Updating technology appraisal recommendations for COVID-19 medicines: revised approach

27 June 2023

Introduction

Following the consultation on the surveillance and update of technology appraisal recommendations for COVID-19 medicines that took place between 6 April and 5 May 2023, NICE has considered the consultation comments. The consultation comments can be found in full in appendix 1 of this document.

This document is structured as follows: 1. What we heard in consultation, 2. New issue – data availability and 3. What we plan to do.

1 What we heard in the consultation

- Stakeholders would like more involvement in the process including:
  - The ability to make submissions
  - The ability to nominate patient, clinical and commissioning experts
  - The draft guidance consultation period should be longer

    NICE response: These steps will be added in but lengthen the process
- Transparency could be increased. For example:
  - Committee meetings should be held in public
  - Review decisions should be made public and consulted on

    NICE response: This will take more resources but given its importance can be implemented
- The cost-recovery charge is too high and companies should not have to pay for surveillance activity

NICE response: Changes to the process in response to the consultation are proposed resulting in a different charge (see section 3)

- The funding time-frame should be reduced from 90 days to 30 days or interim funding should be available

  NICE response: NICE does not have the ability to alter the legal funding timeframe. It is up to commissioners to decide whether to implement recommendations earlier than the 90 day deadline.
- Concerns about data availability in light of reduced testing/ national data collection

  NICE response: This is a key challenge and there have been further developments since the start of the consultation (see section 2)

2 Data availability issues

The continuous surveillance programme was based around 3 core sources of data that were thought to be available. However, since the publication of the draft process, each source of data is now more limited in availability and detail.

UKHSA technical briefings

Since the publication of the draft surveillance and rapid update process, UKHSA have changed how they report on SARS-CoV-2 variant prevalence and growth rates. This is partly due to changes in COVID-19 testing strategies and also a refocus of COVID-19 work within UKHSA. As of June 2023, more frequent reports are published but they are limited in the sample in that only Pillar 1 samples in England (primarily positive tests conducted in hospital) are included now. Previously, the sequencing strategy prioritised hospitalised cases, patients who were receiving specific antiviral therapy, and national core priority studies and was broader than England.

In vitro studies

In the past month (May 2023), searches have only identified one new in vitro evidence study on the monoclonal antibodies included in the MTA.

OpenSAFELY

The OpenSAFELY researchers have advised NICE that when commissioning of the COVID-19 therapies switches to ICBs the data flows will be reduced compared with centralised procurement. Although data on medicines dispensed in primary care will be available, those administered in secondary care settings will not be available.

Overall, the amount of data that was envisaged when the continuous surveillance process was designed is much less than anticipated.

3 What we plan to do

Surveillance

Surveillance of clinical evidence will continue, but it is anticipated that because the amount of data has reduced, the likelihood of triggers for review arising will to be lower.

If the surveillance activity highlights new information that may trigger an update of the TA recommendations, this will be passed to the TA team to consider.

Stakeholders may also submit new information to NICE, and should send information to nice@nice.org.uk, stating the guidance topic it relates to.

The decision-making about whether to review the recommendation will then follow section 8 of the Health Technology Evaluation Manual. Section 8.4 of the Manual describes that NICE considers the surveillance review and determines if it should have a public consultation. A consultation will only take place when the review has identified significant uncertainty in the appropriate decision option. NICE expects that consultations will not be needed routinely.

Update Process

An update will be initiated when an invitation to participate is sent to stakeholders. NICE will aim to minimise the time between a review decision and starting the update process.

Submissions

As outlined in section 1, stakeholders expressed concerns that several steps had been omitted from the process. In particular stakeholders were keen to make submissions. NICE recognises the importance of stakeholder submissions so the revised process will allow stakeholders to make an evidence submission. NICE will give stakeholders 4 weeks to make a submission from invitation to participate.

This is 4 weeks shorter than the usual time allowed for submissions. We will also shorten the external assessment group's (EAG) review to 4 weeks from 8 weeks. This includes a 1 week period for the EAG to seek clarification from the company.

The only way to achieve these shorted submission time frames is for companies to agree to use the existing economic model from the original appraisal. If the company does not agree to this and wants to submit a new model, this will require a full review, with associated longer timelines.

Stakeholder involvement

Stakeholders were concerned with the proposal to have standing patient and clinical experts involved in the committee meetings. In addition it was noted that commissioning experts were not mentioned in the draft process statement. To address these points, stakeholders will be invited to nominate patient, clinical and commissioning experts when a review of the recommendation is initiated, in line with the usual process.

Decision-making committee

Stakeholders requested that the committee meeting is held in public to increase transparency. NICE recognises the importance of transparency, although public committee meetings require more notice to arrange and to facilitate. In addition, given the changes to expert involvement outlined above, topics will be considered at public meetings of the full standing technology appraisal committees, rather than by a subset of the committee.

Consultation on draft guidance

Stakeholders were concerned that the proposed consultation period of 1 week would not allow adequate time for them to respond. So we will revert to a 4 week consultation period when draft guidance is issued.

Appeals and publication

The appeal process and timelines will follow NICE's technology appraisal appeals process guide. Following resolution of any appeals, NICE publishes the final guidance. At this point, the 90 -day funding implementation period applies for commissioners. Requests to vary the funding requirement to take account of net budget impact will be considered in line with section 5.9 of the health technology evaluation manual.

Overall summary

Overall, because steps have been added back into the process (or lengthened) in response to stakeholder feedback, the process is now more similar to the technology appraisal review process, which follows the single technology appraisal process and timeline. Therefore, in order to increase clarity for all stakeholders, there will not be a separate process statement. Instead reviews will follow the health technology evaluation manual, with the exceptions of the shorter submission period and shorter evidence review stage (as outlined above) and no technical engagement. There will also be less time allocated to NICE internal teams to prepare materials for the committee and to draft the guidance documents.

These changes will be clearly documented in the invitation to participate letter issued to stakeholders and must be accepted by the company to proceed. This will result in the following timeline, if a positive recommendation is made at the first committee meeting:

Timeline

Week	Proposed process	Standard process
Week -4	Surveillance trigger identified	Scoping

Week -3	Surveillance review done	
Week -2	Decision to update communicated	
Week -1	Planning update into programme	
Week 0	**Issue Invitation to Participate**	**Issue Invitation to Participate**
Week 1		
Week 2		
Week 3		
Week 4	**Stakeholder submissions**	
Week 5	Clarification step	
Week 6		
Week 7		
Week 8	**EAG critique due**	**Submissions**
Week 9		
Week 10		
Week 11		Clarification step
Week 12	**Committee meeting**	
week 13	Preparation of guidance document	
Week 14		
week 15	Positive recommendation: guidance issued for appeal (3 weeks)	
Week 16		
Week 17		**EAG report due**
Week 18	Appeal period ends	
week 19		Company Factual Accuracy Check
week 20	**No appeals, final guidance**	Progression decision point meeting

week 21		Response to Factual Accuracy Check
week 22		
week 23		
week 24		
week 25		Pre-meeting briefing
week 26		
week 27		
week 28		**Committee meeting**
week 29		Preparation of guidance document
week 30		
week 31		Guidance executive meeting
week 32		**Guidance issued for appeal (3 wks)**
week 33		
week 34		
week 35		Appeal period ends
week 36		
week 37		
week 38		**If no appeals, final guidance**

In addition, a company may propose to further expedite the timelines if it is happy for the review to proceed without a company submission and the need for consequent external academic review. Timelines are subject to NICE and EAG resource availability and capacity.

Cost recovery

Concerns were raised about the proposed cost-recovery charge and the inclusion of costs for the continuous surveillance process. As we now anticipate smaller data flows, this element can be removed from the charging.

The applicable charge will be £106,200 for 2023/24 in line with the charge for a rapid review, if companies agree to use the existing model from the original appraisal (see above: 3. Submissions). If companies instead wish to submit new modelling the standard STA charge will apply - £151,700 for 2023/24.

Because of the speed of potential reviews, it may not be possible to issue the charging invoice and receive payment before starting the rapid update. However, as part of the charging process the company will still need to provide NICE with a Unique Reference Number (URN) as their commitment to pay for the update. NICE reserves the right to not publish final guidance until payment in full has been received.

Appendix 1

Consultation comments

Organisation	Page	Section	Comment
Anthony Nolan	2	2.1.1	We are concerned about how continuous surveillance will be maintained given the reduction in the UK's surveillance activity (for example, the closure of the UKHSA Covid-19 Infection Survey (CIS). We believe that the ability of NICE to respond in a timely way to changes in virus prevalence and/or to the emergence of new variants, will be constrained by the wider reduction in surveillance capacity in the UK.
Anthony Nolan	5	2.2.1	Please specify what "regular intervals" means.
Anthony Nolan	8	2.4.1	We are concerned by the risk of manufacturers not paying a cost-recovery charge and the rapid update process therefore not being able to take place. What contingency measures are in place to mitigate this?
Anthony Nolan	12	2.4.15	We are concerned with the proposed timescales for stakeholder input. 7 calendar days is a very short period for stakeholders to input, especially for organisations with limited capacity and resource. We strongly recommend the time

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			period be extended to 20 calendar days minimum.
Anthony Nolan	14	2.4.17	We are concerned with the proposed timescales for stakeholder input. While we support the principle of a rapid assessment in order for access to the product under review be expediated, the proposed consultation periods are very short. This may mean that some organisations may not have the capacity or resource to respond meaningfully which means the committee will not have sufficient breadth of evidence to consider when coming to a decision. We request that this be considered by NICE and mitigations be put in place, for instance making the consultation process as simple as possible and flexing the timescales.
Faculty of Pharmaceutical Medicine			Appraisal process for new variants Whilst FPM welcomes the NICE initiatives to speed up the appraisal processes, FPM has concerns about the strategy proposed by NICE to conduct new Covid surveillance activities. Covid is now considered a endemic respiratory viral infection which carries similar risks to those posed by influenza and is to be dealt with by the currently available routine care pathways (https://www.england.nhs.uk/coronavirus/documents/transition-of-covid-treatments-to-routine-pathways/). Other than for the cost-effective appraisal of new antivirals or changes in antiviral SmPCs, it would seem appropriate for NICE to step back and allow existing pathways for COVID-19, or leverage other epidemiologically similar, respiratory viral infection – like influenza. This could be used to track continued antiviral effect and advise re suitability of the medicines approved by MHRA and NICE's HTA recommendation for prescribing. The UK collaborates in the WHO Global Influenza Surveillance network and the Crick Institute houses the WHO Worldwide Influenza centre which conducts regular testing of viral variants detected in the UK and elsewhere for susceptibility to vaccines. UKHSA Colindale tests circulating influenza strains for susceptibility to antivirals. The information can be found in the Covid and Influenza weekly reports issued by the UKHSA every Thursday. This existing system provides a model for the same entities to conduct regular testing of new SARS CoV2 variants in the UK against approved antivirals to ensure that these can be expected to be clinically effective.

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			Appropriate guidance can then be given to prescribers as required. Industry partners already provide MHRA & other health authorities with effectiveness data of agents with new variants or can be invited to supply the agents for testing – ensuring appropriate quality of the product used in the test systems. FPM suggests more consideration being given to effective collaborations with UKHSA, MHRA & industry to enable NICE to achieve rapid turnover of health economics assessment. In the absence of a significant shift in antiviral susceptibility (loss of viral susceptibility to any of the approved agents), which should have minimal impact on cost effective analysis and simply result in no longer recommending the antiviral, or a very substantive reduction in the rate of hospitalisations/deaths from the disease among the eligible population, there appears to be no requirement to reassess the cost effectiveness of these medicines when used as currently recommended. In addition, variant change comes in waves, which vary regionally and, in line with the NHSE guidance, routine pathways should be locally determined, as they are for antibiotics and other antivirals. (https://www.england.nhs.uk/coronavirus/documents/transition-of-covid-treatments-to-routine-pathways/) FPM recommends that NICE reconsider this proposal in favour of harnessing existing capacity already conducting the required variant tracking and susceptibility testing allowing NICE to conserve their resources to focus on their core role of assessing cost effectiveness.

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Faculty of Pharmaceutical Medicine			New antivirals FPM suggests that NICE consider similar mechanisms to that proposed for variants which will enable faster HTA assessment of new novel antivirals (small molecules or MAbs) that may be submitted to MHRA for regulatory approval such that cost effectiveness can be immediately assessed as soon as regulatory approval has been obtained. In addition to collaborating closely with UKHSA and MHRA for surveillance data and impact on efficacy, FPM suggests that collaborations with companies could result in submission of relevant data to NICE in support of continued susceptibility of virus strains in circulation in the UK. This will support likelihood of continued clinical effectiveness, as demonstrated in any clinical studies included in the license application. Companies can also be encouraged to provide UKHSA with product supply to enable the UKHSA to continue to test the susceptibility of variants, as they will be doing for established approved antivirals. Similarly, hospitalisation/mortality rates at the time of assessment can be readily tracked by UKHSA (as is done currently) and NICE kept appraised of any significant changes (significantly reduced rate of severe disease/death or significant increases in serious outcomes as appropriate) which may affect the model outcomes for all new antiviral agents as needed. As the parameters for the cost effectiveness model have been established for the products already approved by NICE, the same model can be utilised to establish cost effectiveness of new agents. It would be useful for the model to be shared with applicant companies so that relevant information can be provided within an application for approval. It may also be appropriate to encourage companies to submit their own assessment of cost effectiveness if appropriate, in the interests of fairness. Given that the model has already been used to approve agents for use in the UK, it is presumed that the entire process could be completed within an 8-12 week period, with active collaboration between NICE, UKHSA and the relevant company concerned.

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Faculty of Pharmaceutical Medicine			Possible overall guidance on respiratory virus infection prevention and treatments in the future FPM is aware that in addition to established vaccines and antiviral treatments for influenza and SARS CoV2, new vaccines and antiviral agents are in development. Several vaccines are currently under regulatory consideration for older adults and potentially for young children/pregnant women while antiviral agents may become available for children and older adults in future. These agents, together with effective vaccines and antiviral medications for influenza and SARs CoV2, raise the potential for active management of respiratory viral infections, with the aim of reducing the burden of these disorders on the NHS. FPM suggests that, given the resource challenges within the NHS, it may be appropriate to consider a revised model to explore the potential for broader use, with a view to enabling the NHS to catch up with the backlog of care required for other disorders, which was, again, significantly delayed by the winter 'twindemic' of influenza and covid in 2022-3.
Association of the British Pharmaceutical Industry (ABPI)	General	General	ABPI welcomes the development of the COVID-19 technology appraisal: surveillance and rapid update process statement, which demonstrates NICE's ambition to ensure guidance on COVID-19 therapeutics remains up to date and attuned to the changing nature of the virus beyond the pandemic. This is particularly important for high risk patients and will maximise their chances of having access to clinically and cost effective treatments when they need them.
ABPI	General	General	We understand that the scope of this process is to permit the rapid update of guidance for existing COVID-19 medicines. The process should not be applied in other areas without further consultation. Given the potential urgency around the introduction of medicines to treat COVID-19 variants, it is important that the process is acceptable from a public health perspective and that these medicines are provided to patients in the fastest possible time. The process may need to be flexed in case of need in order to deliver this ambition. Having an agreed process in place is beneficial in terms of aligning stakeholders around the

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			optimal approach. However, there should be a degree of flexibility and pragmatism exercised around the delivery of this process to ensure that appropriate treatments can be provided in a timely manner, whilst also ensuring that the process does not become disproportionately burdensome through excessive update triggers. The process itself must be proportionate to the decision that is going to be made. For example, if a small amount of additional data needs to be reviewed, this may not require such an arduous and costly process to be followed.
ABPI	General	General	It would be helpful for the statement to clearly state the different types/categories of COVID-19 therapy that will be covered by the proposed approach and provide justification for the scope of the process.
ABPI	General	General	It is not clear from the document how the model used in TA 878 will be incorporated in the surveillance and rapid update process and what plans NICE has for keeping it up to date. It would be helpful if this could be clarified. A validation step should be included if updates to the model are undertaken by the NICE team or EAG.
ABPI	1	1.1.3	The guidance covers “medicines on which final technology appraisal guidance has been published”. COVID-19 treatments that get optimised or negative recommendations will have to resource and pay for a full STA plus the fee and additional resource requirements for this update, which does not seem fair. Given the nature of the disease and its ability to mutate and spread, having the most effective treatments available for patients quickly is important. There should be scope via this process to rapidly assess novel, emerging therapies that do not yet have final NICE guidance but work effectively against priority variants of the disease, without requiring them to go through a full STA/MTA. In addition, where regulatory approval of a new medicine is based to some extent on an existing evidence base of a medicine that has already been through STA/MTA, the new medicine should not be required to go through a separate STA/MTA and instead be considered eligible for the rapid review. It would be helpful if this could be included in the process.

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ABPI	2	2.1.3	ABPI welcomes the inclusion of this paragraph and acknowledges the importance of the guidance being associated with the legal funding requirement for NICE medicines.
ABPI	3-6	2.2	The surveillance efforts described (evidence, system intelligence and stakeholder submission) appear to be resource intensive and should be kept under regular review so that they remain proportionate to the evolving risk posed by COVID-19.
ABPI	4	2.2	The frequency of evidence searches may be reviewed over time and is likely to extend beyond the current weekly reviews. It would be helpful to retain the ability to work outside specifically agreed surveillance timelines if there is a clear and compelling enough signal to do so. e.g. identification of a particularly concerning variant against which there is emergent evidence of a loss of neutralisation activity for currently recommended treatments.
ABPI	5	2.2.8	The surveillance trigger needs to identify both instances where a recommended treatment becomes ineffective and where a non-recommended treatment is effective.
ABPI	5	2.2.9	Given the important role of real world evidence (RWE) in relation to COVID-19 therapies, as evidenced in TA 878, there is scope to enhance this section of the document significantly. The RWE section should be expanded to provide greater clarity on what types of RWE, such as observational studies or ongoing assessments, would be permissible to rapid update committees and in what circumstances. It is important that a consistent approach it taken to the use of RWE and the document should link to the NICE Real World Evidence Framework. NICE should ensure that the principles set out within the framework are adhered to in the rapid update process. A shared understanding of how RWE will be applied will support more effective use of resources by companies and NICE.

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ABPI	5	2.2.9	The focus on “changes in baseline hospitalisation rates” is a helpful indicator of the management of COVID-19 but evaluated treatments will be administered in a range of settings and so a range of indicators will be required. For example, TA 878 set out a number of “uncaptured benefits” which would be helpful to include in future COVID-19 evaluations, including impact on incidence and duration of long COVID and the value of treatment options as insurance to those people who are shielding. It is important that due consideration is given to all relevant, available evidence around value. The speed of this process should not be to the detriment of the quality of the process – speed and quality should both be ensured. Moreover, it is important to ensure indicators are aligned with the specific population under consideration; for example, previous assumptions in NICE TAs for baseline hospitalisation rates could be a significant underestimate for treatments being evaluated for certain high-risk populations.
ABPI	6	2.2.12	Stakeholders with additional evidence are invited to send an email to covidsurveillance@nice.org. However, the confidentiality safeguards attached to this email address are not specified. It would be clearer and more prudent to ask stakeholders to email the address to find out how NICE would like them to submit their data, which we presume would be via NICE Docs.
ABPI	6	2.2.14	NICE should be clearer about the circumstances in which a change of cost would trigger a review and should ensure this route is retained for exceptional circumstances and is proportionate. For example, a reduction in price that means a medicine is now cost-effective does not warrant a full review as per the process and could be a much simpler, and less costly, update (under the assumption that the treatment continues to be clinically effective, and further review is not required to demonstrate this).
ABPI	7	2.2.16	Surveillance decisions can include the decision to withdraw a recommendation or recommend a rapid review based on a signal that, “a MAB previously thought to work against a SARS-CoV-2 variant may no longer retain neutralising activity against a new circulating dominant variant”.

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			Given the significance of these two recommendations, it does not seem appropriate that there would be no stakeholder consultation (or even company notification) at any point prior to the decision being made, particularly if it includes delisting. A company submission should be considered and there should be public consultation on the draft guidance change. Time should also be taken to ensure that sufficient RWE has been gathered to determine if effectiveness has been lost. Companies should be informed when one of their products is subject to rapid review decision-making processes due to a trigger being identified via continuous surveillance. Data related to the trigger should be shared with the company so that they are aware of the nature of the consideration. This should be done at the earliest possible opportunity, and at least one week before NICE considers whether or not a rapid update is required, to ensure that the company is best placed to support the rapid update process.
ABPI	9	2.4.2	The cost recovery charge of £125,196 for 23/24 seems unreasonably high given the volume of evidence likely to be available to committees for review. Access to COVID-19 medicines is dependent on a competitive global market. It is essential that the UK remains an attractive destination for COVID-19 medicines to ensure adequate supply can be secured. NICE is permitted to charge fees only on the basis of actual cost recovery, as per the Treasury guidelines on Spending Public Money. It is hard to see how the expedited process that is set out in the process document justifies such a high fee. In comparison, NICE charges £151,700 for an STA (2023/24), which includes review of an extensive evidence package submitted by the company an Evidence Assessment Group report and an ACM with the full committee. Where a treatment has been assessed previously and is now thought to be effective, companies should be exempt from fees for the rapid update process. NICE should clearly justify the actual costs involved in delivering the COVID-19 rapid update process and reduce the charge significantly so that it accurately reflects to the work being undertaken by NICE.

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			Companies should not be asked to pay additional fees to cover the costs of the surveillance elements of the process, which should be funded regardless of any technology appraisal review that is taken forward.
ABPI	10	2.4.4	Companies should be permitted to nominate the patient and clinical experts to support the process, as per current technology appraisal process.
ABPI	10	2.4.6	It is essential that patient representatives can be heard at committee stage and the document should clarify that this will always be the case.
ABPI	11	2.4.9	Companies should be given the opportunity to provide a written submission as they may have relevant data and information to support the committee meeting. Should the EAG put forward health economic evidence that shows a treatment is not cost effective, the company should be allowed enough (i.e. extended) time to respond the EAG report and the company critique should be presented to the committee.
ABPI	11	2.4.10	It should be clarified that the two company representatives who are invited to answer any questions of clarification from the committee will be invited to the committee meeting.
ABPI	12	2.4.17	The “quickest” timeline set out in the table covers 12 weeks and, with the addition of the proposed 90-day NICE mandate being applied to recommended therapies, the overall time from trigger identification to patient access would be six months, or even longer if an external assessment group is required, for example. Whilst the various steps in the table are sensible, there has to be a degree of pragmatism to provide treatments as quickly as possible, particularly, for example, if there is a not-yet-approved medicine that is effective in relation to a new variant. It would also be appropriate in this rapid process to reduce the mandated NICE implementation period from 90 to 30 days in this instance, to align with NICE fast-track appraisal timelines.
ABPI	12	2.4.17	For negative and optimised recommendations, at least two weeks should be permitted for the consultation period.

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Scleroderma and Raynaud's UK	General	General	Whilst there is extensive description on 'triggers' such as changes in viral subtype it has not been discussed how patients will be considered eligible for such treatments (biomarkers, treatments they are receiving or broader medical condition) as part of the rapid review process.
Scleroderma and Raynaud's UK	General	General	We appreciate the necessity of a rapid review process to ensure that TA approved treatments are still appropriate. From our understanding (Fig 1 Pg3), the rapid review process is dependent on a treatment having already undergone a TA – this is a lengthy process given the rate at which new COVID variants arise. There is a need for the original TA process to be accelerated to bring these 'window' dependent yet transformative treatments to patients more quickly.
Scleroderma and Raynaud's UK	General	2.4.16	In light of a negative decision becoming positive under rapid review there is a 90 day implementation window – we are concerned that this time period is too lengthy and will delay or block eligible patients from accessing the correct treatment.
Scleroderma and Raynaud's UK	General	General	We are concerned about how changes in decision (especially a negative decision becoming positive in light of emerging evidence) will be disseminated at pace to patients/ clinical community and how this will be targeted to the appropriate cohort of patients for them to understand that they are now/ are no longer eligible for this treatment.
Kidney Care UK	4	2.2.7	We have concerns whether there will be sufficient data available to inform the system intelligence surveillance scheme. UKHSA's April 2023 Technical Briefing will be the last published in that format and the ONS survey has paused. This has been met with concern by people with kidney disease, who remain at higher risk from Covid-19, as many had relied on that data to help guide their decisions on what restrictions to place on their activities. We would like to know NICE's views on whether sufficient data will remain available to inform this stream and what alternative sources of data will be used?
Kidney Care UK	General		While we welcome the development of the surveillance and rapid update process for already appraised treatment, it is vital that new processes that facilitate faster review of new treatments are developed and put into place. We are aware that NICE have begun to consider this, but we urge them to work with all stakeholders to get an agreed and documented process in place. Given the potential for rapid change in relation to

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			Covid-19 and its treatments, there must be no undue delay in enabling access to effective treatments.
Kidney Care UK	14	2.4.17	We appreciate that the consultation period needs to be truncated to enable rapid review, but we request that stakeholders are given adequate notice of the 7 day period over which the consultation will occur so that we can plan in the time required to review and respond.
Kidney Care UK	12	2.4.16	Will it be possible to shorten the 90-day funding implementation period? It is vital that people who remain at higher risk from Covid-19 can access effective treatments or prophylaxis without delay, particularly given the potential for the efficacy of those treatments to vary over time. Given the significant inequality experienced by people for whom the vaccine does not work as well and who remain at higher risk from the virus, we believe this period should be reduced so that people can access effective treatments without delay.
Kidney Care UK	General		We note the challenges faced by NICE during the appraisal of the treatments and remaining uncertainties. These include the relationship between preventative treatments, perceived efficacy, shielding behaviours and treatment efficacy. NICE have recommended further research into this, but we are not sure how this will be dealt with in reviews of preventative treatments if these uncertainties remain? The reduced anxiety, ability to re-start some activities and associated quality of life benefits are of such key importance to people, some of whom have been shielding for over three years, that it is vital they are appropriately captured in an appraisal.
Kidney Care UK	General		Will inputs into the model be updated during review, for example if there is more clarity on costs of administration once the CMDUs close and the treatments are provided in primary care. These changes may not trigger a review in themselves, but keeping them updated will provide a more accurate assessment of the cost effectiveness of the drug treatments.
Kidney Care UK	General		Please can we check if this surveillance process will include how/if Covid-19 drug treatments are used for children.

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Roche	General	General	Roche supports the ABPI response on the topic and welcomes the development of a rapid update process. Particularly we would like to draw attention to the points mentioned in the ABPI response regarding: Timelines of the review process and broader stakeholder involvement Proportionality and the cost recovery element Due consideration given to all relevant, available evidence around value and RWE The process should not be applied in other areas without further consultation.
Gilead Sciences Ltd	General	General	Gilead appreciates the initiative by NICE to develop a process which allows the monitoring and surveillance of the latest evidence for the treatment of COVID-19, including in-vitro evidence on emerging variants of concern (VOC). Gilead continues to be strongly committed to ensuring that patients with COVID-19 receive the best possible care, especially those patients who have spent significant time in hospital, who are living with uncleared virus or who are still suffering from long COVID. With regards to the suggested NICE process statement Gilead has four main areas of concern on top of the points referenced below which relate to the specific comments on the proposed rapid update process statement. These four main concerns include: A unilaterally triggered surveillance and decision, which is largely driven by NICE without proper company participation in the process The inability of companies to submit new data as part of this process The disproportionately high cost for the industry An approach which seems to favour quick decision making over thorough evidence evaluation

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Gilead Sciences Ltd	General	General	Gilead appreciate NICE's aim of rapid update to the COVID-19 guidance in view of new evidence. However, the draft process statement seeks to achieve this by restricting company participation to such an extent that it would not be a fair or robust process and would also be inefficient. Company participation appears to be limited to: Submitting [unpublished] evidence, in vitro data or change in costs/price – for NICE to consider triggering a review. (NICE is asked to confirm if this is the correct interpretation or if companies can submit any evidence: see below) 2 company representatives attending the committee meeting to answer questions of clarification Providing data or clarification if requested by NICE Responding to consultation on the draft guidance within 7 calendar days Appealing the final decision. If this understanding is correct, the process would be unfair, not robust and inefficient for the following reasons: The rapid review could result in a decision prejudicial to the company (e.g. not reversing a previously negative recommendation despite relevant evidence; reversing a previously positive recommendation; narrowing a previously positive recommendation; recommending a product but within a more limited scope than the licensed indication etc.).

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Gilead Sciences Ltd	General	General	Under general fair process principles (including the right to be heard) as well as NICE manual requirements, there must be an effective mechanism for companies to present relevant data on their product and address potential concerns/objections. In the NICE Manual, NICE undertakes to enable companies to make the best plausible case for their products. The draft process statement does not provide this for several reasons, including: [If our interpretation is correct] companies cannot submit published data that NICE may have missed, to trigger a review. If NICE triggers a review from its own surveillance, companies have no opportunity to make any submission for the committee to consider when they make their decision. The opportunity to comment on the draft decision does not compensate for the lack of company submission – as by then the committee has made its decision and the timelines set do not allow for proper consideration by the Committee of any significant comments made during consultation. If companies submit new data as part of consultation (having not had any opportunity to provide this as part of an upfront company submission), there is no opportunity for them to engage with the Committee (or otherwise comment) on any conclusions the Committee may make on that new data. The opportunity to appeal does not compensate for the earlier process flaws: an appeal panel can only decide upon fair process and whether the decision made is unreasonable considering the evidence in front of it. It does not allow the company to present its case to the decision makers. Without upfront company submissions, the resulting decision will not be robust. Companies are expert on their products and data, and so their effective participation is essential for a robust decision. The proposed process will not be efficient: as currently proposed, it is likely that companies would make substantial comments after draft guidance is issued, resulting in the need to re-draft the guidance. There is also a significant risk that companies would appeal the final outcome, delaying the guidance and absorbing significant NICE resources. It would be far more efficient for NICE to ask stakeholders to make submissions that are then properly considered by the Committee, as part of

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			the Committee meeting, and reflected in the first draft of the guidance that is then subject to consultation. This would both allow the Committee to give proper attention to company submissions, reduce the scale of comments received (and so the need to re-draft guidance) and reduce the risk of appeal. NICE appears to be intentionally omitting Chapter 5 of the NICE Manual – including all requirements for company engagement – from this process. Given the impact on companies, this is unacceptable. Finally, Gilead is concerned that NICE is not allocating sufficient resources to the rapid review process, given that NICE is already operating at capacity and seems to be stretched for resources. Due to the high societal and clinical impact, any COVID review needs adequate resourcing from NICE.
Gilead Sciences Ltd	General	General	The above concerns reflect the key issues currently subject to appeal in the COVID MTA (and possibly also subject to further challenge). NICE should not finalise this process until those issues have been resolved by the NICE Appeal Panel (or, if applicable, judicial review) and the proper outcome of the current MTA is fully understood and the implications for any rapid review process are clearly defined.
Gilead Sciences Ltd	General	General	Consultation on the COVID MTA finished in early December 2022. Please confirm that, as part of this rapid update process, NICE will consider any evidence not considered by the Committee in the COVID MTA (i.e., including evidence published or generated since December 2022) immediately.
Gilead Sciences Ltd	General	General	Whilst the process statement in its current wording is only intended to cover technology appraisal recommendations on medicines for preventing and treating COVID-19, Gilead is concerned that this process statement might be used as a blueprint for other therapeutic areas in the future, which have different evidence

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			requirements and needs that will likely necessitate a different process. Should the intention of NICE be to move towards a “living HTA” approach in future, such a process would require a separate and independent consultation with multiple stakeholders and companies, to ensure a fair process (including a right to be heard) and adequate involvement of a range stakeholders and companies.
Gilead Sciences Ltd	1	1.1.3	[If our interpretation is correct] Section 1.1.3 of the process statements indicates that published final technology guidance must be in place for medicines to be covered by the proposed rapid update process. It is unclear to Gilead how the rapid update process will affect new COVID-19 treatments which haven’t yet been evaluated by NICE, such as products which would go through a single- or multiple technology appraisal. Furthermore, it is unclear to Gilead how the process statement will affect any future STAs companies might want to bring forward. For example, should companies who were part of the COVID-19 MTA want to raise an STA in a different subgroup which was not covered as part of the MTA, would the company be referred to this process and declined the opportunity to submit an STA? Gilead asks that NICE clarifies the scope of the rapid update process and the process statement, notably confirming whether it applies only to the current COVID-19 multiple technology appraisal (MTA), i.e., ID6261 (formerly ID4038) or if it is intended to apply to future MTAs and single technology appraisals (STA) in the COVID-19 treatment space as well.
Gilead Sciences Ltd	4	2.2.4	Section 2.2.4 outlines that NICE will carry out regular searches for new published trial evidence. However, the process statement does not explain how these searches will be carried out. The process statement is vague referring only to a “broad COVID-19 search” failing to provide specific details on the databases to be searched or the search strategy which NICE intends on using. Gilead is concerned that the search strategy developed by NICE will miss crucial evidence depending on the scope of the systematic literature search (SLR) and the search terms used. To limit this risk from arising, Gilead asks

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			that NICE publishes a comprehensive protocol outlining the methods used to by NICE when conduct the SLR, such SLR being undertaken in line with best practice guidance on the development of such materials, which are highlighted by the Cochrane Collaboration guidelines. The SLR will also need to be able to capture various subgroups relevant to each of the products under assessment, which might necessitate the development and maintenance of multiple SLRs with distinct Population, Intervention, Control, Outcome (PICO) criteria. Gilead asks that stakeholders, including companies are invited to comment on the NICE SLR and research methods proposed to ensure a fair and robust process ultimately ensuring that all relevant evidence can be captured and reviewed.
Gilead Sciences Ltd	5	2.2.9	Section 2.2.9 concerns the assessment of real-world evidence (RWE) by NICE, Gilead's interpretation of which being that RWE data will only be used to evaluate baseline hospitalisation rates and the relative effects of Paxlovid compared to Sotrovimab. If Gilead's interpretation is correct, we ask that NICE extend this scope to cover RWE studies for all COVID-19 treatments, especially given how relevant these studies are to further understand key outcomes such as mortality or time to clinical improvement for all treatments used in COVID-19. We ask that NICE confirms that all relevant RWE will be considered and reviewed under this rapid review process and suggest that a separate SLR is designed to identify those RWE studies, as additional evidence to be considered alongside the evidence from randomised controlled clinical trials (RCT).
Gilead Sciences Ltd	6	2.2.12	Section 2.2.12 suggests that stakeholders (including companies) can submit unpublished evidence to NICE for consideration on how it might affect recommendations whilst being silent on other evidence sources. Please clarify that stakeholders (including companies) may submit all relevant evidence – including clinical trials, follow up studies, evidence from registries, real world evidence etc (consistent with Section 1.3.1 of the Manual) – and that company submissions are not limited to unpublished data. Companies are ideally placed to be able to identify relevant evidence as early as possible, and so help NICE keep its guidance up to date. We have learnt from the COVID-19 MTA that

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			even key clinical trial data is not always efficiently picked up in a systematic review. (See e.g., omission of SOLIDARITY in the AG's initial SLR). If stakeholder submissions are intended to be limited to unpublished data, there needs to be far greater transparency and consultation in the search criteria and sources used for NICE's own surveillance. Please also clarify that companies may submit data in any format and may include cost effectiveness analysis in their submission.
Gilead Sciences Ltd	6	2.2.13	See Section 2.2.12 comments above.
Gilead Sciences Ltd	6	2.2.15	Please clarify what are the criteria that will be used to determine if: evidence constitutes a "potential trigger for update" which of the surveillance decisions (as described in 2.3.1) will apply In particular – it is essential that the criteria for determining if the evidence is likely to have a material effect on the recommendations – such that the rapid update process will be triggered – are transparent to all stakeholders. For completeness, please clarify that a rapid update process may be triggered based on relevant RWE data.
Gilead Sciences Ltd	7	2.3	See Section 2.2.15 comments above.
Gilead Sciences Ltd	8	2.3.4	Gilead ask for clarity on the appeal process if there is relevant new evidence and NICE decides not to run the rapid update process
Gilead Sciences Ltd	8	2.4.1	See Section 2.4.1 comments below.
Gilead Sciences Ltd	9	2.4.2	The cost recovery charge of £125,196 suggested in section 2.4.2 is disproportionately high considering the extremely limited involvement and engagement with company stakeholders. This cost is excessive when compared with the 2023/24 cost of a NICE single technology appraisal (STA), which are currently listed as £151,700 for larger companies on the NICE website. Given that an STA process can take up to one year to complete (if not more under certain circumstances) and allows for substantially more interaction between the company and NICE, the proposed recovery

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			charge for the rapid review process is not justifiable. It is not reasonable for NICE to suggest such an excessive cost recovery charge where company engagement and interaction is so limited. Rather than applying a flat fee for all companies for which a surveillance trigger causes a re-consideration of their products effectiveness, the cost-recovery charge should be dependent on the extent of additional evidence, which is considered, and should be limited at a much lower threshold. Additionally, given the high cost of a rapid review, please confirm how companies can elect for their products not to be subject to this process. If companies cannot elect for their products not to be subject to this process, this would create an issue of unpredictable costs.
Gilead Sciences Ltd	10	2.4.7	Please clarify that standards for evidence set out in Chapter 3 of the NICE Manual will apply in this process.
Gilead Sciences Ltd	11	2.4.9	In addition to the General comments above, Section 2.4.9 stipulates that no submissions from companies are invited to inform the rapid update process. Section 2.4.9 is in clear contrast to Sections 2.2.12 and 2.2.13 of the process statement, which [if Gilead's interpretation is correct] allows companies to submit some, albeit limited, data such as unpublished data as well as in-vitro data. Gilead considers it to be critically important that companies get a chance to submit new evidence to NICE to inform the rapid review process. Gilead asks that the wording of section2.4.9 is updated accordingly.
Gilead Sciences Ltd	11	2.4.10	To meet the principles for a fair process, the Committee meeting should be held in public. Given the flexibility of remote meetings, there is no reason why this could not be achieved even in a short time.
Gilead Sciences Ltd	12	2.4.15	Table 2 in section 2.4.15 of the process statement indicates that there will be a 7 calendar days consultation period in case of no change to the recommendation or for scenarios in which a previously positive recommendation gets withdrawn. Given that the COVID-19 MTA (ID6261, formerly ID4038) was an expedited and rushed process, which didn't allow for proper company input and consultation ultimately resulting in 22 points of appeal from three

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			different companies heard over a 2-day period, Gilead is extremely worried about the limited company engagement and interaction proposed by the current draft of the process statement which suggests a mere 7 calendar days of consultation. Allowing only 7 days for stakeholder consultation is far too short and does not allow sufficient time for companies to formulate helpful, complete comments that will enable NICE to achieve a robust decision. It also undermines the fairness of the process. Gilead asks that this consultation period is extended and that companies get a fair chance of voicing their concerns and presenting the most relevant evidence to NICE. Gilead furthermore asks NICE for the flexibility to extend this consultation time if so desired by the company. As a practical issue, key individuals within a company could easily be on holiday for the entire consultation period. Additionally, if company submissions are permitted before the Committee meeting, this would allow an accelerated consultation on the resulting draft guidance while maintaining a fair process. Please clarify that there will be consultation if a previously negative recommendation becomes positive but for a narrower patient population than the product's licensed indication.
Gilead Sciences Ltd	12	2.4.16	The indicative timeline in Table 3 of Section 2.4.17 allows 5 weeks for NICE internal processes, up to stakeholder notification. This is in stark contrast to the short timelines allowed for: Preparation of evidence for the Committee (1 week) Committee consideration of evidence (1 week) Preparation of guidance document (1 week) Consultation on guidance document (1 week) Committee consideration of consultation responses (1 week) (a total of 5-6 weeks). The initial period (weeks -4 to 0 in Table 3) should be reviewed, to accelerate reaching the

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			decision to update and immediately informing stakeholders. Currently there is a 2-week delay between this decision and notifying stakeholders. If the decision could be accelerated and stakeholders were informed immediately, this would allow time for company submissions to be made in time for inclusion in the evidence prepared for the Committee. Additionally, Section 2.4.16 of the draft process statement assumes a 90-day funding implementation period for commissioners. Given the primary goal and motivation behind the rapid review process is to provide swift recommendations in line with the latest evidence to ensure rapid patient access to appropriate therapies there is also a need to ensure quick availability of newly approved therapeutics and their funding. Gilead therefore suggest that a mechanism is set up which will allow patients to gain interim access and companies to get interim funding to cover the period after final guidance to routine commissioning.
Gilead Sciences Ltd	12	2.4.17	The timelines presented in table 3 of section 2.4.17 are very ambitious and Gilead is concerned that a rushed procedure could impact the quality of the review and ultimately recommendation from NICE. While a quick response to emerging VOC and new evidence is desired and supported by Gilead, measures need to be taken to ensure that the quality of the evidence assessment is in line with NICE's high standards. Gilead therefore suggests that depending on the scope of the new evidence which gets considered by NICE, timelines are adjusted to reflect the scope of the additional analysis required to make a justified and fair decision.
UK CLL Forum	4	2.2.3	Evidence surveillance stream: UK CLL Forum represents a group of patients who are at especially high risk from Covid, and we would like to ensure that the continuous surveillance process intends to monitor for new or emerging data which applies specifically to high risk patients groups as well as to the general population.
UK CLL Forum	12	Table 2	Withdrawal of previously positive recommendations may have significant impact on high risk patient groups such as CLL patients and we would request that input from relevant stakeholders is actively sought. We would be

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			concerned that the 7 calendar day short consultation period is short and may not allow adequate time for input from all concerned stakeholders.
AstraZeneca Ltd	General	General	AstraZeneca welcomes the opportunity to provide feedback on NICE's proposed process for the surveillance and rapid update for COVID-19 technologies. Given the complexity and dynamic nature of this disease area, providing timely NICE Guidance is challenging and there are clear limitations to NICE's standard appraisal processes. We acknowledge the progress NICE have made and very much share the view that alternative approaches are required to ensure people who remain at high-risk of poor outcomes from COVID-19 can benefit from timely prophylaxis/treatment from novel therapies. In our response, we have provided commentary highlighting limitations of the current proposal as well as our recommendations as to how this could be appropriately amended so that patients do not suffer further prolonged access to medicines in high need. In addition to the general comments, we have provided feedback on specific sections/statements where more clarity is required. Despite a highly effective vaccine roll out, people who are unable to mount an adequate immune response, or in whom vaccination is not recommended, remain at a high risk of COVID-19 adverse outcomes and continue to suffer significant physical and psychological impact. In England and Wales, COVID-19 had the sixth highest mortality rate in 2022, with 22,454 deaths (3.9% of total deaths) recorded during this time.1 The disproportionate impact that COVID-19 continues to have on immunocompromised individuals is clearly demonstrated through the outcomes reported from the INFORM study.2 This recently conducted observational retrospective cohort study evaluated 12,500,000 individuals to describe clinical outcomes and utilisation of healthcare resources among individuals with COVID-19 in England during the omicron period (January-December 2022). In summary: Despite accounting for approximately 1% of the population in England, severely immune-compromised patients made up: confidential information redacted.

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			Furthermore, specific sub-groups exist within this severely immunocompromised population who are at even higher-risk of averse COVID-19 outcomes, including patient cohorts represented in Group A2 of the Independent Advisory Group [IAG] Report concerning the use of COVID-19 directed antibodies in the prophylaxis setting. Confidential information redacted. There is therefore a clear unmet need for effective therapies to help protect this vulnerable cohort; however, the proposed rapid update process in its current form is insufficient to enable medicines to be available in the NHS in a timely manner and may exacerbate existing inequalities of access to effective therapies in this underserved population. Although we acknowledge the rapid update has the potential to be significantly faster than standard approaches, it does not address the fundamental challenge associated with the dynamic nature of COVID-19 variants in circulation. Furthermore, the scope of the consultation, does not address the known limitations of the standard STA process for new medicines.
AstraZeneca Ltd	General	General	Ensuring Rapid Access to COVID-19 Technologies It is stated in the consultation document that ‘‘changes’ to viral genotype are a continuous process’ and ‘historically, there has been a major sweep approximately every 6 months’. We therefore recommend that any process seeking to deliver rapid updates to NICE Guidance reflects the rate of change of circulating variants observed in clinical practice; failure to do so is likely to result in the loss of meaningful intervention as circulating variants are likely to change during the timeframe of the review process. The current process outlines a 12-week timeline from identification of a surveillance trigger to publication of positive Final Guidance – taken together with the 90-day funding implementation period outlined in Section 2.4.16, the minimum period from the surveillance trigger to implementation is ~6-months. This timeframe does not take into account publication of variant data from the UKHSA (required for surveillance process) nor any delays due to additional assessment being required within the appraisal process (eg. external assessment group review). AstraZeneca’s experience to date with

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			tixagevimab plus cilgavimab [NICE ID6136] also highlighted the complexities associated with Committee decision making and the need for NICE to establish clear in vitro neutralisation thresholds that would determine whether a treatment can be considered cost-effective or not. For context, the FDA issued a statement on 26th January in which it withdrew the Emergency Use Authorisation (EUA) of tixagevimab plus cilgavimab for the pre-exposure prophylaxis of COVID-19. This was because the combined proportion of COVID-19 cases caused by variants to which Evusheld did not have neutralisation against was >90%. The statement later states that the Agency will consider reinstating authorisation of tixagevimab plus cilgavimab if the national prevalence of resistant variants decreases to 90% or less on a sustained basis. It is therefore the position of the FDA that retention of any neutralisation of Evusheld against a variant is sufficient for the issuance of an EUA, and therefore is justifiable to conclude that there is clinical efficacy which outweighs risk. We therefore recommend that NICE provides further clarity on how surveillance of susceptibility of neutralising monoclonal antibodies (nMABs) on the in-vitro neutralisation against the emergence of new variants is expected to be used to make a determination of clinical efficacy to inform conclusions based on cost-effectiveness. Currently, the draft rapid update process lacks clarity and numerical specificity. We therefore recommend that until such point that alternative data becomes available – NICE introduces a framework which concludes that an nMAB can be considered to retain clinical efficacy so long as neutralisation can be achieved (whilst a total loss of neutralisation against a particular variant is likely to mean there's a total loss of clinical effect).

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AstraZeneca Ltd	General	General	Expanding process to medicines that do not have existing TA Guidance Currently, the process only focusses on the COVID-19 therapeutics that have existing NICE Guidance – such an approach does not solve for existing challenges associated with assessing COVID-19 therapeutics within the STA framework and is a missed opportunity to establish a future-proofed process for new medicines; particularly in cases when future medicines may offer sustained activity against COVID-19 variants. At the time tixagevimab plus cilgavimab was selected for a NICE STA [ID6136], it demonstrated in vitro neutralisation against all circulating variants of COVID-19. However, the assessment process has taken over 11 months to conclude, during which time circulating variants have changed and the neutralisation activity has diminished. As such, the Final Draft Guidance for this appraisal does not recommend tixagevimab plus cilgavimab, citing lack of clinical effectiveness versus current circulating variants. Although we welcome the acknowledgement that variants will continue to evolve and neutralising effectiveness may return, this case study highlights the opportunity cost associated with delayed decision making. As outlined in our submission dossier for ID6136, tixagevimab plus cilgavimab was associated with improved mortality, reduced hospitalisation and significant improvements in quality of life, which were unable to be realised in UK clinical practice in contrast to other health systems across the world. The time taken to make a final recommendation has meant immunocompromised individuals have missed a critical opportunity to be protected from the severe outcomes of COVID-19 during the period to which omicron variants were neutralised. NICE must continue to evolve its methods and processes for the evaluation of COVID-19 to ensure this situation does not arise again in the future. AstraZeneca continues to have concerns that the current NICE process for future medicines will continue to delay critical access to such high-risk populations, without consideration of how they can be incorporated within a rapid framework. Although NICE endeavours to reach positive Guidance within 3-months of marketing

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			authorisation for new active substances, this is unlikely to be feasible in this disease area due to the differential pace, flexibility and data requirements between regulatory bodies and the NICE process. We believe there is an opportunity to consider how these medicines can be assessed in a robust and timely manner and are willing to work with NICE to find appropriate solutions.
AstraZeneca Ltd	General	General	Immune-bridging from an existing reference molecule We recommend that the final guidance includes treatments that gain regulatory approval based on immuno-bridging from an existing reference should be considered eligible for the rapid update process, leveraging any existing NICE assessment that has already taken place. Immune-bridging is an approach to clinical trial design used to infer the effectiveness of a new drug candidate through an accepted surrogate for efficacy, and has been used to expand use and accelerate regulatory approval of vaccines for HPV, influenza, and COVID-19. Immune-bridging trials can help reduce development time and accelerate access to important new medicines; these trials are often used when there is urgent need for important, new medicines but full-scale efficacy trials may not be feasible within the timeframe required. Such a route is well established for vaccines and global medicine regulators have previously considered immune-bridging trials as effective forms of evidence of efficacy.3-5 The MHRA approved bi-valent vaccines for COVID-19 using immune-bridging data recognising its benefit in assessing vaccine efficacy in a rapidly evolving variant landscape. The JCVI's confidence in the regulators assessment of this data supported their decision to make rapid recommendations on the inclusion of these specific therapies against emerging variants of concern.

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			Neutralising antibody titres have been shown to be positively associated with protection from disease and are considered correlates of protection (COP) – an expedited route to evaluate clinical and cost-effectiveness for medicines which have demonstrated neutralising antibody titres above a set threshold of protection would be advantageous. This would enable NICE to be agile in its ways of working, provide timely guidance to the NHS, and to use concepts which have been established and accepted by regulators for many years for vaccines. We further recommend that the guidance incorporates a mechanism for NICE to use the modelling approach and agreed assumptions from previous appraisals as a basis for rapid decision making for medicines which are approved based on immune-bridging data. If and when outcomes data are published specific to the new medicine, then the process would enable NICE to re-visit its original conclusions by incorporating these data into the original model.
AstraZeneca Ltd	7	2.2.16 2.2.17	Although AstraZeneca understand stakeholder consultations will not be held in a routine manner, summary outcomes and decision points of these consultations should be published on the NICE website to aid transparency and to ensure the surveillance trigger is fit for purpose. We recommend that NICE provides further information on the validation and approval processes in place to ensure the appropriateness of surveillance decisions, alongside any specific criteria used in the assessment.
AstraZeneca Ltd	9	2.4.2	NICEs proposed cost-recovery charge is disproportionate to the extent of review outlined in the consultation document and further information on how such a charge has been derived is required. Despite the process purporting to reach a recommendation in 7 to 8 weeks from the original surveillance trigger, the proposed charge for the rapid update is greater than existing cost comparison/rapid review programmes and >80% of the total cost of a standard STA/HST appraisal. Given NICEs own acknowledgement that major sweeps of viral genotypes occur approximately every 6 months, and that changes to viral genotype are a continuous process, such a charge could create significant unplanned spend

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			for manufacturers and limit the ability to engage in the process. Moreover, the narrow scope of this consultation (ie. pertaining only to medicines in which final guidance has been published) and the aforementioned challenges in ensuring patients can realistically benefit from timely Guidance could further limit meaningful engagement in the process without changes.
AstraZeneca Ltd	10	2.4.6	We recommend that NICE seeks the input of manufacturers to identify appropriate clinical and patient experts as per the standard TA process
AstraZeneca Ltd	12	2.4.16	As per our comments above on the ability of the proposed rapid update process to enable timely guidance to be published, NICE need to reconsider the 90-day funding implementation period to ensure this process is fit for purpose. By introducing an additional 3-month delay to implementation of a decision, there is a very real risk that Guidance could be eligible for review shortly after (or even during) the implementation period itself. Such an approach is inconsistent with NICEs stated aim of creating a process that can rapidly update technology appraisal recommendations. We recommend that NICE consider leveraging interim funding routes via established processes such as the Innovative Medicines Fund (IMF). At the very least, NICE should look to reduce the mandated implementation period from 90 to 30 days in this instance, to align with NICE fast-track appraisal timelines.
AstraZeneca Ltd	21	6.5.8	AstraZeneca do not believe the decision point criteria for Step 1 of the surveillance review process should be linked to the likelihood of a variant becoming dominant. Such an approach is inconsistent with how international regulators are defining the risk-benefit (ie. =10% of all circulating variants) and does not reflect the complexity and diversity of co-circulating variants. During the 2nd Appraisal Committee for tixagevimab plus cilgavimab [ID6136] and aligned with the approach adopted by the FDA, AstraZeneca proposed that demonstrating a neutralising ability (<10,000) against =10% of all circulating variants would be an appropriate threshold in which to determine clinical effectiveness, and thus suitable for triggering a review during the surveillance process.

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			We recommend that NICE clarify how 'dominance of variants' is being defined, particularly given the observed rise in co-circulation of multiple variants with competing growth potentials across differing sub-lineages of omicron. We further recommend that NICE provide justification as to the appropriateness of the Step 1 decision criteria as, in our view, it is critical that the totality of an nMABs aggregated neutralising ability versus all circulating variants is assessed.
NHS England			Is the process as outlined a good basis for the committee to make decisions and update recommendations? Yes, NHS England (NHSE) are supportive of this process; given the need to rapidly review the effectiveness of COVID-19 therapeutics against emerging variants and as new evidence arises. NHSE recognise the need for a bespoke rapid update process, limited to COVID-19 therapeutics, to ensure the most effective treatments are available to respond to COVID-19 variants. NHSE therefore welcomes the rolling review of emerging evidence for all COVID-19 therapeutics. From a clinical perspective, we are supportive of a mechanism which enables a rapid review which can fast track assessment and, where appropriate, subsequently update NICE recommendations on COVID-19 treatments. To ensure rapid commissioning and adoption of treatments, we ask that this review ensures business-as-usual lead in times are in place such that the NHS can establish service delivery models and have undertaken any necessary pricing negotiations prior to the issuing of final guidance.

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NHS England			Do you have any concerns about the process and, if so, any suggestions to address those concerns? Yes – please note the following concerns: Establishment of new delivery models: The potential short turnaround needs to provide sufficient opportunity to consider potential implementation considerations and implement appropriate service delivery models where necessary. This would apply for all cases, e.g., where a therapeutic is newly recommended or where eligible patient cohorts are expanded. We therefore suggest that an NHSE representative is considered as a member of the decision-making committees. Budget impact: Where a product's budget impact represents a breach of the budget impact test (BIT) threshold, the rapid approval timescales, need to factor in as near as business-as-usual timescales as possible to enable the NHS to undertake any commercial negotiations necessary in good time. Negative impact on certain patient cohorts. We would be keen to be reassured that specific patient cohorts, e.g., autistic people and those with a learning disability, are not discriminated against or disadvantaged by the proposed process. In addition to the process being underpinned by NICE's Equality Scheme, we suggest specific mention is made of those with learning disability and autism. This is because the 2022 report Learning from Lives and Deaths of people with learning disability and autistic people (LeDeR, https://www.kcl.ac.uk/research/leder) showed that the most common cause of death for people with a learning disability based on death certificates during 2021 was COVID-19. The estimated excess deaths during 2021 compared to pre-pandemic years was double that of the general population. We therefore recommend this is considered when selecting committee panel members and when calling upon expertise to support the decision-making process.

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NHS England			Do you feel there are any gaps in the process or areas that need further consideration? National and local commissioner input should be built in as part of the review process and the decision-making committee. A revised budget impact assessment should be undertaken before recommendations change. A rapid internal approval process is required to meet tight turnaround (where there is no consultation period). This is particularly important where decisions are required within a very narrow window of opportunity e.g., to respond to an emerging circulating variant. There should be a consultation on any proposed changes to NICE recommendations (irrespective of whether these are positive or negative) and consideration given on the impact on funding mandate, e.g., if there is a negative to positive or a substantial increase in budget impact. Clarity on continuity of treatment considerations for those COVID-19 therapeutics where the process results in a previously positive recommendation being changed to negative, and how access to patients is withdrawn and/or services changed. This is in cases where the therapeutic is no longer recommended or where only certain patient cohorts are no longer recommended. It would also be useful to understand and set out how this process may interact with the Fast Track Appraisal process currently in development. It would be helpful to set out clearly in the final document why this process is different compared to other processes and if there is consideration for a similar process in other non-COVID-19 therapeutic areas.
NHS England		2.4.1	It would be helpful to understand the process if a company refuses to pay the cost-recovery charge, but it is deemed a benefit to NHS. Will stakeholders be alerted to a company's decision and have the opportunity to comment? NHSE understand that reference to manufacturer agreeing to a cost-recovery charge is important and that this is a new charge compared to other processes which were in place for the rapid C19 review.
NHS England		2.4.1	It would be useful to understand the process should there be an amendment to the marketing authorisation, e.g., if the marketing authorisation is expanded to include the paediatric population.

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NHS England		2.4.4	This refers to the decision-making committee – however, no reference to commissioner (e.g., Integrated Care Board) input, which would help NICE to understand ability to implement updated guidance. This is important as there is a risk that if no input from a relevant commissioner is available, ability to understand ability to implement updated guidance will not be available.
NHS England		2.4.6	This refers to clinical expert and patient expert - involving a commissioning expert (local and national) in the process would be a helpful addition to ensure understanding of ability to implement updated guidance.
NHS England		2.4.6	We are concerned about the appointment of clinical expert and patient expert roles and would like to ensure that they have the relevant understanding for patient cohorts that may be disproportionately impacted by decisions made, e.g., learning disability (including Down's Syndrome) and autism.
NHS England		2.4.9	There are significant concerns that NICE may miss critical information which would inform decision making if submissions are not invited; requesting data/clarification only may result in NICE inadvertently excluding relevant information/data which it is unaware is available. This would present a risk, for example, if no input were obtained from the relevant commissioner, e.g., impact/availability of the accompanying service.
NHS England		2.4.15	There is concern that where there is no consultation for a previously negative recommendation that becomes positive, NHS England (and other stakeholders) have insufficient opportunity to provide comments which may impact the final draft guidance and thus recommendation. It also provides limited opportunity for consideration of system readiness.
NHS England		2.4.16	The draft process statement doesn't provide any details regarding how a Budget Impact Test (BIT) threshold being met is managed, e.g., time available for commercial discussion where rapid timescales are required. NHSE understand that the usual processes apply in these instances. It would be helpful to reiterate this in the statement or set out if there are minimum/maximum timescales. We understand that request for varying timelines also applies in other circumstance e.g., where NHSE raise issues with respect to scale or timing of service delivery

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			models being delivered by the end of an implementation period.
NHS England		2.4.15 Table 2	We are concerned about the consultation period of seven calendar days following the decision to withdraw a previously positive recommendation. General stakeholder consultation with affected patient cohorts and their representative bodies, e.g., for people with a learning disability, may require additional time.
NHS England	General		Clarity is required on whether this process is expected to expand to other conditions or therapeutic areas outside of COVID-19.
NHS England –	General		Clarity on the implementation period should a previously positive recommendation change to a negative recommendation following this process. This is in relation to the therapeutic for entire population recommended and where eligible populations are reduced.
Individual	general	general	The ONS survey was an excellent provider of surveillance data. I am unclear from the document from NICE how we will understand rates of COVID in the community without bias without this neutral means of measuring the number of cases in the community. In addition the withdrawal of free NHS COVID self-testing packs and/or a means of reporting means again the community reporting will be challenging.
Myeloma UK	General	General	NICE should include patient opinions and perspectives throughout the process to ensure evidence collected and reviewed reflects the issues/outcomes most important to patients. The proposal currently only consults patient experts when a review is triggered.
Myeloma UK	7	2.3.1	In the proposed process, evidence reviews that result in a “no update” surveillance decision will not be published. We are concerned this approach will lead to a lack of transparency about the types of evidence reviewed and the decision-making process. A lack of transparency can impact the quantity and quality of evidence and input from stakeholders throughout the process. Regular updates summarising the number of reviews, decisions and pivotal evidence reviewed could help negate this concern.

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Myeloma UK	1	1.2.1	We agree with the triggers listed but think that a significant change in the COVID-19 incidence rates should also be a trigger. Some subgroups don't respond to vaccination and therefore have an increased risk of hospitalisation or death due to COVID-19. If COVID-19 incidence rates increase, the risk for this subgroup will increase, and patients may return to shielding. Shielding impacts psychological well-being and quality of life. Quality of life benefits are part of cost assessments, and therefore a change in incidence rate could impact cost-effectiveness.
Myeloma UK	6	2.2.9	We agree that NICE should include baseline hospitalisation rates in their surveillance programme; however, the data collected/analysed must include hospitalisation rates for specific at-risk populations. A change to the disease could have a greater impact on the hospitalisation rates of at-risk groups due to reduced response to vaccination.
Myeloma UK	12	2.4.15 Table 2	We are concerned that the consultation period for decisions is too short, particularly for decisions that result in the withdrawal of treatment. We believe this could limit the quantity and quality of submissions from patients/patient organisations due to capacity constraints. Therefore, we recommend that the consultation period is increased, particular for recommendations will lead to withdrawal of treatment.
Myeloma UK	9	2.4.2	We are concerned a non-flexible cost-recovery charge could be a barrier to access because the manufacturer may refuse to pay the charge. For example, when the update results in a slight broadening in eligibility criteria. A change of this type would have a big impact on patients but a small impact on business objectives. Furthermore, the charge suggested is higher than the charge for a standard rapid review/cost comparison. Ref: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/charging
Pfizer UK	9	2.4.2	We are concerned that cost recovery charge £125,196 for 23/24 is extremely high as these reviews are not full HTA reviews. We suggest that they should be proportional to how large the update is. We do not agree that industry should fund the building of a new surveillance function for the TA programme. This

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			responsibility should be with Government, DHSC or UKHSA
Pfizer UK	9	2.4.3	We believe that even if quick timelines, NICE should still be able to issue note to company suggesting charges are applicable to enable financial planning on the part of the company
Pfizer UK	11	2.4.9-10	We are concerned about the lack of opportunities and sufficient time for companies to provide evidence. Companies should be able to provide evidence and not just consulted for clarification or on the spot during the meeting. In addition, the decision problem should also be clearly communicated to the company well ahead of the evidence review not during an ACM or in an ACD after the review.
Pfizer UK	12	2.4.15	We are concerned that 1 week is not enough time for consultation on decision, especially if removing guidance or when shifting to a new treatment in only a subgroup when the treatment could potentially be offered to a broader population. Companies need adequate time to generate or identify evidence as a response. We suggest the length consultation time reflect the potential impact a decision will have on patients
Pfizer UK	5	2.2.9	There is lack of clarity in acceptability of different RWE studies. More clarity is required in the weighting of local vs global RWE on the final decision-making process. RWE outcomes in populations outside the England from populations that have similar characteristics as those in England e.g. vaccination status, health deprivation and age distribution, should be considered in the decision making. Current restrictions to treatment in England have limited the feasibility of conducting RWE studies in some population subgroup in England but data might be available from else in the world.
UK Health Security Agency	General	General	The proposal is sensible. The concern is the timeline between the identification of an emerging threat and drafting and disseminating guidance to end-users: will this timeline be reasonable and achievable in terms of improving clinical outcomes?
UK Health Security Agency	4	2.2.7	The capacity in England, and in all probability the rest of the UK and internationally, for SARS COV2 sequencing has reduced in 2022, and will reduce further in 2023. This directly impacts the statistical power behind analysis of variant growth rate and will lengthen the time take to

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			identify new mutations and/or variants of concern. This will directly impact the speed of data availability for in vitro assessments.
UK Health Security Agency	4	2.2.7	The proposal specifically mentions UKHSA's technical briefings as source of intelligence on variant prevalence. Reduction in COVID budget for UKHSA and lower sequence data volumes have led to the decision that UKHSA will no longer produce the technical briefings going forward on a regular basis. Briefings may only be produced in the event of major events. The proposal should be revised in order to identify an alternative/additional source for this intelligence.
UK Health Security Agency	General	General	The UKHSA COVID-19 Therapeutics Programme is designed to detect emerging resistance to COVID-19 therapeutics through genomic and epidemiological surveillance and structural modelling and to initiate public health action in response to concerning signals. There are risks to the programme's ability to perform these analyses and produce outputs that may inform the proposed process. For example, changes in national testing policy from PCR test to LFT in some settings will reduce the number of patient samples that the programme can access from the population eligible for therapeutics that can undergo genomic sequencing. As of 1st April 2023, routine testing ended for the following groups and settings: routine asymptomatic testing, including testing on admission, for staff and patients across all health and social care settings including hospitals and care homes routine symptomatic testing of staff and residents in care settings – routine symptomatic testing also ended in other settings including prisons and places of detention, homelessness and refuge settings and asylum setting all PCR testing outside NHS settings Data on individuals eligible to receive COVID-19 therapeutics (the denominator data) required for epidemiological analyses is currently not being shared with the UKHSA for use within the programme. Transition from COVID-19 medicines delivery units (CMDUs) to regional integrated care boards (ICBs) for referral and provision of COVID-19 therapeutics to eligible patients will introduce changes at the regional and national level in patients receiving COVID-19 therapeutics and

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			if/how patients are recruited to UKHSAs surveillance activity. Discontinuation of NHS Blueteq high cost drug system in 2023 will also disrupt access to data on prescribing of/access to COVID-19 therapeutics in a way that allows linkage to patient data. The programme is working to mitigate these risks whilst transitioning activity to 'business as usual' operation and this will impact the genomic/epidemiological data available to NICE on COVID-19 therapeutics by which to inform recommendations.
Cardiothoracic Transplant Patient Group at NHS Blood and Transplant	General		In general, The Cardiothoracic Transplant Patient Group supports the principles within the proposed process as being a good basis to make decisions and update recommendations. However, the Cardiothoracic Transplant Patient Group does have some concerns which will be detailed below.
Cardiothoracic Transplant Patient Group at NHS Blood and Transplant	5	2.2.9	The example given in the second bullet point is a binary comparison between Paxlovid and sotrovimab. The Cardiothoracic Transplant Patient Group would like to emphasise that the surveillance process must continue to be multi-comparator between medicines as some agents (for example Paxlovid) are unviable for some high-risk groups. The surveillance process must include those agents which have previously been assessed and not recommended by NICE as well as agents which are currently recommended in the guidance.
Cardiothoracic Transplant Patient Group at NHS Blood and Transplant	6	2.2.12	The Cardiothoracic Transplant Patient Group welcomes the inclusion of a stakeholder submission surveillance stream.

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Cardiothoracic Transplant Patient Group at NHS Blood and Transplant	9	2.4.2	The Cardiothoracic Transplant Patient Group have concerns that the cost recovery requirements have the potential to adversely impact subgroups with certain protected characteristics. As an example, the population size of any potential new subgroup for additional inclusion in recommendations would be a significant factor in the company's decision whether to fund the cost recovery of a rapid COVID-19 review process. This population could have a specific disability which is a protected characteristic. The Cardiothoracic Transplant Patient Group does appreciate the requirement for cost recovery and has three process suggestions which could mitigate the potential for discrimination. Basketing - If NICE receive more than one surveillance trigger that relate to different aspects of changing the recommendations for one treatment, then triggers are "basketed" into a single review and hence a single cost recovery charge to the company. Networking stakeholders – In this scenario, NICE receive a surveillance trigger where the company are not willing to fund the review as it relates to a small patient population and hence low potential revenue gains for the company. NICE proactively (and subject to stakeholder approval) link stakeholders with a shared common interest. Stakeholders may then seek to make a wider surveillance trigger case. Tiered rather than single recovery cost – NICE develop a more refined tiered recovery cost structure where review charges that are covered by the company are tiered based on the anticipated size of the patient population and expected number of increased treatment sales generated. This costing structure will mitigate the risk of rarer disabilities being adversely impacted by a single tariff.
The Royal College of Pathologists	General		More frequent, rapid, appraisals are anticipated to be beneficial to patients and healthcare community
The Royal College of Pathologists	General		There are potential problems over lack of sufficient data in the proposed short time frame to make a robust recommendation; a possibility of such rapid evolution of the virus (in this case

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			SARS-CoV-2) that the recommendation is no longer applicable by the time it reaches operational activity; the need to ensure timely dissemination of the advice married to the acceptance of the advice by authorities that control drug access and operationalisation so that maximum benefit can be gained.
The Royal College of Pathologists	General		'Several' triggers are mentioned and the most obvious ones are given. It is not possible to know what additional triggers might be used, but a change in test technology, or new data on the prognostic markers would seem to fit the remit.
Kidney Research UK	General	General	We welcome the announcement from NICE that a new process will be consulted on for reviewing the latest evidence for existing treatments for Covid-19. It is a positive step towards recognising the unprecedented uncertainty facing treatments for a rapidly evolving virus, and we thank NICE for meeting with us recently to discuss this in further depth.
Kidney Research UK	1	1.1.3	We are deeply concerned that a return to 'business as normal' for evaluating new COVID-19 treatments is not appropriate for patients or the National Health Service. We need to see firm proposals for reforming the way we appraise new treatments for COVID-19 to ensure the process is expedited. Addressing the risk of COVID-19 to those who are immunocompromised must be prioritised. As we know, vaccination can be less effective in people who are immunocompromised, including transplant recipients. The importance of the vaccination and booster programme is undoubted, but we must continue to push for more effective strategies and review new data promptly – including for new treatments. Regulators and reimbursement bodies must commit to rapidly reviewing and providing access to safe and effective new treatments. Following traditional health technology assessment routes restricts the opportunity to promptly utilise effective treatments, with a prolonged period of assessment leaving vulnerable patients without potentially life-saving treatment options during periods of high infection rates. This has been exemplified by the process for evaluating tixagevimab plus cilgavimab (Evusheld). Following procurement of the prophylaxis treatment across many European countries, the UK started its own review process in June 2022. We are only just now at the end of its health technology assessment. Efficacy against new

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			variants of the virus has waned, but many lives could have been transformed by access to the treatment during its highest period of efficacy during the summer of 2022. The UK 'missed the boat', and high-risk kidney patients, a significant number of whom remain shielding, have paid the price.
Kidney Research UK	1	1.2.1	The triggers outlined are a good and sound basis for updates. However, we are concerned that there could be gaps in NICE's ability to obtain information and evidence to support the consideration of them. To implement the updates, routine surveillance will be needed on Covid-19 and hospital episode statistics.
Kidney Research UK	7	2.3.1	A concern we have about the proposed process is the risk to transparency, as meetings are not being held in public. The NHS, for which NICE makes decisions about treatment availability, is a publicly funded healthcare system, and it is therefore accountable to the public for the decisions it makes. By involving the public in these discussions, the NHS can ensure that the decisions it makes are transparent, evidence-based, and reflect the needs and concerns of the communities it serves. There is also a lack of transparency about the 'no update' decision where there is new evidence or intelligence. If a decision is made by the NICE team not to update guidance, this should be published and there should be a formal way for stakeholders to register their agreement or otherwise with this decision.
Kidney Research UK	4	2.2.7	It is positive that UKHSA technical briefings will be used to consider the spread and threat of new variants. However, we are concerned that the termination of the ONS Infection Survey could set a precedent that technical briefings will be suspended or become less frequent. Wide sources of information should be available to NICE. This should include non-randomised evidence in support of trial evidence, such as the OpenSAFELY data considered in the assessment of sotrovimab and molnupiravir. UKHSA continuing surveillance of Covid variants is also vitally important.
Kidney Research UK	5	2.2.11	Changes to contraindications of treatments is an area that needs further consideration. Recently in Wales, and through the Renal Pharmacy Group,

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			the safety of Paxlovid in some kidney patients is being considered, with a view to extending the population that can be prescribed it. This should be a part of NICE's remit for the rapid surveillance and update process.
Kidney Research UK	10	2.4.6	Our view is that the appointment of a patient expert is necessary. However, restricting the selection criteria solely to those patient experts who have prior involvement with Covid guidance would significantly limit the pool of potential candidates. It is essential to consider the option of recruiting individuals from stakeholder organisations or other individuals who possess the necessary interest and expertise in this field.
Kidney Research UK	12	Table 2	The balance between the need for a rapid response and the need to obtain useful stakeholder insight will no doubt have been finely considered. However, a week will likely not provide a long enough period for patient organisations to submit useful insight to the process. On such a matter of importance to patients, this will cause considerable concern about the validity of decisions. Rapid processes must not be solely designed to cut the time allowed for stakeholder input. We would also ask for additional clarity with regards to whether a week in 'calendar days' could mean a very limited number of days over a bank holiday period, for example.
GlaxoSmith Kline	28	6.5.27	If there is no published data would the company be requested to provide unpublished data?
GlaxoSmith Kline	37	Appendix 3	In Appendix 3 the authors have stated that they are identifying preprints through the Europe PubMed Central database, however the details on how they are doing this are scarce (there is a line to say that "this will be adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage"). Given that the contents and mechanisms for searching ePMC, are very different to OVID, it would be very useful to be able to see the adapted strategy. Also, given that the search strategy should be reviewed regularly using any information provided by the technical team or other experts, and that new terms will be added when new variant/sublineage is identified, it would be helpful to receive regular updates from NICE on their search criteria.

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			Line 16 page 40 in the Medline search strategy should include ‘S309’
GlaxoSmith Kline	5	2.2.9	Due to the case-mix and the current NICE recommendation to only use sotrovimab for patients who are ineligible for treatment with Paxlovid, a robust assessment of relative effectiveness of sotrovimab versus nirmatrelvir/ritonavir is challenging.
GlaxoSmith Kline	11	2.4.9	The proposed rapid process timelines may be suitable for a treatment which is not currently recommended, and a surveillance trigger initiates evaluation. However, we believe the process and timelines are unsuitable for treatments that are recommended. In this situation, it is important that a company submission can be provided to ensure that all relevant published and unpublished data are considered during the re-evaluation of a recommended treatment. It is unfeasible for a company to generate and synthesise evidence and provide a response in a 1-week consultation timeframe where a trigger occurred a few weeks prior. A greater period from trigger to review by the committee and consultation would enable all relevant data to be considered before the publication of draft guidance. We believe that in the situation where a recommended treatment has received a surveillance trigger, a robust process should begin to ensure that all available evidence is considered by the Committee, enabling them to reach an informed decision. It is important to ensure that the Company is given suitable time to prepare a response and ensure that all relevant data can be generated and synthesised. The re-evaluation of treatments that are already recommended and where there are no alternative treatments recommended is likely to be a complex decision. The process should enable robust input from stakeholders to enable the Committee to reach a fully informed decision.

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GlaxoSmith Kline	6	2.2.12	It is important that stakeholder submissions also enable consideration of any type of data that may inform the decision, including economic analyses using the latest relevant data and sub-group analyses to ensure that the value of the treatment is appropriately captured. Patient organisations listed as stakeholders should also be invited to provide a submission, to ensure that the patient voice is heard during the decision-making process.
GlaxoSmith Kline	14	Table 3	Companies should be notified as soon as NICE identifies a trigger or as soon as the trigger evidence is undergoing surveillance assessment to allow for companies' preparation, given the extremely dynamic nature of the disease and the virus. Companies' need to be aware of the information early enough to enable speedy internal reviews of the evidence's impact and evaluate the effects on the medicine's value to patients. For transparency and in the interest of the patients, it is counterintuitive to health equity to only inform companies after or during the surveillance decision phase, as this leaves companies with little time to generate and review the evidence needed to make an informed contribution to the decision.
GlaxoSmith Kline	4	2.2.7	The UKHSA currently generates internal weekly reports for variant growth rates, but these are only published monthly (or less frequently going forward) once the weekly reports have been aggregated. A monthly report may be too late to help a company generate evidence and inform the decision-making process, and therefore we request that companies receive the weekly UKHSA growth rate data to ensure that evidence generation can begin earlier.

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GlaxoSmith Kline	General		We are concerned with the emphasis placed on in vitro neutralisation data in the decision-making process outlined in the 'COVID-19 technology appraisal recommendations: surveillance and rapid update process statement'. The IVAG acknowledges that there is no consensus on the exact relationship between in vitro neutralisation data and clinical outcomes for COVID-19 (such as reducing hospitalisation rates or mortality), and that there is no validated tool for appraising in vitro neutralisation data. Moreover, the variability of in vitro results based on cell lines and assay systems and a lack of models to incorporate the role of Fc-effector function, which triggers the body's own innate immune cells to fight SARS-CoV-2 infection, may also contribute to inconsistency between clinical effect and in vitro results. Sotrovimab, which binds to receptors outside of the receptor-binding motif, is also particularly impacted by cell lines that overexpress ACE2. In vitro neutralisation studies that utilise assays overexpressing ACE2 should not be used as they are known to substantially underestimate the neutralisation effects of sotrovimab and thus do not represent the actual activity of the molecule against a particular SARS-CoV-2 viral variant [Walker, 2023]. The IVAG acknowledges that when new SARS-CoV-2 variants emerge, it is likely that numerous groups of scientists will generate and publish in vitro data and considers it important that results are broadly consistent across studies. The literature shows large variance in in vitro neutralisation study results, which would materially impact clinical pharmacology models leading to different conclusions based on the EC50/90 values used. For example, two recent studies have shown very different results for IC50/EC50 for sotrovimab against authentic XBB.1.5 variant, ranging from approximately a 2-fold to a 33-fold shift in neutralisation versus wild-type [Addetia, 2023; Wu, 2023]. Modelling based on these different scenarios alone could lead to very different recommendations. In addition, there is no validated clinical pharmacology model for sotrovimab that can consistently and reliably correlate in vitro neutralisation to predicted clinical efficacy [Sager, 2022]. The IVAG has indicated that the

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			mechanism of sotrovimab differs from other nMAbs and that it may have additional beneficial effects beyond neutralisation through effector functions. Sotrovimab has been shown to mediate antiviral activity through multiple mechanisms of action in vitro and in vivo, including neutralisation and effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) [Bruell, 2022; Cathcart, 2022; Case, 2022; Addetia, 2023]. In vitro neutralisation activity may only be a partial determinant of sotrovimab efficacy; Fc mediated effector functions may contribute additional antiviral effects against SARS-CoV-2 variants and may contribute to the consistent clinical effectiveness of 500 mg IV sotrovimab observed in Real World Evidence (RWE) studies between Omicron BA.1, BA.2 and BA.5 variant eras, despite reduced neutralisation activity against these variants in vitro [Harman, 2022; Patel, 2022; Zheng, 2022; Zheng, 2022; Evans, 2023; Patel, 2023; Zheng, 2023]. In the absence of a reliable correlation between in vitro neutralisation and efficacy, other data modalities, including pre-clinical in vivo and observational, become important. Given the limited treatment options available to patients at the highest risk of progression to severe COVID-19 disease, and that oral or intravenous antivirals may be impractical, contraindicated, cautioned against, or otherwise precluded from use due to clinically significant drug-drug interactions [EMC SmPCs, 2023], GSK urges NICE to build sufficient time into the review process to enable a thorough evaluation of all available evidence for sotrovimab, not limited to in vitro neutralisation data but including in vivo, RWE and expert opinion. In addition, in the situation where there is reduced in vitro neutralisation activity of sotrovimab against a new variant, GSK recommends that NICE does not withdraw sotrovimab until an assessment of clinical effectiveness has been made through a well-constructed, rapidly deployed, independent RWE study, conducted for example by an academic group specialising in open data sets such as OpenSAFELY, or by the NHS or another affiliated group. Historical in vitro neutralisation data from previously circulating variants together with corresponding clinical outcomes from RWE

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			studies should also be taken into consideration to help guide future decision making. This could help prevent an otherwise valuable treatment from being removed prematurely based on in vitro neutralisation data alone and help to avoid patients being denied what for some, might be their only treatment option.
GlaxoSmith Kline	General		No reference is made as to where studies investigating the in vitro or in -vivo effector functions of sotrovimab, including ADCC, ADCP, and binding affinity would be incorporated into the rapid review process as a potential trigger.
UK Kidney Association	5	2.2.11	Does intelligence gathering include data on rate and severity of adverse events (including in specific clinical groups) associated with the different drugs? Might data on adverse events trigger a review of recommendations for a specific drug and should this be stated explicitly in the process statement?
UK Kidney Association	34	6.5.37	In the 3rd outcome of this step, where there is some neutralisation at higher concentrations but substantial fold change compared with ancestral variant, expert input will be sought. Is it anticipated that the eligibility of various specific vulnerable patient groups would be reassessed if a specific drug is demonstrated in vitro to be less effective e.g. might some clinically vulnerable

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			groups be reassessed as ineligible on such in vitro data?
UK Kidney Association	General		The process statement is clearly written and seems well thought through.
Blood Cancer UK	General	General	To answer question 1, 'Is the process as outlined a good basis for the committee to make decisions and update recommendations?', Blood Cancer UK welcomes the initiative to introduce a rapid update process for Coronavirus (COVID-19) technology appraisal recommendations. People with blood cancer often do not receive the same, if any, level of protection from vaccinations and therefore continue to be vulnerable to poor and severe outcomes if they contract COVID-19. Because of this, antiviral, therapeutic and pre-exposure prophylactic treatments are incredibly important for protecting people with blood cancer from severe COVID-19 and for giving them the confidence to return to more normal social mixing, including returning to the workplace. The quicker safe and effective technologies are made accessible to immunocompromised people the better, and the outlined process is a step in the right direction. We appreciate also, that the accelerated timeline includes a consultation period for stakeholders, such as Blood Cancer UK, to provide input when no update is made or recommendations are withdrawn. We also welcome the commitment to continuous surveillance, although we have concerns about the status of some of these sources.
Blood Cancer UK	General	General	To answer question 2, 'Do you have any concerns about the process and, if so, any suggestions to address those concerns?', we have a number of concerns regarding surveillance, cost effectiveness and the implementation of recommendations. On cost effectiveness, we find it difficult to understand how the committee could judge that a price increase relating to a currently effective medicine could warrant withdrawal of recommendations, which is a possible outcome of this new process. Many immunocompromised people, such as those with blood cancer, remain vulnerable to severe COVID-19 and have been taking personal precautions since the shielding programme ended. This group is not homogenous, their immunosuppression is caused by various factors, such as blood cancer, and many are taking medications for pre-existing conditions that may have contraindications with certain COVID-19 medicines. For this reason, all effective

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			medicines need to be available to ensure there are as many paths to treatment or protection as possible.
Blood Cancer UK	General	General	To answer question 3, 'Do you feel there are any gaps in the process or areas that need further consideration?', we feel the new process fails to address the problem identified that sparked this rapid update process when it was announced on 16 March 2023, in response to NICE's announcement that the pre-exposure prophylaxis, Evusheld , was not recommended for vulnerable adults at high risk of severe COVID-19. In response to this announcement, Director of Medicines Evaluation at NICE, Helen Knight, said, 'the ambition is that we will be able to produce updated recommendations in as little as 6 to 8 weeks from receiving a positive signal of effectiveness.' However, this resultant process only applies to existing treatments, which for pre-exposure prophylaxis is therefore only Evusheld, which was found to only offer clinical benefit for variants circulating earlier in the pandemic. This means that unless Evusheld is found to offer protection against future variants, this process makes no difference to future pre-exposure prophylactic medicines. Any new medicines offering pre-exposure protection against current or future variants of the virus, would follow the current single technology appraisal process, where there is a target – not commitment - to release guidance within 90 days of marketing authorisation. The need for a rapid review process of existing treatments surely implies at least an equal need for a rapid review process for new treatments.
Blood Cancer UK	4	2.2.7	The statement lists the UK Health Security Agency's (UKHSA) monthly technical briefing documents on novel SARS-CoV-2 variants as a source of intelligence on new SARS-CoV-2 variants under investigation in the UK to understand growth rates of new variants and sublineages and any new mutations identified in circulating variants that potential impacts on the neutralising activity of MABs. However, in the since published 52nd technical briefing, dated 21 April 2023, the briefing states that 'due to changes in testing and availability of samples for sequencing, this is the last routine variant technical briefing in this format.' The briefing also acknowledges that the 1 April scaling back of PCR testing directly affects genomic surveillance

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			and that since the pause of the Office for National Statistics (ONS) COVID-19 Infection Survey (March 2023), 'samples available for sequencing are limited to hospital admissions and some research studies.' We would like to know how NICE is working with the UKHSA to ensure there is continued surveillance of variant prevalence and growth rates, key triggers outlined for this rapid update process, and what NICE will do if UKHSA does not announce new community surveillance?
Blood Cancer UK	7	2.3.1	For transparency purposes, we feel that when 'no update' is made following new evidence significant enough to trigger this process, that information should be published on why the committee reached the 'no update' decision.
Blood Cancer UK	9	2.4.2	The statement outlines a new cost recovery charge that companies must pay for the rapid update process and that this charge 'includes building a new surveillance function for the TA programme.' We welcome the prospect of a new surveillance function for the technology appraisal programme, however we would like to know more about what this function is expected to do and if it will be overseen by NICE.
Blood Cancer UK	10	2.4.6	We would like to see further clarification about how clinical and patient experts will be selected for the decision making committees, and details of if and when the 'pool of clinical and patient experts who have previously been involved in developing NICE guidance on COVID-19' might be reviewed or expanded.
Blood Cancer UK	12	2.4.16	Given that special measures are being taken to speed up this process to respond to the evolving threat that COVID-19 poses to immunocompromised people, could the 90-day funding implementation period after the publication of new guidance be shortened too? This is a further delay to medicines reaching the people that need them, and allows time for the medicines to become less effective, given the changing nature of circulating SARS-CoV-2 variants.
Blood Cancer UK	17	6.4.1	We welcome the formation of the In Vitro Advisory Group (IVAG) and that in vitro evidence is a key trigger for the rapid update process. However, we would like to see further emphasis placed on real world evidence, including from international examples, as a trigger in this process.

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Leukaemia Care	General	General	We are concerned that this approach may not be fit for purpose for the review of COVID-19 treatments as it takes place only after the standard NICE appraisal process has concluded. The duration of the standard appraisal process is such that a COVID-19 treatment which might have been effective against circulating COVID-19 variants at the start of the appraisal process might not be towards the end because the variants would have changed within that timeframe. We therefore believe a shorter alternative to the standard NICE process is necessary, alongside a subsequent rapid review process, like the one suggested.
Leukaemia Care	General	General	We are pleased about the inclusion of a patient expert in the committee meetings of the rapid review process proposed, however we are concerned that without a patient organisation submission or consultation, this expert involvement is not sufficient to be reflective of the entire cohort for which the treatment is being considered. As a result, this could lead to significant gaps in understanding patient experience. This is particularly true for treatments which are being looked at in the context of several subgroups of patients, which is something that would typically be addressed in a patient organisation submission.
Leukaemia Care	General	General	In light of any new evidence triggering the rapid review process, we also propose that the NICE team considers the cost-effectiveness of the treatment in individual patient subgroups rather than only for the patient cohorts collectively. This is because it might be the case that a new piece of evidence renders the treatment cost-effective for one (perhaps higher risk) subgroup, such as those with leukaemia, but not for the subgroups combined.

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Shionogi	General	General	The intended focus of this proposed surveillance and rapid update process is unclear. This is compounded by varying terms used across NICE/MHRA documents to describe the different types of therapeutics for COVID. NICE TA 878 refers to 'antivirals' (e.g., nirmatrelvir plus ritonavir) and 'neutralising monoclonal antibody' (e.g., sotrovimab) and 'anti-inflammatory' (e.g., tocilizumab). We assume that these are mutually exclusive categories of intervention, all of which may be considered relevant for this new process. However, the draft statement contains specific references to 'monoclonal antibodies (MABs)' (e.g., in sections 2.2.5, and 2.2.7), and other parts of the draft statement (e.g., sections 2.2.9, 2.3.4, Appendix 1, and the MHRA 'Responding to emerging COVID-19 variants of concern' document) suggest that the focus is on MABs rather than antivirals. Anti-inflammatories are not mentioned. The MHRA 'Responding to emerging COVID-19 variants of concern' document refers to 'antiviral drugs' and 'monoclonal antibodies (mAbs)' at the outset, then refers only to 'antiviral medicines' in its statement of purpose, then lists both mAbs and products considered antivirals by TA 878 in its scope, and then refers to mABs and 'small molecules' in the introduction. We assume 'mAbs' are equivalent to 'neutralising monoclonal antibody', but it is unclear what 'small molecules' refers to (antivirals?), and whether this document addresses anti-inflammatories in any way. This document also contains content suggesting that that the impact of new variants is limited/focused on mAbs. We request that NICE make their intended focus of this new process completely clear, i.e., is the aim to re-evaluate only MABs, or also antivirals (and/or also anti-inflammatories)? We also suggest that clarification of the terminology used to describe the different categories of therapeutic agents is required.

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Shionogi	1	1.2.1	The focus on ‘a change in the disease that significantly changes the hospitalisation or mortality rate’ (as a trigger) is increasingly outdated, and misplaced/unnecessary. As highlighted in the TA 878 FAD, there are a wider range of factors and outcomes that are already – and which will increasingly be – important for the future management of COVID (e.g., the nature/level of symptoms associated with acute COVID, the impact of long-COVID, and the ex-health ‘societal’ impacts of COVID). More importantly, changes in the disease per se are not relevant triggers for re-evaluation; the only relevant triggers are those related to potential changes in COVID variants and in the efficacy of therapeutics. We therefore suggest that this ‘trigger’ should be deleted. We also suggest that NICE should develop a pragmatic ‘gating’ trigger system. This could involve the following type of steps: Has a new COVID variant emerged, that is already – or is likely to become – a dominant variant? If yes, proceed. Does the in-vitro efficacy of therapeutics differ for this new variant (i.e., are there therapies which NICE have not approved which are more efficacious against this new variant compared to previous variants, or are there therapies which NICE have approved which are less efficacious against this new variant)? If yes, proceed.
Shionogi	1	1.2.1, 2.2.14	NICE should be cautious about unconditionally using ‘emergence of a new variant of SARS-CoV-2…’ as a trigger for reviews of its recommendations. Some new variants might be insignificant (and these cases might also be potentially numerous), and NICE must therefore adopt a pragmatic approach to determining whether the emergence of any individual new variant merits a review. Similarly, NICE should exercise caution and be pragmatic about unduly reviewing recommendations in response to any small change in cost.

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			Also, do NICE intend that cost alone should be a sufficient trigger for a review?
Shionogi	7	2.2.16	The process statement indicates that stakeholder consultations and surveillance decisions will not be published. What is the reason for this? We propose that they are all published for transparency.
Shionogi	9	2.4.2	The new cost recovery charge of £125,196 should be justified by NICE, by sharing the breakdown of that costing estimate. Considering that these are reviews of existing guidance (i.e., without need for further economic modelling or extensive committee deliberation on a wide range of factors that were relevant for the initial guidance but unaffected by the specific impact of new variants on therapeutic efficacy levels), that amounts seems high, particularly when considering existing NICE fees (£143K for full STAs and only £100K for Rapid Reviews). Industry cannot be expected to pay for 'background' COVID surveillance activities (i.e., monitoring for the emergence of new variants) that should be funded regardless of these NICE technology reviews.
Shionogi		2.4.6	We welcome expert involvement in the process. More details would be needed on the "pool" of experts referred to in the guidance. We suggest this requires a qualifying statement, e.g., that clinical experts are required to have the relevant expertise as per section 1.2.10 of the draft manual for health technology evaluation.
Shionogi	General	General	The focus of this re-evaluation process appears - potentially - to be focused on the impact of new variants on MABs (subject to the clarifications outlined in comment 1 above). However, it is uncertain whether the efficacy of antiviral therapies will be impacted as new variants emerge. We therefore suggest that the scope of this new process should not exclude antivirals (or anti-inflammatories) without further justification and consensus. Another consideration is that resistance may

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			impact the efficacy of therapeutics against existing COVID variants. NICE could therefore also consider whether – and how – its guidance should reflect the emergence of resistance, alongside the emergence of new variants.
Shionogi	General	General	The proposed scope of these reviews is limited to technologies that have already been appraised by NICE, but we suggest that it could/should be expanded to allow NICE to rapidly evaluate emerging technologies that have not yet been appraised, particularly if previously recommended technologies may have lost their efficacy to treat COVID. For example, it would be beneficial for NICE to be able to react quickly to this potential scenario: - a previously appraised (and recommended) technology is ineffective against a new COVID variant, but there is a new technology available (licenced, but not appraised by NICE) which is effective against that new variant. NHSE may also wish NICE to rapidly evaluate new technologies that are likely to be more cost-effective than existing recommended therapy, e.g., in this scenario: - a new technology is available (licenced, but not appraised by NICE), which is effective against all/new variants, and significantly less expensive that previously recommended alternative technologies. In both these scenarios it would be in the public interest for NICE to be able to issue updated guidance – including recommendations on emergent technologies – as quickly as possible. The existing NICE processes (e.g., FTAs and the pilot 'PATT' programs) are not yet suitable for this purpose.
Evusheld For The UK	General	General	Whilst we welcome the approach to establish this new post decision process, we are concerned that as in the original assessment process, no threshold has been set or even mentioned as to what will trigger the rapid update process assessment. What rise in efficacy will be sufficient to trigger this? How many variants will there need to be a change seen in to start this process? It is clear from the discussions during

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			the review panels that one of the main stumbling blocks is establishing the acceptable limit of efficacy of this and other drugs of this nature, which has led to circular discussions on a binary decision. Therefore, it has to be questioned as to the parameters that are or will be set in order to start the assessment. This issue needs to be clarified, otherwise it will simply push this question further down the line in what needs to be a quick, clean and efficient process in order to allow this or a similar drug to be authorised rapidly to avoid missing another window of opportunity to the detriment of patients
Evusheld For The UK	General	General	We are concerned that although a significant step forward, this process will only deal with drugs already assessed in a full technology appraisal. It is of vital importance that a new rapid technology assessment is devised to allow any new Covid-19 drugs such as new versions of monoclonal antibodies to have a new much faster and efficient method of appraisal. For the patient cohorts these drugs are specially aimed at, speed of implementation of this is imperative, and it is therefore critical that a new pathway is devised that will allow such drugs to be correctly and safely appraised, without prejudicing the window of use, as has happened with Evusheld. We have already seen with post exposure Covid 19 treatments, that such drugs have been accessible to patients whilst still undergoing a full technology appraisal. Patients with the need for such drugs are still living with the effects of the pandemic daily, and innovative and accessible solutions need to be found. Time is of the absolute essence.
Evusheld For The UK	11	2.4.10	It is noted that there is no intention to hold meetings in public. For transparency, it is essential that such meetings are public. There is no reason they could not be held with access to stakeholders virtually in a basic form. As it is accepted that speed is a major factor, the need for presentations etc can be done away with, but such meetings should still be accessible to allow stakeholders as a minimum to evaluate the evidence being presented.
Evusheld For The UK	7	2.3.1	We are concerned that it is intended for no information to be published if an assessment results in no process being triggered. Our view is that it is essential that any evidence that is reviewed, must be published to allow review of the evidence by stakeholders and peers to allow an understanding of why a no, to trigger the

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			process has been reached. It will also give stakeholders a clear direction on the evidence assessed and avoid repetition in any submission that may be made by stakeholders for consideration of new evidence, and it will also help to build a picture of what evidence still falls below the standard deemed necessary.
Evusheld For The UK	4	2.2.7	The entire process for the evaluation and trigger is based on surveillance of information from various sources, however a mainstay mentioned within the document is the reliance on the UKHSA technical briefing documents, which have now been suspended as has ONS data, how is that loss of data with regards to existing prevalence of variants and the introduction of new ones to be accounted for and how will the review process now effectively assess data
Evusheld For The UK	10	2.4.6	The role of the lay member and clinical expert are of extreme importance in this process due to both the responsibility that comes with the position they hold and the fact they will hold this position for 12 months. It is our view that as the lay member will be a voice for all stakeholders, there should be some facility for stakeholders to approve the choice of the lay member, and that of the clinical expert. We suggest that a stand in for both positions is put in place as soon as possible, until someone can be placed in the positions with the agreement of the other stakeholders, as the process is time sensitive.
Lymphoma Action	1	1.1.3	We broadly agree with the process outlined to update recommendations however we want to ensure there is a rapid process for all new potential medicines for preventing and treating COVID-19 too, not just existing ones. Changing variants will likely mean there will be new medicines or combination medicines for preventing and treating COVID-19 in the future and it is important these are considered too.
Lymphoma Action	10	2.4.6-2.4.9	Whilst we understand that in order for the process to be rapid it must be streamlined in some ways, there is a need for greater stakeholder input, particularly patient experience as this is important in the committee's decision making. Whilst having a patient expert as an advisory member of the committee is welcome, this does not fully capture the breadth of patient experience across all people impacted by COVID-19 treatments (particularly as there are a number of conditions that can make an individual immunocompromised). Having a greater pool of

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			patient experts and advisors and/or patient organisations input would be beneficial.
Lymphoma Action	General	General	Additionally, with the process being a rapid review, there may be a level of scepticism from patients and the public. Having more patient experts and advisors on the committee and involved in these decisions could increase public confidence.
Lymphoma Action	3	2.2.1	If the maintenance of technology appraisal recommendations must be supported by continues surveillance, there is a risk about surveillance and data collection as UKHSA priorities change with new health concerns.
LUPUS UK	General	General	We are concerned that the proposed process only applies to medicines that have already been through a full Technology Appraisal and will not include new treatments, including new prophylactics. This means the short window of opportunity in which new monoclonal antibodies are most effective will continue to be missed, as was the case with Evusheld. This will perpetuate the inequity experienced by people at highest risk from COVID-19 in the UK. In addition, this may also discourage pharmaceutical companies from developing new monoclonal antibodies or introducing them to the UK market, as they are unlikely to be approved while still effective. It is essential that the rapid COVID-19 appraisal process include new medicines, or mechanisms for mitigating the length of time the full process takes, such as patient access while a treatment goes through a full appraisal, as occurred with post-exposure treatments for COVID-19. The currently proposed process seems more likely to withdraw recommendations for treatments than to introduce potentially effective treatments into use by the NHS. It has been suggested by NICE that some treatments could regain efficacy as new variants emerge, but no modelling has been shared about the potential likelihood of this occurring.
LUPUS UK	10	2.4.6	We are concerned that this section implies only one clinical expert and one patient expert will be recruited to the sub-committee. Given the short notice they will have before each meeting, it would be better to have a pool of experts to draw upon to ensure expert involvement is available. A pool of experts would also help to ensure the expert has knowledge or experience of the

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			particular issue. As there will be no consultation with patient organisations before each committee meeting it is vital that representation is ensured. The proposal says that the NICE team will identify the experts from the pool of clinical and patient experts who have previously been involved in developing NICE guidance on COVID-19. However, there may be some problems that arise from this: The commitment to be on call for 12 months is very different from the original commitment of contributing to the appraisal process. What process will be used to identify experts if there are insufficient volunteers from the existing pool or a volunteer must cut short their commitment during the 12-month period? If stakeholders disagree with the selection of experts, is there any way to appeal or propose alternative experts from those in the existing pool?
LUPUS UK	7	2.3.1	We are concerned that no information will be published if the internal assessment by the NICE team results in the update process not being triggered. The guidance states that “no information is published” if the decision not to update is reached when new evidence is reviewed. However, there is a lack of clarity about the threshold for new evidence to trigger a change in recommendation. Without publishing, for example, a log of evidence considered, there is a complete lack of transparency about internal decision-making processes, and there is also no opportunity for stakeholders to appeal, which is more important given there will be no submission from stakeholders prior to any decision. Logging evidence considered will also prevent repeat submissions of the same evidence or may prompt stakeholders to submit further evidence.
LUPUS UK	11	2.4.10	We are concerned that the meetings will not be held in public. Given that the committee meetings will be held on Zoom, and NICE already has processes in place to make these public, it should be feasible to maintain this current transparency. The meetings could still have separate public and private sections, and a PowerPoint presentation need not necessarily be prepared. If needed, the committee should increase capacity, such as having a dedicated administrative member to enable this.

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LUPUS UK	12	2.4.15	We are concerned that the consultation for stakeholders is only seven calendar days. As a small patient organisation, we do not often have the flexibility in our capacity to make a meaningful contribution in such a short period of time. This will reduce the patient voice in consultations, which is often vital in highlighting areas of unmet need, inequities or where incorrect assumptions about a patient cohort have been made.
LUPUS UK	9	2.4.1	We are concerned that the recommendations are frequently binary (yes/no). Decision-making could be more precise if, instead, a threshold of efficacy and a clearly defined eligible patient population were recommended. As dominant variants change, this would also guide the review and appraisal process more clearly.
Merck Sharp & Dohme (UK) Limited (MSD)	General		Is the process as outlined a good basis for the committee to make decisions and update recommendations? No – the proposed process does not form a good basis for the committee to review decisions and make updated recommendations. The proposal appears to have a sole focus on IVAG which means it is unclear how this can be leveraged to ensure that a fair assessment of additional clinical evidence (including RWE studies) can be leveraged within this framework. Within its original press release, NICE mentioned that supplementary evidence could constitute real world studies and in-vitro studies, in particular for monoclonal antibodies (mAbs). During the COVID-19 assessment, NICE recognised the evolving nature of COVID-19 could have implications on the relevance of the final guidance issued. As acknowledged in the outlined process, there is a need to consider supplementary evidence - real world studies and in-vitro studies – in addition to randomised controlled trials (RCTs) because of the changing nature of COVID-19. We are concerned that the process statement under consultation lacks clarity in definitions. This will result in multiple interpretations of the proposed process criteria and requirements. Importantly, it fails to provide a clear framework for the submission of real world evidence, other than in-vitro data. The framework needs to allow for the activity of AVs to also be monitored by introducing a mechanism for review and update of the AV clinical evidence base. The current focus on in-vitro mAb studies seems only aimed

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			at considering the ongoing effectiveness assessment for mAbs alone. The proposed rapid update process is overly restrictive for assessing technologies other than mAbs. RWE appears not have been given its due consideration within this framework unless it falls under the class of studies exploring the in-vitro neutralisation activity. Whilst we understand that mAbs are potentially subject to increased COVID-19 selective evolutionary pressures and the need to have a framework for ongoing surveillance for new variants and in-vitro data is justified, equally so, we do consider that the clinical evidence for AVs may also become less certain as changes in population immunity and COVID-19 variants continue to take place. We therefore consider it to be of paramount importance that real world data (other than in-vitro studies) is surveyed systematically and a clear path is developed to appraise the evidence for AVs to ensure optimal allocation of NHS resources in the long run. We ask that NICE develops this in the updated process statement post consultation.
MSD	General		Do you have any concerns about the process and, if so, any suggestions to address those concerns? We have significant concerns that this rapid update is reliant upon the previous assessment process which suffered from serious flaws. There is a need to systematically identify, collate and conduct a thorough assessment of the wider evidence base beyond RCTs, including real world evidence sources, in line with the NICE manual of health technology evaluation. This will ensure the true value (clinical and societal) of antivirals (AVs) and other technologies, in the endemic phase, can be captured. Given the exclusion of all but one real world evidence source in the initial COVID-19 assessment this new rapid update process is a welcome acknowledgement of the importance of these evidence sources. We are concerned that this rapid update process will suffer from the same weaknesses as the original process. Whilst NICE aims to issue speedy recommendations, this should not be at the cost of rigour and transparency. The proposed timelines can only be achieved with the use of “abbreviated committees” and extremely

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			limited company involvement throughout the process. We are believe this will result in poor quality recommendations. MSD is concerned that NICE having the primary role for data analyses, unless EAG support is required due to complexity, risks flaws being introduced as a critical checking/validation step would be removed. We do not think this is the right way to strike the balance between evidence evaluation and rapid decision making. Whilst we understand the need for speed this must not jeopardise the rigour of the process and its quality. We therefore ask that steps to improve transparency are taken. This should include an earlier company notification and an explicit statement that companies participating will be consulted throughout the process. Manufacturers may be aware of data nuances, having spent significant amount of time assessing COVID-19 related evidence, and should be notified earlier in the process so they can prepare a brief submission around key areas of uncertainty that the AC would wish to discuss during the meeting. Manufacturers are there to support the value of their product to the NHS and the proposal currently severely limits this. The exceptionality of COVID-19 guidance may require a framework such as this. However, this framework is not necessary for other disease areas under NICE's remit. As such it should be explicitly stated that this new rapid review framework is not intended to be rolled out in the future to the standard TAG programme (STA, MTA or HSTs) other than updating the COVID-19 MTA guidance.
MSD	General		Do you feel there are any gaps in the process or areas that need further consideration? We identified substantial gaps (see above and a brief summary below): • Lack of consideration of RWE other than those concerning in-vitro neutralisation activity. Considering the RCT pitfalls due changes in viral pathogenicity and population immunity MSD considers that the full extent of RWE needs to be actively surveyed and assessed on a regular basis because RWE can describe the use of COVID-19 therapeutics and their benefits in the real world setting, acting as a supplement to the

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			RCT evidence base. The importance of RWE is reflected in the NICE manual and should therefore actively feature within this proposal. • Limited meaningful engagement with manufacturers. MSD understand the need for speedy updates pertaining to COVID-19 but this should not be achieved at cost of rigour and transparency. Manufacturers should be active contributors throughout the three statges of the evaluation process. Unclear definitions of various key concepts of the process, its mechanics and definitions.
MSD	1	1.1.3	MSD suggests clarifying whether technologies with a negative recommendation can also be re-assessed, should new evidence become available .
MSD	1	1.2.1	MSD suggests adding more detail on what is classified as a trigger – are these triggers exhaustive? Or can the manufacturers also propose ad-hoc what they consider several triggers that may warrant a rapid review of evidence? What studies (and designs) that could be considered in this process needs to be defined clearly by NICE.
MSD	2	2.1.1	The definition of what will be considered “real world evidence” should be expanded given the lack of review of RWE in the previous process. The limitations of RWE and pragmatic RCTs need to be consistently applied, including for PANORAMIC and OpenSafely. RWE should be defined as per the NICE manual and appraised with NICE’s standard methods and rigour.
MSD	3	Figure 1	Please add in company notification and different stages in the graph for clarity and NICE-Company engagement stages.
MSD	3	2.2.2.	Does the “stakeholder submission” within the “multifaceted” surveillance proposed not contradict para 2.4.9 whereby it is noted “no submissions are invited from stakeholders, including the company”? Please clarify. What would a stakeholder submission entail in this instance to aid NICE in “trigger identification”?
MSD	4	2.2.4	Please elaborate how search results are prioritised and what is meant by “relevant studies” being triaged – what does NICE consider to be the relevant type of evidence? Are RWE studies (other than *in-vitro* studies) included?

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MSD	5	2.2.9	What is defined by “large change in hospitalisation rates”? Are data actively collected for recommended technologies for community/outpatient use to inform future updates? We request clarity as to that RWE will be actively monitored for technologies within the MTA’s final scope.
MSD	5	2.2.10	What is defined by regular interval? It is unclear how the review of the data detailed in 2.2.10 differs from the review of the data captured by the broad searches that are run on a weekly basis. Please specify. Can companies submit in confidence data that could constitute as triggers?
MSD	6	General	We are concerned with use of emails to communicate updates and ask that NICE confirm that NICE Docs will be used to transfer across any sensitive information in this process as per usual STAs.
MSD	8	2.3.4	There are potential consideration if mAbs are to be eliminated on the basis of new *in-vitro* evidence when NICE does not review in parallel alternative AVs to cover with a new recommendation patient groups that cannot be treated with Paxlovid currently due to high risk of DDIs and other contraindications.
MSD	8	2.4.1	Please clarify our understanding that if automatic, no fee will be collected if the manufacturer participates?
MSD	10	2.4.4. & general	We are very concerned with the proposal for a limited set of committee members reviewing the evidence and what this may mean, especially for updated changes of positive to negative recommendations and what this may mean for transparency when a “6 member committee” goes ahead to undo a full committee recommendation and variations which could arise as a result of this proposal.
MSD	10	2.4.6	NICE should publish the nominated lay and expert members on annual basis and should also ensure contingency plans are in place to cover absences.
MSD	10	2.4.7	Please clarify that the economic evaluation will be or will not be based on the current MTA Model developed by Sheffield? There is a need to review this model on regular basis to ensure it remains relevant for decision making. This model lacks sufficient functionality as per NICE Manual of technology evaluation for the endemic phase and including things like probabilistic analysis results. We urge NICE addressed this prior to any updated reviews taking place to ensure robust conclusions are made.

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MSD	11	2.4.9	We do not see any obstacles in companies submitting their interpretation of key evidence. This appears to resemble a step similar to the MTA “Targeted evidence submissions” that were mostly disregarded by the AG during the ongoing MTA for ID4038. We consider that an early flag to the company ahead of the anticipated update could give sufficient time for a company submission including the response to specific questions that the AC will be discussing during its deliberations with manufacturer presence.
MSD	11	2.4.13	Please clarify – would the company be consulted even if it is public domain? NICE need to ensure that all stakeholders are consulted and concerns addressed to avoid the pitfalls seen in the MTA for ID4038 otherwise the outcomes of the rapid updates would be questioned.
MSD	11	2.4.14	Please clarify which external assessment group – the one previously worked on ID4038?
MSD	12	2.4.15 & General	Please clarify: the outline of the rapid review process above does not mention any aspects of quality assessment or discussion of how the evidence will be considered within the context with the existing evidence base. Will heterogeneity be considered, for example? MSD considers that the MTA evaluating treatments for COVID-19 overlooked some key aspects of the established process for systematic reviews, crucially a full quality assessment by the EAG of the included studies. And all the other usual aspects of an evidence review and the areas of uncertainty raised in the MTA? Some information around the issue of quality assessment is presented in Appendix 4, but the information is specific to studies evaluating mAbs not RCTs or other evidence of importance such as RWE.
MSD	13	Table 2	We are concerned with the limited consultation process especially when a positive guidance turns to negative guidance for a technology. Patient groups and HCPs may not be able to contribute at such short notice.
MSD	13	2.4.16	In order for NICE to meet this milestone, companies need to be engaged as active stakeholders in the process, in case any value discussion is required.

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MSD	14	Table 3	Please mark a placeholder of “external assessment group” data review in the timeline. We also propose that at week -2 (surveillance report update) affected companies are notified in confidence that their technologies may be under assessment in due course given this “surveillance decision to update” noting timeline communication at a later stage. We request a manufacturer abbreviated submission is delivered for consideration by week 1. Please add in week 2 “; .. company participation” for clarify.
MSD	16	General	NICE needs to define the new types of evidence submitted and extend these beyond the *in-vitro* studies. To that regard checklists for RCTs and RWE should be added to note how the critical appraisal of all types of evidence will be conducted in line with NICE’s expected standards.
MSD	16	6.2.3	Typo: “For these reasons, in vitro studies are not thought to fully replicate the conditions seen in humans, and the evidence type and its quality may differs from standard clinical trial evidence.”
MSD	17	6.3.1	Whilst MSD understand clearly the differences between mAbs and AVs, it is important to note the need for continued assessment of clinical evidence base for AVs. The current framework does not make explicit statements around this issue and therefore needs substantial expansion.
MSD	24	6.5.15	NICE should share all relevant documents including the search strategy and results and extractions of the SLR updates with manufacturers.
MSD	55	Appendix 3	Searches should be expanded to explicitly capture study designs of RCTs and observational RWEs.
MSD	38	Appendix 3	Please expand Pango abbreviation. With regards to “Then, manual deduplication is used to assess low-probability matches” MSD asks that full access to results, extractions and critical appraisal of studies is provided to manufacturers participating.
MSD	42	Appendix 4	We also ask that RCT and observational study checklist criteria are included within the document.
MSD			Please clarify number of reviewers assigning quality scores.
MSD	45	Table 2	Please add a column to specify score range for each category for transparency.

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Individual			Please may I raise a point for consideration in the current situation. One reason for changing the guidance is if there is a change in the disease. This is already happening due to the large changes in population immunity globally. In the immune naive population (no vaccination, no prior infection), a major cause of severe illness was COVID-19 pneumonitis due to immune processes ('exuberance'). Trials of immune modulators demonstrated reductions in mortality in hospitalised patients eg. Dex, tocilizumab etc. Currently, due to changes in population immunity, severe illness due to COVID-19 pneumonitis driven solely by immune processes is much less common. This is manifest in the clinical experience in hospitals. The majority of admissions are for complications of COVID-19 infection (not immune pneumonitis) on a background of other health conditions or frailty. For persons with chronic underlying lung and heart conditions, hypoxia may be present due to destabilisation of the underlying comorbidity rather than pneumonitis. In this situation, strong immune suppression (eg with tocilizumab) may not be appropriate. Existing trial evidence does not reflect this changed situation. Two questions arise: 1. Should the current clinical guidance for immune modulators be refined? (Accepting the rapid changes that were made to reflect the MTA findings) 2. How will the review process pick up such changes in immune landscape and hence disease presentation? What threshold would be used to trigger a review since there may not be any trials re-assessing interventions already recommended?