NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tixagevimab–cilgavimab for preventing COVID-19 ID6136

Stakeholder comment form

Please use this form for submitting your comments on the draft remit, draft scope and provisional list of stakeholders. It is important that you complete and return this form even if you have no comments otherwise we may chase you for a response.

Enter the name of your organisation here: Evusheld for the UK

Comments on the draft remit and draft scope

The draft remit is the brief for an evaluation. Appendix B contains the draft remit. The draft scope, developed from the draft remit outlines the question that the evaluation would answer.

Please submit your comments on the draft remit and draft scope using the table below. **Please take note of any questions that have been highlighted in the draft scope itself** (usually found at the end of the document).

If you have been asked to comment on documents for more than one evaluation please use a separate comment form for each topic, even if the issues are similar.

Please complete this form and upload it to NICE Docs by **Friday 12 August 2022.** If using NICE docs is not possible please return via email to scopingta@nice.org.uk If you have any questions please contact Michelle Adhemar, Project Manager on 44 (0)20 7045 2239 or at the above email address.

If you do not have any comments to make on the draft remit and draft scope, please state this in the box below.

We note, for reasons of acknowledgment, that these comments have been jointly prepared by Prof Martin Paul Eve, Nikola Brigden, Mark Oakley, and Dr Jo Daniels.

Comment 1: the draft remit and proposed evaluation route

Section	*Notes*	Your comments
Appropriateness of an evaluation and proposed evaluation route	*NICE welcomes comments on the appropriateness of evaluating this topic and the evaluation route proposed (single technology appraisal, multiple technology appraisal or highly specialised technology evaluation).*	We believe, for reasons of urgency, that the usual timescales of the Single Technology Appraisal track are inappropriate. This track may be appropriate for the long-term deployment of tixagevimab–cilgavimab for preventing COVID-19, but it must be in conjunction with an interim authorisation. The context in which we are operating is one of rapid change and we require flexibility to

Section	*Notes*	Your comments
		protect our patient body, as we have seen with vaccines and anti-virals.
Wording	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	Yes.
Timing Issues	*What is the relative urgency of this evaluation to the NHS?*	This evaluation is of extreme relative urgency and the usual timescales are inappropriate given the rapidly evolving viral situation. We are about to head into a winter covid season in which the immunocompromised will consume much NHS bed space if hospitalized. Given the demonstrated efficacy of tixagevimab–cilgavimab in reducing hospitalization (92% in a recent real-world Phase Four observational study (Kertes et al., 2022) and extremely promising results in France (Nyguen et al., 2022), it is urgent that this therapy be approved in good time for the winter season. We suggest that an emergency interim authorization would be appropriate given the urgency. For more see: ● Kertes, Jennifer, Shirley Shapiro Ben David, Noya Engel-Zohar, Keren Rosen, Beatriz Hemo, Avner Kantor, Limor Adler, Naama Shamir Stein, Miri Mizrahi Reuveni, and Arnon Shahar. ‘Association between AZD7442 (Tixagevimab-Cilgavimab) Administration and SARS-CoV-2 Infection, Hospitalization and Mortality’. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 29 July 2022, ciac625. ● Nguyen, Yann, Adrien Flahault, Nathalie Chavarot, Cléa Melenotte, Morgane Cheminant, Paul

Section	*Notes*	Your comments
		Deschamps, Nicolas Carlier, et al. 'Pre-Exposure Prophylaxis with Tixagevimab and Cilgavimab (Evusheld©) for COVID-19 among 1112 Severely Immunocompromised Patients'. Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 1 August 2022, S1198-743X(22)00383-4. There is also evidence to suggest that length of time shielding/in quarantine is associated with poorer mental health (Brooks et al. 2020); rates of mental health in the clinically vulnerable group are already significantly higher than the general population (Rettie & Daniels, 2020; Daniels & Rettie, 2022) Length of time shielding during COVID-19 has been associated with poorer mental health (Daniels & Rettie, 2022), with reported increased rates of mental health difficulties over time when comparing two samples (Rettie & Daniels, 2020; Daniels & Rettie, 2022). These data indicate a more urgent response is required; we should expect to see deterioration in mental health in those shielding equivalent to time spent indoors - there are ethical implications for witholding or delaying potential life-saving treatment, particularly as during this time those clinically vulnerable may contract COVID-19. Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *The lancet*, *395*(10227), 912-920. Rettie, H., & Daniels, J. (2021). Coping and tolerance of uncertainty: Predictors and mediators of mental health during the COVID-19 pandemic. *American Psychologist*, *76*(3), 427. Daniels, J., & Rettie, H. (2022). The Mental Health Impact of the COVID-19 Pandemic Second Wave on Shielders and Their Family Members. *International Journal of Environmental Research and Public Health*, *19*(12), 7333.

Section	*Notes*	Your comments
Any additional comments on the draft remit We re-emphasize that an emergency interim authorization, as with other Covid therapeutics, would be appropriate here to accelerate the timescale, given the urgency. We are unsure, given the urgency of the timescale for the patient groups that we represent, whether the Single Technology Appraisal process is the most appropriate route for an urgently needed therapeutic.		

Comment 2: the draft scope

Section	*Notes*	Your comments
Background information	*Consider the accuracy and completeness of this information.*	It is important that this group are recognised as being psychologically vulnerable due to the long-term effects of shielding because of their clinically vulnerable status (Daniels & Rettie, 2022; Rettie & Daniels, 2020). This has been well documented and provides important context for a NICE evaluation, with precedent in other NICE guidelines. The psychological impact of extensive behavioural measures directed at sustaining life has been pervasive, and should be considered when gaining a fuller understanding of the context of those who are clinically vulnerable. These additional behavioural measures have affected all aspects of life for this patient group, including coping, social interaction, family relationships, health, access to healthcare/medications and work. The impact of this long-term quarantine has been most recently reported in *The Lancet* (Brooks et al. 2020). A significant proportion of this population are experiencing mental health problems to a clinical level, with evidence suggesting that the mental health of those shielding others is also signficantly affected (Daniels & Rettie, 2022). Further data can be provided on this.
Population	*Is the population defined appropriately?*	The population group can be more specifically defined than it is currently.

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		All patient groups listed in NHS England RAPID-C19. 2022. 'Defining the Highest-Risk Clinical Subgroups upon Community Infection with SARS-CoV-2 When Considering the Use of Neutralising Monoclonal Antibodies (NMABs) and Antiviral Drugs: Independent Advisory Group Report'. GOV.UK. 30 May 2022 should be administered this therapy without the need for an antibody test as they are "unlikely to mount an adequate immune response to COVID-19 vaccination". We note that the scope considers "the impact of vaccination status or SARS-CoV-2 seropositivity on the clinical evidence base of each intervention, generalisability to clinical practice and interaction with other risk factors will be considered in the context of the appraisal." However, the marketing authorisation is for groups who are "unlikely" to mount an adequate immune response, not groups proven to have done so. Seropositive antibody results should, therefore, not be required.
Subgroups	*Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? If subgroups have been suggested in the scope, are these appropriate?*	There should be scope for additional discretionary inclusion on the advice of individual clinicians where there is a genuine belief that the patient is "unlikely" to have mounted an adequate vaccine response.. It may be wise to conduct further subgroup analyses on those who are already defined as being at high risk (as described by NICE in the background); and those from the differing clinical groups who may not benefit from intervention, e.g. those with organ transplants vs. COPD for example.
Comparators	*Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?*	Vaccines might be comparators, although the point is that this population do not respond well to such therapies. We presume that 'no prophylaxis' includes placebo as per the published studies. However, it may be beneficial to state that all control comparators will be included so that

Section	*Notes*	Your comments
		the widest scope of evidence is included; these will naturally fall into RCT trials which provide the highest quality evidence.
Outcomes	*Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	A body of research indicates that the mental health and psychological wellbeing of those who have been Clinically Extremely Vulnerable (CEV) and of those who are still shielding (due to following guidance to take additional precautions and known vulnerability) has been adversely affected (e.g. Rettie & Daniels, 2020; Daniels & Rettie, 2022) with 40% reporting clinical levels of health related anxiety. This is significantly higher than those in non-vulnerable groups (<5%). It is also noted that withholding treatment from those whose lives are at risk is ethically and morally questionable, and will bear a significant psychological burden to the patient. None of the outcomes measured here includes the psychological impact of shielding, or withholding treatment, including HRQoL; this is a fairly insensitive measure of psychological distress. The long-term cost of mental health problems in those with health problems is well documented (Kings Fund, 2012). This aspect might be measured using a brief psychological measure such as the combined GAD-7 PHQ-9, or the DASS. The cost savings of reducing the (already established) mental health impact will be significant and should be taken into account in the economic analysis for cost-benefit analysis.
Equality	*NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the draft remit and scope may need changing in order to meet these aims. In*	Evidently many of those who will be most affected will be those covered under the equality act due to long-term health problems and disabilities. These groups are known to be most physically and psychologically vulnerable over the pandemic, and it is important that charities and patient representatives are involved in the decision making process so the impact can be fully considered.

Section	*Notes*	Your comments
	particular, please tell us if the draft remit and scope: ● *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;* ● *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;* ● *could have any adverse impact on people with a particular disability or disabilities.* *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*	It is also more likely that those with long-term health problems and/or multiple morbidities will also be more likely to be experiencing socioeconomic deprivation. Thus this should be considered if the prophylactic is distributed outside of a trial (e.g. travel to treatment centres presenting additional costs to those immunocompromised should not lead to economic disadvantage to those most vulnerable, for reasons beyond their control). Those eligible are also more likely to experience mobility difficulties, or be homed in health and social care settings (learning disability, older people, mental health) treatment must be accessible for all groups. It is important that any roll out of this medication is well publicised among both patient groups and clinicians. Those from BAME background and immunocompromised are likely to be at higher risk, more likely to be from low socioeconomic background, and less likely to be engaged with health services when these aspects are present. Therefore it is vital that a roll out also targets those from under-represented groups to achieve equity of care.
Other considerations	*Suggestions for additional issues to be covered by the evaluation are welcome.*	
Questions for consultation	*Please answer any of the questions for consultation if not covered in the above sections.*	

Any additional comments on the draft scope

1. How would these people be identified in practice?

Through the same mechanisms as those identified as eligible for additional vaccinations i.e. those who are immunocompromised/CEV.

We reiterate that all patient groups listed in NHS England RAPID-C19. 2022. ‘Defining the Highest-Risk Clinical Subgroups upon Community Infection with SARS-CoV-2 When Considering the Use of Neutralising Monoclonal Antibodies (NMABs) and Antiviral Drugs: Independent Advisory Group Report’. GOV.UK. 30 May 2022 should be administered this therapy.

Section	*Notes*	Your comments

2. Where do you consider tixagevimab–cilgavimab will fit into the pathway for preventing COVID-19?

As a prophylactic, this should initially be rolled out to all those meeting the criteria, regardless of vaccination status or seropositivity results. Further research is needed to support the degree of utility the vaccination has in context of the prophylactic; i.e. evidence is needed to consider whether prophylactic-only should be recommended, or whether vaccination should continue in those groups who are less responsive to the vaccine. This will influence where on the pathway this falls, however, unequivocally this should be available to all who meet the specific criteria as early as possible.

3. Do you consider that the use of tixagevimab–cilgavimab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Yes. Unequivocally mental health, when patients are able to a normal functioning level, engaging in enjoyable activities, socialising and returning to work.

The socio-economic benefits of a currently isolated social group returning to the wider world – and to work – should also be taken into account.

4. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

Three papers explore this with those who are identified as clinically vulnerable.

- Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: rapid review of the evidence. The lancet, 395(10227), 912-920.
- Daniels, J., & Rettie, H. (2022). The Mental Health Impact of the COVID-19 Pandemic Second Wave on Shielders and Their Family Members. International Journal of Environmental Research and Public Health, 19(12), 7333.
- Rettie, H., & Daniels, J. (2020). Coping and tolerance of uncertainty: Predictors and mediators of mental health during the COVID-19 pandemic. American Psychologist, 76(3), 427.

These are published in respected journals with n=>720 in each paper; there are also other smaller scale studies which speak to the same issues.

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

Section	*Notes*	Your comments

• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tixagevimab–cilgavimab is licensed;

• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

• could have any adverse impact on people with a particular disability or disabilities.

Yes, as described above, there are natural barriers to treatment for those who are more severely disabled, older, disengaged from the healthcare system or from deprived backgrounds. Particular consideration of equity of access should be given to those who are in health and social care settings, e.g. those with learning disabilities, older peoples homes, and those harder to reach such as those with more significant mental health problems, all of whom we know from the research are likely to have poorer compliance and health-related behaviours.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

Gathering data on the uptake of the vaccinations in these specific hard-to-reach groups may be useful; gathering qualitative data/survey data from charities and patient groups on these issues; secondary data analysis of Genera Practice Data for Planning and Research (GPDPR) datasets.

Comment 3: provisional stakeholder list

The provisional stakeholder list (Appendix C) is a list of organisations that we have identified as being appropriate to participate in this evaluation. If you have any comments on this list, please submit them in the box below.

NICE is committed to promoting equality and eliminating unlawful discrimination. Please let us know if we have missed any important organisations from the list, and which organisations we should include that have a particular focus on relevant equality issues.

If you do not have any comments to make on the provisional stakeholder list of consultees and commentators, please cross this box: X

Comments on the provisional stakeholder list

Comment 4: regulatory issues (to be completed by the company that markets the technology)

Section	*Notes*	Your comments
Remit	*Does the wording of the remit reflect the current or proposed marketing authorisation? If not, please suggest alternative wording.*	
Current or proposed marketing authorisation	*What are the current indications for the technology?*	
	What are the planned indications for the technology?	
	FOR EACH PLANNED INDICATION:	
	Which regulatory process are you following?	
	What is the target date (mm/yyyy) for regulatory submission?	
	What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable)?	
	What is the anticipated date (mm/yyyy) of EU regulatory approval?	
	What is the anticipated date (mm/yyyy) of UK regulatory approval if different to Europe?	
	What is the anticipated date (mm/yyyy) of UK launch?	
	Please indicate whether the information you provide concerning the proposed marketing authorisation is in the public domain and if not when it can be released. All commercial in confidence information must be highlighted and underlined.	

Section	*Notes*	Your comments
Economic model software	*NICE accepts executable economic models using standard software, that is, Excel, DATA, R or WinBUGs. Please indicate which software will be used. If you plan to submit a model in a non-standard package, NICE, in association with the EAG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the EAG with temporary licences for the non –standard software for the duration of the evaluation. NICE reserves the right to reject economic models in non-standard software*	

Please complete this form and upload it to NICE Docs by **Friday 12 August 2022.** If using NICE docs is not possible please return via email to scopingta@nice.org.uk If you have any questions please contact Michelle Adhemar, Project Manager on 44 (0)20 7045 2239 or at the above email address.