervention losing its effectiveness. Further, a currently ineffective intervention could become effective again in the future if a different new variant is susceptible to it. We suggest that NICE produces guidance on the basis of the broad available	Thank you for your comment. The scope has been updated to consider the impact of vaccines and the impact of variant-specific treatment efficacy.

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		evidence base and allows the NHS to assess the effectiveness of all treatments each time a new variant arises and/or a vaccine/booster is widely utilised. <u>Evidence requirements</u> Due to the unique features of this appraisal, much of the real-world evidence, which is required in order to establish the patient population at baseline, among other things, is not available to companies. Datasets such as RECOVERY, will be required by companies and the EAG, and we therefore ask that NICE makes this evidence available at the earliest possible opportunity. In addition, the following data sets would be essential to support robust modelling: • ISARIC • ICNARC • DECOVID • TACTIC • PHOSP-COVID Data requirements which can partly be addressed by these sources include, baseline data, length of stay on general ward, length of stay / cost data ICU, post-discharge QoL. <u>Additional touchpoints</u> Due to the complexity of this appraisal, we request that NICE provides the opportunity for additional dialogue between companies, NICE and the EAG. This is essential to allow sharing of information, testing of potential approaches and discussion of the most appropriate way to handle complexity.	Within a multiple technology appraisal, if the assessment group requires access to unpublished data, NICE will try to facilitate this. However, if the assessment can be based on publicly available data, this will be most transparent for all stakeholders. Thank you for your comment. The timelines for this appraisal, will be shared at the earliest opportunity. The appraisal will not follow the usual process, given the scale of this appraisal.

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	Merck Sharp & Dohme (UK) Limited	Whilst the CUA assesment framework is adopted by NICE, it is limited with regards to capturing additional benefits that these products have for the society and the health system. MSD ask that these are adequately identified and quantified in the HTA process to avoid disadvantaging these technologies during the appraisal process.	Thank you for your comment. Any innovation or clinical benefit not captured in QALY calculations will be considered qualitatively by the committee. However, wider societal benefits would not be included in the appraisal. The NICE health technology evaluation manual states that *"…in exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* The aim of an evaluation of treatments for COVID-19 is to inform the management of COVID-19 as it becomes a routine part

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			of NHS work, rather than an exceptional circumstance. The NICE health technology evaluation manual states that *"Productivity costs should be excluded from the reference case."*
	Roche	Variants of concern are not mentioned anywhere and they should be. As stated above, the efficacy of some treatments may vary depending on the variant and not taking this into account in an assessment would limit the applicability of the assessment, if the scope is not restricted.	The scope has been updated to acknowledge the impact of variant-specific treatment efficacy.
	Faculty of Pharmaceutical Medicine	Data sources must include evaluation of the significant amounts of real-world evidence available such as ISARIC and ICNARIC.	Thank you for your comment. No action needed.
	British Infection Association	The subgroups should include vaccinated/ previously infected/naïve to infection or vaccinated/exposed but unlikely/not expected to develop an immune response as the outcomes from COVID-19 and thus potential benefits of treatments would be expected to differ in these groups.	Thank you for your comment. The scope has been updated to acknowledge the impact of variant-specific treatment efficacy and vaccines.
	Long Covid SOS	As sometimes treatments within the acute covid stage also include antibiotics due to suspected or secondary respiratory infection, it would be good to gather evidence on outcomes to see if they differ. Especially as there is a theory that the gut microbiome may play a role in preventing Long Covid https://www.bmj.com/company/newsroom/ma ke-up-of-gut-microbiome-may-be-linked-to-lo ng-covid-risk	Thank you for your comment. The appraisal would not involve data generation, but rather data collection. Although post-COVID-

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			19 syndrome will be an important consideration, it won't be the focus. The focus will be on the clinical- and cost-effectiveness of therapeutics to treat COVID-19. These treatments might have an impact on the incidence or severity of post-COVID-19 and this will be an exploratory outcome, if there is clinical data to support this.
	University of Bristol	See above re: including disruption to life and health services through the implementation of the treatment protocols	Thank you for your comment. No action needed.
Innovation	Eli Lilly and Company Limited	Baricitinib has specific immunomodulatory effects compared to rather broad and unspecific immunosuppression that is associated with steroid treatment. Another clinical benefit includes the relatively short half-life of baricitinib, especially when compared to Tocilizumab " up to approximately 13 hours vs approximately 16 days" respectively. This allows for more flexible schedules using baricitinib in clinical practice (EMA Olumiant SmPC; EMA Tocilizumab SmPC).	Thank you for your comment. Any innovation or clinical benefit not captured in QALY calculations will be considered qualitatively by the committee.

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		While the benefits of baricitinib did not meet statistical significance on the primary endpoint, treatment with baricitinib reduced 28-day all-cause mortality by 38·2% when used with standard of care which included 79.3% participants were receiving systemic corticosteroids at baseline of which 91.3% were on dexamethasone. This treatment effect observed is considered the highest in comparison to other large scale clinical trials for COVID-19 (Manconi et al, 2021; The Recovery Collaborative Group, 2021) In addition, when considering tolerability of baricitinib there is little or no increase in serious adverse events (Manconi et al, 2021). References: 1. EMA Olumiant SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/olumiant 2. EMA Tocilizumab SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/roactemra 3. Marconi, Vincent CAhn, Mi-Young et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial; The Lancet Respiratory Medicine, Volume 9, Issue 12, 1407 – 1418 4. Recovery Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19; New England Journal of Medicine, 2021.384(8), pp.693-704. 5. Recovery Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial; Lancet 2021; 397: 1637–45	

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	Gilead Sciences	Remdesivir, as the first approved medicine for the treatment of COVID-19, represents a significant innovation and a 'step-change' in the treatment of the disease. Since it was made available in the early stages of the pandemic it has remained a backbone of standard of care for hospitalised patients, with tens of thousands of hospitalised patients treated with remdesivir in the UK to-date, and >9 million COVID-19 patients globally. Despite the number of variations seen, and the fact that some treatments are thought to be less effective in some recent variants, remdesivir has been a constant treatment option. There are a number of system level benefits brought about by effective treatment of COVID-19 that would not typically be captured in the appraisal, including the ability to discharge patients earlier reducing the need to delay or cancel planned procedures for non-COVID patients. These benefits are distinct from usual benefit of discharging patients early due to the direct relationship between patients occupying temporary COVID-19 wards and occupying HCPs' time where they would ordinarily be caring for other types of patients.	Thank you for your comment. Any innovation or clinical benefit not captured in QALY calculations will be considered qualitatively by the committee.
	GlaxoSmithKline	Yes, sotrovimab represents an innovative treatment option for the early treatment of COVID-19 in symptomatic adults and adolescents (aged 12 years and over and weighing at least 40kg) who are at risk of progressing to severe covid infection. • Sotrovimab is step change in care that results in a clinically and statistically significant reduction in all-cause hospitalization and/or death in high-risk patients with symptomatic, mild to moderate COVID-19. • Sotrovimab was engineered to retain effectiveness against virus mutation. [1-4]	Thank you for your comment. Any innovation or clinical benefit not captured in QALY calculations will be considered qualitatively by the committee.
	Humanigen, Inc.	Whether in the community setting, the Emergency Room/Casualty, or the hospitalised setting, there is a need to differentiate therapies which may be used for mild/moderate patients from therapies for people who have COVID-	Thank you for your comment. Any innovation or clinical

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		19 pneumonia and showing signs of hypoxia ($SpO_2 \leq 94\%$ on room air or require supplemental oxygen support). This latter group is at more significant risk of progressing to IMV and death. Need to optimize both the sequencing of agents and possible combinations of agents for different patient types in different stages of the disease. There is currently limited follow-up data for COVID patients so the ultimate cost of COVID is yet to be characterized, including long COVID. It may be informative to use data on IMV patients in other conditions such as ARDs and the sequelae in order to understand this better. Understanding the threshold that NICE will apply will be useful. Will a therapeutic that may prevent IMV and death be considered within the cost-effectiveness threshold for end-of-life therapies? This would seem appropriate. QALY is an appropriate measure but may not have a lot of clinical utility. The use of Numbers Needed to Treat and Numbers Needed to Harm could be helpful.	benefit not captured in QALY calculations will be considered qualitatively by the committee. In the appraisal the end of life criteria would not be considered, as this will be evaluated through the new methods guide. The new methods guide implemented a severity modifier, which will be taken into account if the criteria were met. It is expected that numbers needed to treat (NNT) will be implicit in the modelling results.
	Merck Sharp & Dohme (UK) Limited	MSD considers molnupiravir to be a highly innovative treatment option that has a potential to make a significant and substantial positive impact on health-related benefits for non-hospitalised patients with mild-moderate COVID-19 disease which have at least one risk factor for developing severe illness. Its unique mode of action means that it may remain active against all variants of COVID-19 to date although in vitro clinical research may be required to confirm this against new variants. 3	Thank you for your comment. Any innovation or clinical benefit not captured in QALY calculations will be considered qualitatively by the committee.

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		Monupiravir is administered orally and is well tolorated and unlikely to cause Drug Drug Interactions (DDIs).2 Patients may also have a preference for oral therapies versus those administered intravenusly in an outpatient setting. The above attributes may result in additional health-related benefits for patients with polypharmacy and their carers that may not be captured under the current standard QALY framework but are essential for decision making purposes and relevance of recommendations.	
	Pfizer UK	Paxlovid has a conditional market authorisation for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID 19. Paxlovid has the potential to reduce hospitalisations and progression to severe COVID 19 which will lead to significant benefit for patients' quality of life and will reduce the burden of the disease on their life. This has a broader impact on society as people can quickly return to their productive lives. Paxlovid also provides additional insurance and spectrum value as it remains effective against variants of concerns for example Omicron. Pfizer has several ongoing clinical trials with anticipated readout dates as follows: 1. Data from 3 Ph2/3 studies PFIZER: EPIC-HR(NCT04960202) completed and results available. 2. PFIZER: EPIC-SR(NCT05011513), final results expected Feb 2022. 3. EPIC-PEP(NCT05047601) final results expected Q3 2022., EPIC-SR EPIC-PEP Additional relevant UK clinical trials include:	Thank you for your comment. Any innovation or clinical benefit not captured in QALY calculations will be considered qualitatively by the committee.

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		1. PANORAMIC: Homepage — PANORAMIC (panoramictrial.org) 2. RECOVERY: Welcome — RECOVERY Trial	
	Roche	Some COVID-19 treatments can result in health-related benefits that are unlikely to be appropriately captured in the QALY calculation for the time being, as stated above in the "Economic Analysis" section. Some example include: ● COVID-19 has an impact on hospital capacity and waiting times for other treatments increased. ● Burn out of hospital staff has been important, as such professional caregiver disutility should be taken into account. The benefit some treatments may have on long COVID is currently difficult to estimate.	Thank you for your comment. Any innovation or clinical benefit not captured in QALY calculations will be considered qualitatively by the committee.
	Sobi Ltd	Anakinra is well established medication used to treat a variety of inflammatory conditions. Anakinra's pending MHRA approval for the treatment of COVID-19 (and it's EU approval) represents the only current therapeutic with a prognostic biomarker to guide treatment success. The goal of anakinra treatment is to prevent severe disease in adult patients with COVID 19–related pneumonia. Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker of disease severity and progression. Early suPARguided treatment with anakinra prevented progression to severe respiratory failure in adult patients with COVID 19 and pneumonia (Kyriazopoulou et al., 2021a; Kyriazopoulou et al., 2021b). In the SAVE-MORE study, mortality was reduced in the SOC + anakinra treatment group by 55% compared to SOC alone (Kyriazopoulou et al., 2021b). Having the ability to 'guide' successful treatment outcomes represents an innovation in the potential to make a significant impact on health related benefits including accelerated hospital discharge.	Thank you for your comment. Any innovation or clinical benefit not captured in QALY calculations will be considered qualitatively by the committee.

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	British Infection Association	Yes	Thank you for your comment. No action needed.
	Metabolic Support UK	Have not seen any RWE or data linked to potential health-related benefits in the documents or scope so we would like to see some impact data for each of these technologies.	Thank you for your comment. The scope does not usually include real world evidence or specific data sets. Appropriate real world data and data about health-related benefits will be included in the appraisal.
	NHS England and NHS Improvement	We suggest no reason to depart from NICE's standard approach to innovation. It should be recognised that the UK has been world leading in its COVID research and in its collaborative approach to evidence generation, review and deployment and NICE's recommendations may therefore be of significant importance beyond England.	Thank you for your comments. No action needed.
	University of Bristol	Yes to all, but my comments above relate to this	Thank you for your comments. No action needed.
Questions for consultation			
How many people who need supplemental	Gilead Sciences	According to the definition used in NICE's rapid guideline, patients requiring supplementary oxygen are defined as having severe disease.	Thank you for your comments. No action needed.

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oxygen progress to severe COVID-19?	Humanigen, Inc.	Use of biomarkers, such as CRP, per the ISARIC 4C Consortium algorithm, to predict mortality risk and the appropriate therapeutic selection.	Thank you for your comments. No action needed.
	Merck Sharp & Dohme (UK) Limited	MSD is unable to respond to this question with certainty at this stage without conducting a thorough review of the clinical literature to date. We also understand that this will be dependent upon underlying comorbidities and risk factors. We suggest ISARIC, PANORAMIC and GOV.UK as the best sources of evidence to address this question although the generalisability of these sources will also need to be scrutinised further[vi]	Thank you for your comments. No action needed.
	British Infection Association	This question needs separation into those expected to have some immunity and those who would not be expected to have immunity.	Thank you for your comments. The impact of immunity and vaccinations will be considered, where possible, in any economic model.
Have all relevant interventions for these settings been included in the scope?	Eli Lilly and Company Limited	Based on the latest evidence the relevant interventions have been reflected.	Thank you for your comments. No action needed.
	Merck Sharp & Dohme (UK) Limited	MSD understands that the interventions listed across these settings are complete and up to date at this point in time. However, more interventions may become available during the assessment process which may impact upon the robustness of final recommendations. With that in mind, we urge NICE to postpone the HTA appraisal activities and reschedule at a later stage. What is not yet clear, and cannot be determined by a HTA, is how these products are best used. Clinical experience with accompanying data	Thank you for your comment. As managing COVID-19 becomes a routine part of NHS work, plausibly towards the end of 2022, both the clinical and cost-effectiveness of treatments will need to

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		collection is needed to understand the exchangeability of these products, any unique characteristics they may have (positive or negative).	be explored to guide future commissioning and funding decisions.
	British Infection Association	Remdesivir, tocilizumab, casirivimab and imdevimab, baricitinib, sotrovimab, molnupiravir, anakinra, lenzilumab and PF-07321332 and ritonavir have been included. How were these selected? Please provide clarity and add options for future agents. This is not a comprehensive list of COVID-19 treatments (does not include dexamethasone nor respiratory support) and some of these agents have previous NICE C-19 guidance and some do not.	Thank you for your comment. The treatments included in the scope are expected to have marketing authorisations for treating COVID-19 within the next year.
Which treatments are considered to be established clinical practice in the NHS for treating people hospitalised with COVID-19**?**	Eli Lilly and Company Limited	Dexamethasone has been proven to be effective and is established in clinical practice. However, as patients progress to more severe states additional treatments should be considered. Based on its positive benefit/risk ratio baricitinib should therefore be considered as part of the treatment algorithm.	Thank you for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it.
	Gilead Sciences	The treatments set out in NICE's rapid guideline and NHS England's commissioning policies (those published for at least one month) represent established clinical practice.	Thank you for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care,

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			which is routinely funded by the NHS with no strong rationale to appraise it.
	Merck Sharp & Dohme (UK) Limited	For patients who are hospitalised for treatment of COVID-19, the treatment would depend upon severity. The NICE RAPID C-19 guideline and evidence summaries produced by NICE include the current SoC used in the NHS.[vii] For patients who do not require hospitalisation, the standard of care is evolving as new therapeutic agents and effectiveness data become available. The options available would be dependent upon comorbid conditions and/or the the presence of risk factors. This means that there is a need for the current SoC to reach an equilibrium before NICE can conduct an assessment. However, these individuals may also receive over-the-counter symptom-alleviating medications that may not be adequately costed if these are not contraindicated to their assigned therapeutic. *Molnupiravir can either be used in the community setting or may also be used for patients which have been admitted to the hospital and who do not require high levels of respiratory support. As per the SmPC, molnupiravir should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset*.**Error! Bookmark not defined.**	Thank you for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it.
	British Infection Association	This question is within NICE existing guidelines e.g. for dexamethasone, Remdesivir, tocilizumab/sarilumab, oxygen/appropriate respiratory support.	Thank you for your comment. No action needed.
Are the outcomes listed appropriate?	Eli Lilly and Company Limited	Yes, mortality is considered the most relevant treatment outcome.	Thank you for your comment. No action needed.

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	Merck Sharp & Dohme (UK) Limited	Substantial additional outcomes are needed to accurately measure the impact of COVID-19 and the potential value of treatments. If scenarios around public health planning and/or outbreaks are needed, then both the modelling approach and the outcomes needed will have to be adjusted to ensure accurate assessment.	Thank you for your comment. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data.
	British Infection Association	Yes but suggestions added	Thank you for your comment. No action needed.
Are there any subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?	Eli Lilly and Company Limited	Currently we do not have the data to show significant effects in particular subgroups however we are looking into this but data is still ongoing.	Thank you for your comment. No action needed.
	Gilead Sciences	Hospitalised patients may be grouped by oxygen requirement, as set out in the response to the populations section above. In addition, NICE may consider high risk groups within these populations.	Thank you for your comment. The appraisal will focus on 2 populations: people with mild COVID-19 at risk of progressing to severe COVID-19 and people with severe COVID-19.
	Merck Sharp & Dohme (UK) Limited	Potential subgroups of interest for this appraisal may include: ○ Patient groups at high risk for developing severe disease and for patients. It is likely that not all high-risk patients will have the same response to either COVID-19 or COVID-19 treatments, therefore it is likely the high-risk population will need further sub-division.	Thank you for your comment. The appraisal will focus on 2 populations: people with mild symptomatic COVID-19

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		○ Patients with polypharmacy and in need of products that may cause fewer DDIs. ○ Those groups which cannot be vaccinated for various medical reasons or for those that are unlikely to mount an immune response to vaccination. ○ Understanding how novel variants may impact all of the above is also required in order to the NICE recommendation to remain relevant	at risk of progressing to severe COVID-19 and people with severe COVID-19. The risk of progressing to severe COVID-19 will be based on the characteristics from key clinical trials and would feed into the risk calculations used in the model. The impact of vaccines and variants has been considered in the updated scope.
	Roche	Subgroups: Risk factors such as age should be considered separately.	Thank you for your comment. The treatments will be evaluated within their marketing authorisations.
	Sobi Ltd	Sobi would also like to highlight that anakinra use in the SAVE-MORE study is guided by Soluble urokinase plasminogen activator receptor (suPAR), a biomarker of disease severity and progression. This prognostic biomarker allowed for the selection of patients at most risk of disease progression. This personalised medicine approach may represent a more cost-effective treatment strategy. In the SAVE-MORE study, mortality was reduced in the SOC + anakinra treatment group by 55% compared with SOC alone (Kyriazopoulou et al., 2021b).	Thank you for your comment. No action needed.

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	British Infection Association	Yes- the subgroups based on expected immune responses is important. Risk factors are important but it needs clarity on the risk factors in a relatively immune (post-exposure or post-vaccination) population rather than relying solely on risk factors cited in early studies as some groups considered to be high-risk originally may be lower risk once vaccinated and this needs clarification.	Thank you for your comment. The risk of progressing to severe COVID-19 will be based on the characteristics from key clinical trials and would feed into the risk calculations used in the model.
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 proposed remit and scope may need changing in order	Merck Sharp & Dohme (UK) Limited	Please see our response above.	Thank you for your comment. No action needed.

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to meet these aims.			
Do you consider that the use of any of the technologies could result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculations? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.	Merck Sharp & Dohme (UK) Limited	See response above. MSD has highlighted the substantial limitations associated with undertaking an MTA at this time, with many elements in the scope not defined to the extent needed. MSD urge's NICE to extensively revise both the timing and the scope of the assessment so that any recommendation is appropriate and relevant.	Thank you for your comment. The timelines for this appraisal, will be shared at the earliest opportunity. The appraisal will not follow the usual process, given the scale of this appraisal.
To help NICE prioritise topics for additional	Eli Lilly and Company Limited	No, we do foresee any barriers. Product in supply and priced in over 70 countries for RA and AD.	Thank you for your comment. No action needed.

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adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.	Gilead Sciences	• There are no barriers to the implementation of remdesivir in clinical practice as it is already established standard of care. • However, there may be barriers to other treatments based on limited manufacturing capacity, and potentially reduced efficacy against recent variants.	Thank you for your comment. Product supply will be considered as part of implementing any positive guidance.
	Merck Sharp & Dohme (UK) Limited	MSD has been privileged to support the UK Government and the NHS in a time of crisis. Considering the limitations extensively discussed above, MSD believes it is appropriate to initiate a formal HTA and is not in a position at this time to enter the standard NICE HTA process and adequately support the value of molnupiravir by presenting a robust submission to NICE. MSD strongly urges NICE to reconsider the timing and the routing of this appraisal to allow for a robust future assessment to take place. MSD will continue to advocate for open dialogue between the companies and NICE to identify the most optimal process for HTA routing once the NICE scheduling permits the initiation of a formal clinical and cost-effectiveness evidence review. We are concerned that the technologies won't be adopted post HTA because the recommendations will not be accurate. Enormous societal damage could result from an assessment that is compromised due to the limited data currently available.	Thank you for your comment. This work will be of importance when managing COVID-19 becomes a routine part of NHS work, plausibly towards the end of 2022. As a technology appraisal takes 6 to 9 months to produce draft recommendation it is appropriate to begin the scoping exercise. NICE considers the resources available to the NHS when determining value for money. So, the opportunity cost of continuing to fund treatments that are not cost-effective, during an endemic, must be considered.

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			The scope has been updated to acknowledge the impact of variant-specific treatment efficacy and vaccines.
NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising this topic through this process.	Merck Sharp & Dohme (UK) Limited	MSD disagrees with NICE's proposal to use the MTA process for this topic. The reasons are elaborated extensively above.	Thank you for your comment. No action required.
Additional comments on the draft scope	Eli Lilly and Company Limited	Please see comments on post-meeting pathway suggestion in the slides uploaded.	Thank you for your comment. This suggestion has been noted.
	Gilead Sciences	Given the increased complexity of this appraisal, we ask that there are additional touchpoints between the companies, NICE and EAG both prior to and following submission. We would also ask that NICE clarifies whether additional data may be submitted at various points during the process.	Thank you for your comment. The timelines for this appraisal, will be shared at the earliest opportunity. The

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			appraisal will not follow the usual process, given the scale of this appraisal.
	GlaxoSmithKline	[redacted]	Thank you for your comment. This has been noted.
	Humanigen, Inc.	We need to be careful about suggesting that medicines that fall into a common class are interchangeable and target similar populations. Immunomodulatory antibodies such as lenzilumab, tocilizumab, sarilumab etc., have distinct modes of action and likely have different “ideal” patients. If we do not target these therapies to the appropriate patient group, not only will there be inappropriate use, but also potential loss of therapeutic options for patients as they progress. Therefore, sequencing of therapies within the same class would be an important consideration.	Thank you for your comment. The treatments will be evaluated within their marketing authorisations and compared with each other where appropriate.
	Pfizer UK	Is this about comparing the relative efficacy of different therapies with other Covid 19 treatments or only comparing each treatment in turn with the relevant comparators.	Thank you for your comment. The treatments will be evaluated within their marketing authorisations and compared with each other where appropriate.
	Sobi Ltd	Sobi would also like to comment on the additional slide provided by NICE on 28th January regarding the treatment pathway and where the various interventions would be positioned. Anakinra is positioned in the slide as covering high-flow oxygen, mechanical ventilation and ECMO categories	Thank you for your comment. This has been noted.

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		which is not accurate. Anakinra is approved in the EU and under review by the MHRA for C19 patients on low-flow/high-flow oxygen prior to escalation for more invasive treatments such as mechanical ventilation or ECMO. Therefore the slide should be amended to reflect anakinra's positioning across pre-inflammatory and inflammatory categories but only the low flow and high flow oxygen boxes.	
	Sobi Ltd	In the sections NICE Related Recommendations and NICE pathways: Anakinra NICE Evidence Summary 26 - It is important here to ensure anakinra is differentiated from HLH associated hyperinflammation and Covid-19 hyper-inflammation so it is positioned in the right group of patients, this is also important in terms of any data that is assessed.	Thank you for your comment. A distinction between HLH associated hyperinflammation and COVID-19 hyperinflammation has been noted. This evidence summary has not been deleted from the scope, to ensure completeness of the related NICE recommendations.
	Long Covid SOS	Any publications about the prevalence of Long Covid as a consequence of Covid-19 should also be referenced in this scope rather than just as a description within the paragraph. The subsequent development of a chronic health condition, with the individual, familial and economic effects this may incur, because of having had a Covid-19 infection has not been adequately counted so there is a data deficit in this area.	Thank you for your comment. Although post-COVID-19 syndrome will be an important consideration, it won't be the focus of the appraisal. The focus will be on the clinical- and cost-effectiveness of therapeutics to treat

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			COVID-19. These treatments might have an impact on the incidence or severity of post-COVID-19 and this will be an exploratory outcome, if there is clinical data to support this. This data would not normally be stated in the scope.
	NICE Managing COVID-19 Therapeutic subpanel	The environment for this appraisal is rapidly changing (eg, covid-19 variants, vaccination policy, available interventions). If possible, to be most helpful in informing decisions, the structure of the economic model(s) developed in the appraisal should be such as to enable rapid revisions and updates when new evidence (either for the identified interventions and/or additional interventions) becomes available. Equity issues: In the community setting, access to some treatments (e.g. those which require infusions) may be restricted for patients with limited access to healthcare facilities. Lack of evidence in specific groups (e.g children, pregnancy, immunocompromised individuals)	Thank you for your comment. Equality and equity considerations will be taken into account in the appraisal. Any clinical effectiveness evidence will be based on publicly available living network analyses, ensuring the data are as up to date as possible. Wider literature and assumptions, using expert opinions will be used to support lack of

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			robust evidence in the appraisal.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Thoracic Society
Royal College of Anaesthetists
Royal College of Pathologists
British Infection Association
Kidney Care UK
Thrombosis UK
All Wales Therapeutics and Toxicology Centre
Department of Health and Social Care
Scottish Medicines Consortium
School of Health and Related Research (ScHARR)

References:

- Eli Lilly and Company Limited:
    1. References within responses.

- Gilead:

1. Cevik, M., Kuppalli, K., Kindrachuk, J. & Peiris, M. Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ* **371**, (2020).
2. Wu, Z. & McGoogan, J. M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* **323**, 1239–1242 (2020).
3. NHS England. *Interim Clinical Commissioning Policy : Antivirals or neutralising monoclonal antibodies in the treatment of COVID-19 in hospitalised patients (Version 5)*. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/09/C1560-ii-interim-ccp-antivirals-neutralising-monoclonal-antibodies-treatment-of-covid-19-in-hospitalised-patie.pdf (2022).
4. NHS England. *Interim Clinical Commissioning Policy: Neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19*. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/12/C1560i-interim-ccp-antivirals-or-neutralising-monoclonal-antibodies-non-hospitalised-patients-with-covid19.pdf (2022).

5. NHS England. *Interim clinical commissioning policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older)*. https://www.england.nhs.uk/coronavirus/publication/interim-clinical-commissioning-policy-remdesivir-for-patients-hospitalised-with-covid-19-adults-and-children-12-years-and-older/ (2021).
6. Kalil, A. C. *et al.* Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N. Engl. J. Med.* **384**, 795 (2021).
7. Kalil, A. C. *et al.* Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial. *Lancet. Respir. Med.* **9**, 1365–1376 (2021).
8. Kreuzberger, N. *et al.* SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. *Cochrane database Syst. Rev.* **9**, CD013825 (2021).
9. Self, W. H. *et al.* Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. *Lancet. Infect. Dis.* (2021) doi:10.1016/S1473-3099(21)00751-9.
10. NIH. ACTIV-5 / Big Effect Trial (BET-A) for the Treatment of COVID-19 - NCT04583956 - ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04583956.
11. NIH. ACTIV-5 / Big Effect Trial (BET-B) for the Treatment of COVID-19 - NCT04583969 - ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04583969.
12. NIH. ACTIV-5 / Big Effect Trial (BET-C) for the Treatment of COVID-19 - NCT04988035 - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04988035?cond=COVID-19&fund=01&draw=2&rank=15.
13. Polizzotto, M. N. *et al.* Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. *Lancet (London, England)* (2022) doi:10.1016/S0140-6736(22)00101-5.
14. Mylonakis, E., Somersan-Karakaya, S., Sivapalasingam, S., Ali, S. & Sun, Y. Casirivimab and Imdevimab for Treatment of Hospitalized Patients With COVID-19 Receiving Low Flow or No Supplemental Oxygen. *Open forum Infect. Dis.* **8**, 2021 (2021).
15. Publications, O. & Oximetry, C. C0445-remote-monitoring-in-primary-care-jan-2021-v1.1. 1–6 (2021).
16. Elvidge, J. *et al.* Best-practice guidance for the health technology assessment of diagnostics and treatments for COVID-19. (2021) doi:10.5281/ZENODO.5530468.
17. *Disparities in the risk and outcomes of COVID-19*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/908434/Disparities_in_the_risk_and_outcomes_of_COVID_August_2020_update.pdf (2020).
18. Gilead Announces New England Journal of Medicine Publication of Data Demonstrating Veklury® (Remdesivir) Significantly Reduced Risk of Hospitalization in High-Risk Patients With COVID-19. https://www.gilead.com/news-and-press/press-room/press-releases/2021/12/gilead-announces-new-england-journal-of-medicine-publication-of-data-demonstrating-veklury-remdesivir-significantly-reduced-risk-of-hospitalization.
19. Roback, J. D. & Guarner, J. Convalescent Plasma to Treat COVID-19: Possibilities and Challenges. *JAMA* **323**, 1561–1562 (2020).
20. Razai, M., Osama, T., McKechnie, D. & Majeed, A. Covid-19 vaccine hesitancy among ethnic minority groups. *BMJ* **372**, (2021).
21. A review of research into vaccine uptake in the UK | Local Government Association. https://www.local.gov.uk/our-support/coronavirus-information-councils/covid-19-service-information/covid-19-vaccinations/behavioural-insights/resources/research.

- Merck Sharp & Dohme (UK) Limited:

1. PANORAMIC RCT: https://www.panoramictrial.org/

2. Summary of Product Characteristics for Lagevrio®: https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio

3. MSD News release: https://www.merck.com/news/merck-and-ridgebacks-molnupiravir-an-investigational-oral-antiviral-covid-19-medicine-demonstrated-activity-against-omicron-variant-in-in-vitro-studies/

4. Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002): https://www.clinicaltrials.gov/ct2/show/NCT04575597

5. Bernal et al 2021, NJEM, “Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients”; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8693688/

6. Docherty et al. 2020, BMJ, “Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study” https://pubmed.ncbi.nlm.nih.gov/32444460/

7. NICE, 2022, “COVID-19 Rapid guideline: managing COVID-19”; https://www.nice.org.uk/guidance/ng191/chapter/Recommendations

- Sobi Ltd:
    1. Kyriazopoulou E, Panagopoulos P, Metallidis S, Dalekos GN, Poulakou G, Gatselis N, et al. An open label trial of anakinra to prevent respiratory failure in COVID-19. Elife. 2021a Mar 8;10. doi:http://dx.doi.org/10.7554/eLife.66125
    2. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, et al Early anakinra treatment for COVID-19 guided by urokinase plasminogen receptor. medRxiv. 2021b:2021.05.16.21257283. doi:http://dx.doi.org/10.1101/2021.05.16.21257283