FAO xxxxxxxxxxxxx Executive Director

Gilead Sciences Ltd

280 High Holborn, London WC1V 7EE

Sent by e-mail only: xxxxxxxxxxxxxxxxxxxxxxx

14 March 2023

Dear xxxxxxxxxxxx

**Re: Final Draft Guidance — Therapeutics for people with COVID-19 [ID4038]**

Thank you for your letter of 7 March 2023, lodging an appeal against the above Final Draft Guidance (FDG).

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to provide an initial view on whether they are within the permitted grounds of appeal ("valid") and are at least arguable. The permitted grounds of appeal are:

* 1(a) NICE has failed to act fairly, or
* 1(b) NICE has exceeded powers;
* (2) the recommendation is unreasonable in the light of the evidence submitted to NICE.

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information, are arguable, and fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn.

I have had regard to both the NICE Manual[[1]](#footnote-1) and its Process Statement[[2]](#footnote-2) when forming my initial view of your appeal points.

***Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly***

**Appeal point 1(a).1 For lack of time and resource allocated to this MTA, companies were not given the opportunity to make a full evidence submission and NICE refused Gilead’s request to submit an economic model, resulting in important evidence not being considered by the Committee.**

I am minded to refer this appeal point to the Appeal Panel. In order to assist preparation for the hearing I make the following observations.

* The Process Statement states that “*This multiple technology appraisal will follow all the steps in* [the process set out in NICE’s Manual], *but re-sequenced and with shortened timelines*”. It therefore appears to me that an appellant could in theory make an arguable ground 1(a) appeal point that the Committee failed to “follow all the steps” in the Manual (whether owing to the timing set out in NICE’s Process Statement or for any other reason).
* A challenge to the processes themselves, as set out in the Manual and Process Statement (i.e. the steps that the Manual requires and the approach to sequencing and timing set out in the Process Statement), as opposed to the committee’s compliance with those processes, would be outside of the scope of the appeals process and would be a matter for NICE.
* I am mindful of your view that the alleged departures were caused by NICE’s resequencing and/or shortening of NICE’s usual timelines in accordance with the Process Statement. That resequencing and/or shortening in itself cannot in my view be the subject of an appeal point, however I am minded to agree that an Appeal Panel can properly explore whether the approach taken to evidence submission departed from the requirements of the Manual and Process Statement.
* I understand your point to be that some steps or requirements as to evidence in the Manual (with which the Process statement committed to comply) were not followed in this appraisal. I note you argue that lack of time and resource are not adequate reasons for refusing to accept evidence from a company.
* I consider potentially relevant parts of the Manual (www.nice.org.uk/process/pmg36) include:
	+ 1.3.1 *Companies are invited to submit evidence on the technology or technologies being evaluated…”*
	+ 1.3.30: “*For a multiple technology evaluation (including all diagnostic evaluations), the EAG creates a report that independently synthesises the evidence from published information and any evidence submissions about the clinical effectiveness and value for money of the technologies.* *In addition to a systematic review of the clinical and cost evidence, the external assessment report normally includes an economic evaluation and an economic model informed by a review of the evidence. Evidence requirements are explained in section 3.”*
	+ Section 3.1.1 “*A comprehensive evidence base is fundamental to the evaluation process. Evidence of various types and from multiple sources may inform the evaluation. To ensure that the guidance issued by NICE is appropriate and robust, the evidence and analysis, and their interpretation, must be of the highest standard possible and transparent*.”
	+ 5.5.6 “*NICE aims to make sure that companies bringing technologies forward for possible use in the NHS can make the best plausible case for its product, to the ultimate benefit of the NHS and patients…”*
	+ 5.5.8 “*NICE invites the company to provide an evidence submission using a detailed submission template…”*
	+ 5.5.16 “*If the company plans to submit an economic model or is required to do so, it should inform NICE which software will be used…*”
	+ “5.6.1 *For multiple technology evaluations, the EAG develops an assessment protocol, derived from the final scope of the evaluation. The assessment protocol outlines what the EAG will do during the evaluation and the information it will provide in the external assessment report*. *5.6.2 After receiving the company's evidence submission (when needed), the NICE technical lead and the EAG assess whether the submission is complete and whether the decision problem is specified appropriately with reference to the final scope.”*
	+ *“5.6.13 The EAG prepares a report on the clinical and cost effectiveness or cost savings of the technology. The report is usually based on a review of the company's evidence submission (except for diagnostics guidance and multiple technology evaluations in technology appraisals and highly specialised technologies) and advice from the EAG's clinical experts.”*
	+ *“5.6.15 For diagnostic guidance, companies do not normally provide an evidence submission. For multiple technology evaluations in technology appraisals and highly specialised technologies, the companies are invited to provide an evidence submission but are not formally required to do so. The EAG does an assessment of the clinical outcomes and cost effectiveness of the technologies, and diagnostic test accuracy where relevant. The assessment is based on systematic reviews of the literature, data provided by the companies, information from the experts or specialist committee members, and modelling of patient outcomes, costs and cost effectiveness. The EAG's assessment highlights the uncertainties in the evidence and may include an analysis of the value of reducing those uncertainties.”*
* It seems to me that while para 5.5.16 suggests that an economic model might be part of the company’s evidence submission, the Manual does not expressly create a right for companies to submit an economic model in a multiple technology appraisal or an obligation on NICE to allow companies to do so.
* However, there is an arguable ground 1(a) point that the Committee departed from the steps required by the Manual (which NICE committed to follow in the Process Statement) and I am minded to refer this to a Panel for exploration.

**1(a).2 For lack of time, the EAG relied on pre-existing living systematic reviews and network meta-analyses which were not originally designed to address the decision problem and were not sufficiently validated, resulting in significant flaws in the information considered by the Committee.**

I am minded to refer this as a valid appeal point for much the same reasons as set out at 1(a).1 above. It is arguable that the evidence relied on by the EAG did not meet the requirements set in the Manual. My observations above apply equally to this appeal point and I hope will assist preparation for the hearing.

I note your appeal letter cross refers under 1(a).2 by stating “See further Ground 1(a).5”. I draw your attention to the appeals process guide:

*“If the context for different appeal points overlaps, it is not necessary to repeat the same points under more than 1 appeal point, but appellants must set out the argument they wish to make under each ground in detail. They must not refer the Appeal Panel to earlier text without clearly indicating how that text relates to the current appeal point.”*

As a general note - if when making appeal point [x] you wish to rely on an argument made under different appeal point [y], then given the length of your arguments under each appeal point, I invite you to explain in your response to this letter exactly which part of the argument under point [y] you wish to rely on for point [x] and why more than one appeal point is required.

**1(a).3 Cost-effectiveness estimates were not informed by a probabilistic sensitivity analysis without adequate justification, and so the Committee failed to sufficiently explore parameter uncertainty.**

I do not regard this as a valid appeal point.

I note para 4.7.13 of the Manual states: “*In general, scenario analyses should also be probabilistic. When only deterministic base-case or scenario analyses are provided, this should be justified…”).*

I consider the reasons set out by the EAG and Committee clearly explain and justify the approach taken.

I refer in particular to section 3.4 / page 54 of the EAG’s Assessment Report[[3]](#footnote-3), which explains the EAG’s approach in detail, noting that three deterministic analyses were run to “circumvent” the additional time required by a PSA and that these:

*“analyses were supplemented by sensitivity analyses and are believed to provide the NICE appraisal committee with pertinent information relating to the true uncertainty in the decision problem, which will be much larger than any difference between the mean results from a PSA and from a deterministic analysis using the mean of the distribution.”*

In other words, the EAG believed that its analyses provided the Committee relevant information relating to the true uncertainty and that considering the sensitivity analyses in this appraisal would be more important / relevant for the decision problem than any difference between a probabilistic or deterministic analysis.

Therefore I consider it unarguable that this appraisal unfairly departed from NICE’s published process or that it otherwise followed a procedurally unfair process in its approach to sensitivity analyses.

**1(a).4 The Committee did not consider the cost-effectiveness of remdesivir for severe COVID-19 and so denied Gilead the opportunity to discuss commercial agreements that would mitigate or resolve the uncertainty around the ICERs.**

I do not regard this as a valid appeal point.

I refer to pages 3-4 of the FDG which summarise why the Committee made its recommendations:

* For mild COVID-19, clinical evidence suggests that remdesivir is effective compared with standard care but “*is not recommended because the likely cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources*”. Para 3.28 of the FDG provides the ICERs.
* For severe COVID-19, clinical evidence suggests that remdesivir has limited effectiveness compared with standard care *(“because it does not reduce mortality rates, but the evidence is uncertain*”); accordingly, remdesivir is “*not recommended because [it is] unlikely to be effective at treating severe COVID-19 and it is not possible to reliably estimate [its] cost effectiveness*.”

As you acknowledge in your appeal, the Committee provides a detailed rationale for its approach to both clinical and cost effectiveness, particularly at paras 3.20 and 3.30 of the FDG. The latter explains:

“*For remdesivir, the committee considered the threshold analysis of mortality rate ratios between 0.85 and 1.00. The committee concluded there was insufficient evidence to show meaningful difference in mortality benefit compared with standard care (see section 3.20). The committee was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS. Because there is substantial uncertainty about whether remdesivir is effective (in terms of mortality benefit) at treating COVID-19 it considered that it is not possible to reliably estimate remdesivir’s cost effectiveness*

In my initial view if (as here) a committee considers that, based on the available evidence supporting clinical effectiveness, it is highly uncertain that a treatment would be clinically effective in the context of current clinical practice (including changing variant prevalence) in England, i.e. the evidence does not suggest QALY gains or any potential QALY gains are highly uncertain in the context of current clinical practice in England, then procedural fairness cannot require the Committee to calculate and publish an ICER or ICER range.

I therefore consider this appeal point 1(a).4 unarguable.

As to your detailed arguments against the committee’s approach to generalisability and clinical effectiveness, including the application of a “ceiling effect or threshold” (per para 3.20), I see no arguable ground 1(a) point that any aspect of the Committee’s decision-making was procedurally unfair.

**1(a).5 The Committee did not conduct a thorough assessment of treatments for children with severe COVID-19 and the resulting failure to recommend any treatment for children with severe COVID-19 is unfair and discriminatory.**

I do not regard this as a valid ground 1(a) appeal point.

I note para 6.2.29 of the Manual:

*“The committee will consider carefully…whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost effectiveness or cost savings. The committee may recommend a technology for subgroups of the population only if there is clear evidence that the characteristics defining the subgroup influence the effectiveness or value for money of the technology...* *When considering subgroups, the committee pays particular attention to its legal obligations with respect to legislation on human rights, discrimination and equality.”*

I consider the procedural obligation on the Committee is to consider carefully whether the effectiveness evidence suggests differential cost effectiveness or cost saving for any subgroup.

Para 3.6 of the FDG explains that age was considered by the Committee, who noted it is a protected characteristic under equalities legislation, but was not adopted as an independent risk factor for the reasons at 3.6

In addition the FDG specifically considers the position of children at para 3.6 FDG under the heading “Treatment for children”:

*The committee noted that the summary of product characteristics for nirmatrelvir plus ritonavir in the mild COVID19 setting and tocilizumab in the severe COVID-19 setting do not recommend these treatments in people under 18 years. In the mild COVID-19 setting the committee has recommended sotrovimab for people for whom nirmatrelvir plus ritonavir is unsuitable. Sotrovimab’s marketing authorisation includes adolescents (aged 12 years and over), so this would be an option for them, if they have a high-risk of progression to severe COVID-19 as defined by the McInnes report. For younger children the only option in this setting is remdesivir. However, the ICERs were very high and not considered a cost-effective use of NHS resources. By only recommending tocilizumab in the severe COVID-19 setting there is a risk of indirectly discriminating against children and young people. However, the alternative treatments had substantially higher ICERs and were not considered a cost-effective use of NHS resources.*

This shows the Committee identified children as subgroup, understood that remdesivir is the only licensed option for children aged under 18 in the severe COVID-19 setting and for those under 12 in the mild COVID-19 setting and explored the cost effectiveness of remdesivir. Having done so they concluded the ICERs were still very high and not considered a cost-effective use of NHS resources. For this reason remdesivir could not be recommended for children with severe (or mild) COVID-19. In my view the Committee has followed an appropriate process in its consideration of children with severe COVID-19.

I therefore consider it unarguable that the Committee unfairly failed to consider the possibility of subgroups by age or that the Manual imposed a procedural obligation on the Committee to adopt a subgroup of children with severe COVID-19.

I note your appeal letter does not appear to argue that the effectiveness evidence suggests differential cost effectiveness or cost savings for children. Rather your argument is that children with severe COVID-19 should have been considered as a subgroup because remdesivir is the only COVID-19 treatment that is licensed in the UK for paediatric patients. I see nothing in the Manual that requires the Committee to carry out subgroup analysis in these circumstances as a matter of procedural fairness.

I do not consider it arguable that the European Convention on Human rights (ECHR) or Equality Act 2010 can form the basis of a 1(a) point here. I note the Committee was aware that it was recommending no licensed treatment for under 18s and was mindful of the requirements of equalities legislation and of NICE’s statutory function to recommend treatments that are cost effective (see para 3.32 (Equality issues) of the FDG). If you wish to make an appeal point that the FDG breaches human rights and/or equalities legislation then I invite you to put that as a new appeal point under ground 1(b) in your response to this letter and explain specifically why you consider the Committee’s approach was unlawful in breach of human rights and/or equalities legislation.

In reaching the above initial view, I have had regard to the appeal decision to which you refer in your appeal letter (against Dinutuximab for treating high-risk neuroblastoma [ID799]).[[4]](#footnote-4) At paragraphs 14-28 of the decision the Panel discussed an appeal point under ground 1b that “*There has been a breach of Section 11 of the Children Act 2004, Article 3 of the UN Convention on the Rights of the Child and human rights legislation*.” In that case the fundamental issue for the panel expressed in lay terms was whether NICE's processes had properly accounted for the fact that the target population for this technology was a paediatric patient group. In my view that appeal is not obviously comparable to the present appeal. I am also mindful that in determining the prospects of success of appeal points, I can have regard to and be guided by past decisions of the Appeal Panel, but I am not strictly bound by them (see the NICE appeal process guide). I invite you to explain specifically which part of the appeal decision you consider supports any ground 1(b) appeal point you make in your response to this letter.

**1(a).6 The Committee has not given any adequate reasons for not addressing the distinction between patients with severe COVID-19 on low-flow oxygen and those on high-flow oxygen despite this clear distinction being made in current guidance.**

A valid appeal point in respect of arguable inadequate reasons.

That is because the distinction between high and low-flow oxygen sub groups seems to have validity (I consider this at least arguable) and there may be a different level of evidence for mortality benefit between these two sub groups, such that cost effectiveness may have been different as compared with the full patient population.

In those circumstances it is arguable that reasons ought to be provided as to why “lower oxygen needs” was not considered as a potential subgroup. Other than the statement at 3.20 FDG that “*clinical experts considered that remdesivir is currently used in some people with lower oxygen needs but its use is not clearly defined”,* I have not identified an explanation in the FDG or committee papers of the reasons why the population requiring “low-flow oxygen” was not considered as a potential subgroup. Therefore I consider this point arguable.

**1(a).7 Gilead was not given a fair hearing because it was not given the opportunity to discuss key issues at the appraisal committee meetings.**

I note your argument refers to three specific issues:

1. In the first ACM (18 October 2022), each company was only given the opportunity to answer one question, and in the briefing to companies before the meeting, the Chair emphasised that he was primarily interested in hearing from Committee members and not companies and warned companies against requesting to speak on the virtual call “*as this would make him very unhappy*”
2. In the second ACM (24 January 2023), Gilead only had the opportunity to ask if SOLIDARITY data would be included (to which the Committee Chair replied that SOLIDARITY data was “*firmly in”*) and (by contrast to sotrovimab) was not given the opportunity to discuss the real-world evidence.
3. The Committee Chair’s comment that SOLIDARITY data was “*firmly in*” was potentially misleading as Gilead was not told, and so was not given the opportunity to discuss, the main reason why the Committee ultimately did not recommend remdesivir - namely the Committee’s conclusion that, despite the inclusion of SOLIDARITY in the EAG model, the Committee considered that, in view of generalisability concerns it was not possible reliably to estimate remdesivir’s cost-effectiveness in treatment of severe COVID-19.

I am not minded to refer this as a valid point.

In respect of points (1) and (2) above, while I agree that NICE aims to ensure companies can make the best plausible case for their products (para 5.5.6 of the Manual), I do not consider that NICE’s processes or procedural farness more generally require a specific level of involvement for companies in the appraisal committee meetings as a matter of procedural fairness. Rather, 1.3.6 and 5.7.11 of the Manual are clear that companies attend the committee meeting for the purpose of answering questions from the committee and comment on any matters of factual accuracy. On that basis I do not consider the matters described at (1) and (2) to be arguable. as a valid appeal point.

As to your point 3 (namely that it was arguably unfair that the company had no opportunity to respond to the Committee’s concern that, in view of generalisability concerns, it was not possible to reliably estimate remdesivir’s cost-effectiveness in treatment of severe COVID-19), I can see no procedural requirement for the Committee to pre-warn the company expressly (and provide an opportunity for comment) that the inclusion of additional SOLIDARITY data did not change the draft recommendation in respect of remdesivir.

**1(a).8 NICE treated Gilead unfairly compared to another stakeholder company by refusing to consider new data that could potentially change the Committee’s final conclusions.**

A valid appeal point.

**1(a).9 The Committee has not given adequate reasons why differences in standard care give rise to significant concerns about the generalisability of SOLIDARITY data.**

I am not minded to refer this as a valid appeal point. That is because the Committee has provided detailed discussion of the SOLIDARITY data at 3.13 of the FDG. The Committee appear to understand the SOLIDARITY data and its limitations very well: the FDG explains the Committee considered the inclusion of SOLIDARITY in the NMA important and appropriate for remdesivir and goes on to explain that (and why) the Committee considered the applicability of the mean-efficacy estimate from SOLIDARITY to the current NHS setting to be highly uncertain and likely to be the ceiling efficacy estimate. The FDG gives detailed reasons for this conclusion, i.e. that SOLIDARITY was early in the pandemic, there was no clinical evidence available for remdesivir in the context of the current endemic setting with the new Omicron variant. While I appreciate you disagree with the Committee’s approach, I consider it unarguable that more reasoning is required in the FDG as a matter of procedural fairness.

**1(a).10 The Committee’s exclusion of treatment effects for hospital time to discharge data for remdesivir is unfair because these treatment effects were reflected in the base-case ICER results for tocilizumab.**

I am not minded to refer this as a valid appeal point.

I note table 4 at page 26 of the Assessment report did not include “Time to discharge” data for remdesivir (unlike tocilizumab). However this was flagged in multiple consultation comments and corrected. FDG para 3.23 shows the Committee was aware of this issue:

“*One consultee highlighted during draft guidance consultation that the time to discharge data from ACTT-1 should have been included for remdesivir. In response the AG included the time to discharge data for remdesivir which resulted in a large reduction in the cost-effectiveness estimates*.”

Therefore any procedural unfairness from not originally including ACTT-1 was rectified.

There is no procedural unfairness in the Committee considering the time to discharge data for remdesivir and deciding that this should be removed, for the reasons explained at 3.23 FDG.

I accept that the Committee included time to discharge data for tocilizumab, which at face value suggests an unfair difference in treatment of two products. However there appear to be relevant differences between these two products, notably the data sources / studies relied on for time to discharge data were different (the data relating to tocilizumab being more recent metaEvidence). The FDG gives detailed reasons for removing this data for remdesivir that do not appear to apply equally to tocilizumab. Given the apparent differences in circumstances between tocilizumab and remdesivir I do not consider that the Committee including the time to discharge data for tocilizumab and not the (different) time to discharge data for remdesivir is sufficient to show arguable procedural unfairness.

**2.1 The Committee’s conclusion that significant uncertainty remains in terms of generalisability of the trial evidence for remdesivir in severe COVID-19 is unreasonable because it ignores clinical practice and in-vitro data that has not been countered**.

A valid appeal point.

**2.2 The Committee’s recommendations are unreasonable because, ignoring clinical need and practice, they fail to recommend any antiviral treatment for patients with severe COVID-19.**

I do not consider this a valid appeal point. NICE’s statutory remit is to appraise the cost-effectiveness of technologies for use within the NHS. It is unarguable that in the absence of any cost effective treatment NICE is obliged as a matter of reasonableness to recommend treatments it does not consider to be cost effective.

Conclusion

The above sets out above my initial views on all of your appeal points.

In respect of your points which I am not minded to refer on you are entitled to submit further clarification and/or evidence to me within the next 10 working days, and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held which is likely to be held remotely.

Once I have made my final decision, and where there is more than one appellant, each appellant will receive the valid appeal points of the other appellants and their redacted appeal letter. This is to enable appellants to avoid duplication at the hearing where there are overlapping appeal points. If the appeal letter and/or responses to scrutiny contain confidential information please ensure you have provided a version with this information redacted by 28 March 2023.

Ordinarily appeals are conducted on the basis of the appellants’ written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be before the panel that you would wish to rely on you must let the NICE Appeal team know by return of letter, indicating what the material is, why it is desirable to submit it, and when it will be available, by no later than 29 March 2023. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

Yours sincerely

Mark Chakravarty

Non-Executive Director

National Institute for Health and Care Excellence

1. <https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741> [↑](#footnote-ref-1)
2. <https://www.nice.org.uk/guidance/gid-ta10936/documents/supporting-documentation> [↑](#footnote-ref-2)
3. <https://www.nice.org.uk/guidance/gid-ta10936/documents/assessment-report> [↑](#footnote-ref-3)
4. <https://www.nice.org.uk/guidance/gid-tag507/documents/appeal-decision> [↑](#footnote-ref-4)