28 March 2023

Dr Mark Chakravarty

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Dear Dr Chakravarty,

Final Draft Guidance – Therapeutics for people with COVID-19 – ID4038

Thank you for your initial scrutiny letter dated 14th March 2023, in which you provide your initial view on the admissibility of the points of appeal set out in Gilead’s letter of appeal of 7th March 2023. We note that, as of 21st March 2023, the ID number for this appraisal has changed from ID4038 to ID6261.

As suggested in your letter, we provide further detail to elaborate or clarify those appeal points that you are currently not minded to refer to the Appeal Panel.

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

Appeal point 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

You express the initial view that this is not a valid appeal point because the reasons set out by the EAG and Committee clearly explain the approach. However, this point of appeal does not relate to an alleged lack of transparency but to a failure to follow NICE’s published procedures, as further explained below.

You refer to the reasoning provided at section 3.4 (pp.54) of the EAG’s Report (EAG Report 30 June 2022) which explains the EAG’s approach, noting that three deterministic analyses were run to *circumvent* the additional time required by a probabilistic sensitivity analysis (**PSA**), and were *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 the section of the EAG Report that you cite, the EAG recognised that PSA *is the most appropriate method for providing the most accurate estimation of the ICER, however this could not be undertaken within the deadlines of the project. This was because there was a need to calculate the proportion of patients treated in the community who are admitted to hospital, and die within this estimate, as the model assumed that deaths due to COVID-19 only occurred in the hospital (see Section 3.1.2). This calculation added considerable computational time.*

It was to *circumvent this problem* thatthe fact that the EAG resorted to deterministic analyses. This underscores the lack of time and resource allocated to this appraisal (as further set out in our appeal letter).

Applying the same principles as for appeal points 1(a).1 and 1(a).2, lack of time and resources are not adequate reasons for not conducting a PSA, as expected by the Manual and which the EAG itself recognised was *the most appropriate method for providing the most accurate estimation of the ICER*.

We also note that, in the absence of a PSA, there is no evidence to support the assumption that *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*.

The expectation for PSA is clear:

* In addition to the Manual’s requirements at paragraph 4.7.13 (cited in our appeal letter), paragraph 4.7.12 of the Manual sets the principle that PSA should be used for the base-case: *The committee's preferred cost-effectiveness estimate should be derived from a probabilistic analysis when possible unless the model is linear. If deterministic model results are used, this should be clearly justified, and the committee should take a view on if the deterministic or probabilistic estimates are most appropriate. However, in general, uncertainty around individual parameters is not a reason to exclude them from probabilistic analyses; rather, that uncertainty should be captured in the analysis.*
* The importance of undertaking PSA is further emphasised by the NICE Decision Support Unit (**DSU**), which provides *further information on technical aspects of health technology evaluations* (the Manual, Introduction – Further Information and Advice). The NICE DSU Technical Support Document 6 (**TSD6**)[[1]](#footnote-2) on embedding evidence synthesis in probabilistic cost-effectiveness analysis states: *There are two main reasons for advocating probabilistic methods in decision making. The first is that they can provide a form of sensitivity analysis which allows investigators to easily see the joint impact of the uncertainty in multiple parameters on the expected costs, benefits and on decision uncertainty. … A second reason is that, faced with uncertainty… decision makers generally chose the decision option, D, that delivers the highest expected net benefit* (DSU TSD6 pp.7)*.*

The NICE DSU continues: *It is therefore essential that software solutions are adopted that ensure that the complex uncertainty structure in parameter estimates is faithfully propagated through the decision model.*

* In addition, paragraph 4.7.2 of the Manual states: *The model should quantify the decision uncertainty associated with a technology. That is, the probability that a different decision would be reached if the true cost effectiveness of each technology could be ascertained before making the decision.*
* Paragraph 4.7.20 of the Manual also emphasises that the *computational methods used to implement an appropriate model structure may occasionally present challenges in doing probabilistic sensitivity analysis. Clearly specify and justify using model structures that limit the feasibility of probabilistic sensitivity analysis. Models should always be fit for purpose and should allow thorough consideration of the decision uncertainty associated with the model structure and input parameters. The choice of a 'preferred' model structure or programming platform should not result in the failure to adequately characterise uncertainty.*

Applying the above requirements to the Committee’s consideration of remdesivir:

* The appraisal did not follow the procedure set out in the Manual which requires that, in general, scenario analyses should be probabilistic and that any other approach must be *justified* (paragraphs 4.7.12 and 4.7.13).
* The requirement set out in the Manual that omission of PSAs must be justified, was heightened in circumstances where the EAG recognised that *probabilistic analysis was the most appropriate method for providing the most accurate estimation of the ICER* (EAG report v.3 3 October 2022 para 3.4 pp 60) and did not conduct these solely due to lack of time and resource (i.e., limitations on the scope of the appraisal imposed by NICE without consideration of the implications for the fairness of the appraisal and the reasonableness of its conclusions).
* The explanation provided by the Committee at section 3.10 of the final draft guidance (**FDG**) do not justify the failure to conduct PSA. The Committee acknowledges that *consultees highlighted the lower efficacy scenarios were arbitrary and a probabilistic sensitivity analysis would be a better way to capture the uncertainty.* The Committee goes on to note that *the heterogeneity in the trial populations and the generalisability issues across the trials made the uncertainty challenging to parameterise. Therefore, the appropriate type of uncertainty would not have been captured in the probabilistic sensitivity analysis.*

This does not justify the failure to conduct PSA for the following reasons:

* PSA is necessary in order to appropriately explore parameter uncertainty. Heterogeneity is a different kind of uncertainty that represents the variability in treatment efficacy among different patients due characteristics which can be observed or explained (e.g., vaccination status, level of natural immunity, circulating variants of concern, etc.).
* The deterministic analysis conducted by the EAG explores parameter uncertainty, not heterogeneity. So the fact that PSA might not have captured heterogeneity is not a valid justification for not conducting PSA. As acknowledged in section 3.10 of the FDG, the *AG cautioned the committee that the lower and higher efficacy scenarios had limitations because they represented a different uncertainty to that in the evidence base; they represented uncertainty on the estimates in the trial and were therefore sensitive to the number of events in each trial, rather than the context in which the trial happened. Therefore they would not be sensitive to changes in efficacy against new circulating variants of concern*.

The uncertainty due to heterogeneity should have been explored thoroughly given its ability to impact the Committee’s decision (see e.g. Manual 4.7.20 above). To the extent that the Committee relied on the EAG’s deterministic analysis as a proxy for uncertainty due to heterogeneity, this was inappropriate and not based on evidence, and again not a valid justification for not conducting PSA.

If heterogeneity was too great, then it would not have been appropriate to combine evidence from the different studies.

* Although the uncertainty may have been challenging to parameterise, this was not impossible and the main reason why PSA was not conducted was the lack of time and resource, as highlighted by the EAG (see above). This is contrary to the Committee’s responsibility to explore all uncertainties, including parameter uncertainty.
* The EAG Report (13 January 2023, pp.34) summarises this concisely: *The EAG highlights that the three efficacy analyses are not intended to be a substitute for probabilistic sensitivity analyses.*
* In section 3.30 of the FDG, the Committee explains that it *was mindful that when considering uncertainty, it should take into account the likelihood of decision error and its consequences for patients and the NHS*. However the Committee did not give any adequate explanation for how the likelihood of decision error and its consequences were considered, especially given that PSA, which would normally be used to quantify the probability of decision error (i.e., the error probability that a given treatment is not cost-effective), was not conducted. This decision error could have been visualized in a cost-effectiveness acceptability curve (CEAC) if a PSA had been conducted, thereby providing the Committee with adequate evidence to support its decision-making.

The Manual clearly expects PSA unless there is a clear justification. No such justification was given in this case: lack of time is not a valid reason or justification for an incomplete and unfair appraisal. A PSA is necessary to adequately explore parameter uncertainty and should have been conducted. The Committee’s explanation, relating to heterogeneity, does not justify its failure to require a PSA.

Appeal point 1(a).4 The Committee did not consider the cost-effectiveness for 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

Your position is noted. While we do not agree that this is correct, we do not propose to challenge this part of your initial view regarding appeal point 1(a).4.

Appeal point 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

You express the view in your letter that the procedural obligation (in paragraph 6.2.29 of the Manual) in relation to the duty to consider subgroups *is to consider carefully whether the effectiveness evidence suggests differential cost effectiveness or cost saving for any subgroup*.

However, paragraph 6.2.29 of the Manual also states: *When considering subgroups, the committee pays particular attention to its legal obligations with respect to legislation on human rights, discrimination and equality.*

Therefore, while you say that, if Gilead wishes to advance a point of appeal that the FDG breaches equalities legislation this should be brought under Ground 1(b) of NICE’s appeal procedures, we respectfully suggest that such a point may properly be brought under either Ground 1(a) or Ground 1(b). Gilead is therefore content for the point currently brought under appeal point 1(a).5 to be considered under either or both Ground 1(a) or 1(b).

To clarify our point of appeal:

* As accepted by the Committee, age is a protected characteristic under the Equality Act 2010 and the Committee’s appraisal of remdesivir engages Articles 2, 8 and 14 of the European Convention on Human Rights (ECHR), annexed to the 2010 Act.
* You refer, in your letter, to the Committee’s consideration of age at section 3.6 of the FDG. However, section 3.6 addresses only age as a risk factor in older adults and not as a protected characteristic in children.
* The position of children in terms of impact of COVID-19 and risks is considered at sections 3.1 and 3.5 of the FDG and the Committee agrees that there are a proportion of children who have a high-risk of severe COVID-19 infection.
* The clinical effectiveness of remdesivir may be different in children (compared to adults) and children may have fewer treatment options than older persons as a consequence of their age. It is therefore necessary, in accordance with NICE’s procedures and the provisions of the Equality Act 2010, for the Committee to consider the particular situation of children when assessing use of the technology. However, the assessment by the Committee at section 3.20 of the FDG makes no distinction between children and adults in this respect and assumes that the clinical effectiveness of remdesivir is the same in both subgroups in the context of severe COVID-19 infection and that the data relating to the overall cohort are *uncertain*. Therefore, despite the evidence given to the Committee regarding the particular unmet medical need of certain groups of children to severe COVID-19 infection (FDG sections 3.1 and 3.5) and recognising that for children with severe COVID-19 infection, there is no licensed alternative to remdesivir, the Committee gave no consideration to its clinical effectiveness specifically in such subgroups.

No systematic review was undertaken with respect to children and so no adequate consideration was given.

* We understand the reference in your letter to the Committee’s consideration of the specific situation of children to mean section 3.32 of the FDG, which addresses the Committee’s consideration of its equalities duties. In this section, the Committee recognised that its guidance in the severe COVID-19 setting might discriminate against children on the ground of age, but stated that *the alternative treatments* [e.g., remdesivir] *had substantially higher ICERs and were not considered a cost-effective use of NHS resources*.

However no ICERs or ICER ranges were calculated for remdesivir in severe COVID-19 either in relation to all patients or specifically for children, even though no alternative treatment options are available for this subgroup. We therefore disagree with the conclusion in your letter that *the Committee explored the cost effectiveness of remdesivir* in children. The FDG gives no indication that the Committee did anything other than apply to children its conclusions in relation to the entire population of patients with severe COVID-19, without giving any consideration to whether cost-effectiveness would be different in younger patients.

* You express the initial view that the Manual does not impose *a procedural obligation on the Committee to adopt a subgroup of children with severe COVID-19*. However while Gilead does not suggest that the Committee was required to *adopt* such a subgroup, the legislation which established NICE requires that such a subgroup is given proper consideration. Section 233(1) of the Health and Social Care Act 2012 requires NICE to take account of the clinical need of patients when exercising its functions. There are no licensed treatments other than remdesivir for children with severe COVID-19 and accordingly such patients have a high clinical need. In these circumstances it was incumbent on NICE to consider usage of remdesivir in the subgroup of children with severe COVID-19 infection, if it concluded that a recommendation for use across the licensed indication would not be made. The FDG however gave no indication that any analysis considering the clinical or cost-effectiveness of remdesivir specifically in children with severe COVID-19 was requested, prepared or considered by the Committee.
* At section 3.33 of the FDG, the Committee considered how health inequalities could be addressed: *The Committee said that in theory it would be willing to accept an ICER slightly more than what is usually acceptable if it addressed such health inequalities*.

The Committee concluded: *Even considering greater flexibility, the ICERs of alternative treatments to tocilizumab and for younger children were substantially higher than what is considered a cost-effective use of resources*.

However, despite the wording of section 3.33, there is no indication that the Committee in fact complied either with its procedural obligations or its equality duties. In particular, there is no transparency in relation to the flexibility which the Committee was apparently prepared to offer or how this was applied to remdesivir. Furthermore, as stated above, there is no indication at all that the Committee considered the clinical and cost-effectiveness of remdesivir in the subgroup of children with severe COVID-19 and the basis for the statement regarding the ICER for younger children is unclear.

Finally, you refer to the appeal of the final evaluation document for dinutuximab for treating high-risk neuroblastoma [ID799]:

* You say that in that appeal, *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* and suggest that this is *not obviously comparable to the present appeal*. You do not explain why you consider that the dinutuximab appeal is not obviously comparable and we believe that it is. The dinutuximab appeal related to a technology intended for a paediatric patient group and the current appeal in relation to remdesivir relates to a technology initially indicated in adults and adolescents aged 12 years and older, weighing at least 40 kg. An extension to the marketing authorisation indicates use in paediatric patients under the age of 12 years who are at least 4 weeks of age and weighing over 3 kg.
* You also say that *in determining the prospects of success of appeal points,* [you] *can have regard to and be guided by past decisions of the Appeal Panel, but* [you are] *not strictly bound by them*. However, NICE’s guide to the technology appeals process states (paragraph 5.1) that the test for determining whether an appeal should proceed to a full hearing is whether *the appeal falls into one or more of the grounds and is arguable*. Paragraph 5.1 indicates, as you say, that past decisions of the Appeal Panel are not binding at the initial scrutiny stage, but goes on to say that *the non-executive director for appeals gives greater weight to past decisions on legal or quasi-legal issues and less weight to decisions on factual issues*. In the current appeal, the issue raised, like that in the appeal in relation to [ID799], is a legal issue relating to the requirement to consider the situation of children in the context of NICE’s procedural obligations and duties under equalities legislation. It would be a matter of real concern if this legal issue was admitted in one appeal but excluded at the initial scrutiny stage in another, irrespective of the final conclusion of the Appeal Panel.

In summary, while NICE has a procedural obligation to consider subgroups of patients and to comply with its equalities duties, there has been no specific consideration given in this appraisal to the situation of children with severe COVID-19 infection and clinical effectiveness and cost-effectiveness conclusions applicable to all age groups have been applied to children without assessment of whether this is appropriate. Such an approach does not comply with NICE’s procedural and equalities obligations.

Appeal point 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

Your position is noted. While we do not agree that this is correct, we do not propose to challenge your initial view regarding appeal point 1(a).7.

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

Your position is noted. While we do not agree that adequate reasoning for the Committee’s conclusions have been provided, we do not propose to challenge your initial view regarding appeal point 1(a).9 under Ground 1(a).

This appeal point sets out deficiencies in the Committee’s reasoning for its conclusions. By the cross-reference made from appeal point 2.1 to appeal point 1(a).9, Gilead relies on these same deficiencies to demonstrate that the Committee’s conclusion regarding generalisability of the clinical trial evidence for remdesivir in severe COVID-19 is unreasonable.

Appeal point 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

In your letter, you accept *that the Committee included time to discharge data for tocilizumab, which at face value suggests an unfair difference in treatment of two products*.

You suggest, however, that there are differences between remdesivir and tocilizumab which might justify a difference in approach, notably that the data sources/studies relied on for time to discharge data were different (the data relating being more recent metaEvidence). You say that the FDG gives detailed reasons for removing these data for remdesivir and that such reasons do not appear to apply equally to tocilizumab. You therefore express the initial view that the fact that the Committee included the time to discharge (**TTD**) data for tocilizumab and not the (different) TTD data for remdesivir is not sufficient to show arguable procedural unfairness.

While we note the differences that you have identified in the initial scrutiny letter between remdesivir and tocilizumab on this point, these were not referenced by the Committee either in the FDG or otherwise as explaining the different approach. By contrast, in the FDG the Committee clearly discusses TTD as a treatment benefit in general, as applicable to all products. In view of the Committee’s reasoning and conclusions (further set out below) the treatment effects for TTD should be retained or removed from all products and it is unfair to treat remdesivir differently from other technologies.

The Committee considered the question of TTD and whether it should be reflected in the analysis in the context of all products and did not distinguish between remdesivir and tocilizumab. In the FDG section 3.23:

* the Committee explains that *Evidence on each treatment showed a relative reduction in time spent in hospital* (emphasis added).
* the Committee repeats the same concerns about TTD as it had previously set out in the draft guidance (**DG**) (section 3.15), before the ACTT-1 data for remdesivir had been considered. In particular the Committee says in both the FDG and the DG: *the AG [had previously*] *noted that [this][time to discharge] data was collected during [early stages of] the pandemic, which could lead to substantial generalisability concerns because the context of care has changed [in the endemic setting*]. *The Committee noted that in clinical practice, time to discharge can sometimes overestimate time in high-cost health states because it can depend on multiple factors (for example waiting for a negative COVID-test). Time to discharge was also considered more important for people who are being discharged to a care home.*

Only the parts in brackets differ between the two versions of the guidance.

It is also unclear to which section of the EAG Report the Committee is referring in this section. EAG Report (v.3 3 October 2022) paragraph 3.2.4.2 refers to ACTT-1 and raises generalisability concerns but not in the context of TTD, which was only addressed after consultation, at paragraph 4.4.8 in the EAG additional analysis post NICE Appraisal Consultation Document (13th January 2023).

* Similarly, in the FDG (section 3.23) and in the DG (section 3.15), the Committee refers to the fact that the [E]AG *included scenarios that removed treatment effects on time to discharge and clinical improvement at 28 days to try to account for these potential uncertainties*. [DG only: *It noted that the model was not sensitive to these parameters and they had minimal impact on the cost-effectiveness*.] [FDG only: *At the first meeting*] *the committee considered these scenarios to be plausible but [potentially] conservative if treatments had effects outside of hospitalisation and mortality.*

The key difference between the FDG and the draft guidance for consultation is the Committee’s conclusion:

* In the DG, the Committee simply concluded that it *considered* [the effects outside of hospitalisation and mortality] *were difficult to disentangle from the evidence available*.
* However, in the FDG, the Committee commented that *it was not presented with additional evidence on time to discharge or clinical improvement and was uncertain about the treatment benefit in the endemic setting. The committee concluded it was reasonable to remove these treatment effects.*

As explained above, *these treatment effects* relate to all products – i.e., the *evidence on each treatment* referenced in the opening part of the FDG section 3.23.

The only other main difference between the DG and FDG was the Committee’s recognition that TTD data would result in a large reduction in the cost-effectiveness for remdesivir.

Without any reasoning from the Committee to distinguish TTD for remdesivir from TTD for tocilizumab, the inconsistency in approach between these two products is not justified and is unfair.

We note that the TTD for remdesivir result from a large (n=1,062), randomised, double-blind, placebo controlled trial (ACTT-1) funded by the National Institute of Allergy and Infectious Diseases ([NCT04280705](https://clinicaltrials.gov/ct2/show/NCT04280705)). The design of this trial took account of other factors that might in practice affect TTD, including those highlighted by the EAG. The fact that ACTT-1 was conducted as a randomised controlled trial also mitigates unwanted effects in the observed TTD outcome compared to open-label studies, which have the inherent risk of measuring prolonged TTD when patients have knowledge of receiving active treatment, therefore delaying TTD in open-label trials.

In your letter, you suggest that *the data sources/studies relied on for time to discharge were different (the data relating to tocilizumab being more recent metaEvidence).*

However, the initial EAG Report (30 June 2022, Appendix 1, Table 23) shows that the underlying TTD data for tocilizumab was derived from two studies. These studies were conducted in a similar period to ACTT-1, with actual primary completion dates for REMDACTA (1 February 2021, [NCT04409262](https://clinicaltrials.gov/ct2/show/NCT04409262)) and EMPACTA (18 August 2020, [NCT04372186](https://clinicaltrials.gov/ct2/show/NCT04372186)) being close to the actual primary completion date of the ACTT-1 trial (21 May 2020, [NCT04280705](https://clinicaltrials.gov/ct2/show/NCT04280705)). The Committee has not commented on the relative timings of these studies for TTD for tocilizumab compared to ACTT-1 for remdesivir.

Overall therefore, we do not accept that there is any credible reason for treating remdesivir differently from other technologies in the context of TTD data and the Committee does not suggest otherwise in the FDG or anywhere else.

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

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

Your position is noted. While we do not agree that this is correct, we do not propose to challenge this part of your initial view regarding appeal point 2.2.

Clarification of other cross references

In your initial scrutiny letter, you invite us to explain the cross references made between the appeal points. To the extent not addressed above, we respond to this invitation below, for appeal points that you are minded to refer to the Appeal Panel:

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

At line 144 of Gilead’s appeal letter, we refer to the flaws in the EAG approach described at appeal point 1(a).2, namely that:

* the pre-existing living systematic reviews and network meta-analyses were not designed to address the decision problem and so the EAG’s reliance on these sources did not meet the requirements of the Manual;
* the EAG did not have time to conduct appropriate quality checks on the third-party living system reviews and network meta-analyses; and
* the EAG did not have sufficient time to perform its role.

The point made at line 144 of Gilead’s appeal letter is that these flaws meant that the limited opportunity that Gilead had to comment on the EAG model or to provide other evidence later in the process could not compensate for the lack of opportunity to make its own full evidence submission and cost-effectiveness model.

At lines 166 and 170 of Gilead’s appeal letter, we refer to appeal point 1(a).6 and 1(a).3 because in these appeal points we describe in detail how the EAG and Committee did not address the distinction between patients on low-flow vs high-flow oxygen, and how the EAG did not conduct nor the Committee consider PSA. By contrast, Gilead would have addressed these issues if it had been given the opportunity to submit a cost-effectiveness analysis.

Appeal point 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

At line 227 to line 240 of Gilead’s appeal letter, we explain how the EAG’s approach limited its ability to conceptualise a model according to the decision problem and how the EAG itself acknowledged, for example, that the same treatment effects (including age) were assumed to be applicable regardless of study characteristics.

At line 241 of Gilead’s appeal letter, we refer to appeal point 1(a).5 because, as described in this appeal point (line 503 onwards), the EAG also recognised *other possible criteria for selecting subgroups include but are not limited to age; immune system competence, comorbidities, seroprevalence, vaccination status and the predominant SARS-CoV-2 variant* but that *it did not have the time to explore the impact of these characteristics.*

This context further demonstrates how the EAG’s approach (for lack of time) limited its ability to conceptualise a model according to the decision problem, to the prejudice of patients and Gilead.

At lines 298-300 of Gilead’s appeal letter, we refer to appeal points 1(a).5, 1(a).6 and 1(a).10 as examples of issues arising from the truncated time in which the preliminary evidence and modelling was developed. For example:

* in appeal point 1(a).5, we describe how, *due to time constraints* the EAG did not consider subgroups, including based on age. Consequently, the Committee has not considered children with severe COVID-19 as a subgroup;
* appeal point 1(a).6 concerns the Committee’s failure to address patients with severe COVID-19 on low-flow oxygen as a subgroup, which – in view of the EAG remarks not considering subgroups *due to time constraints* appears to be another consequence of an issue arising from truncated time for the preliminary evidence and modelling; and
* in appeal point 1(a).10, the identified issues result in part from the fact that, due to the significant limitations in the EAG’s approach resulting from the lack of time allowed, ACTT-1 data was not included in the base-case.

Appeal point 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

At line 592 of Gilead’s appeal letter, we refer to appeal points 1(a).5 and 2.2 for examples of vulnerable groups for whom there may not be an alternative antiviral treatment or any treatment available.

This is to illustrate the impact of the Committee’s decision: by failing to distinguish between low-flow and high-flow oxygen, the Committee has failed to consider a subgroup of patients with severe COVID-19 who would benefit most from remdesivir and for whom remdesivir would be a clinically and cost-effective treatment: this subgroup would include for example children with severe COVID-19 (as described in appeal point 1(a).5) and immunocompromised patients with severe COVID-19 (as described in appeal point 2.2).

Conclusion

We trust that the further clarification set out in this letter has sufficiently clarified our appeal points 1(a).3, 1(a).5, 1(a).9 and 1(a).10 so as to demonstrate that these points should be referred to the Appeal Panel.

Thank you in advance for considering Gilead’s further submissions in this appeal. We are available to answer any questions you may have or provide further clarifications.

Yours sincerely,

xxxxxxxxxxxxx Executive Director, Gilead Sciences Ltd

1. Dias, S., Sutton, A.J., Welton, N.J. & Ades, A.E. NICE DSU Technical Support Document 6: Embedding evidence synthesis in probabilistic cost-effectiveness analysis: software choices. 2011. Last updated April 2012. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/evidence-synthesis [Accessed 16 March 2023]. [↑](#footnote-ref-2)