xxxxxxxxxxxxxxxxxxx (Senior Director, Patient Access)

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Sent by e-mail only: xxxxxxxxxxxxxxxxxxxxx

21 June 2022

Dear xxxxxxxxxxxxxxxxxxx

**Re: Final Appraisal Document — Esketamine for treatment-resistant depression [ID1414]**

Thank you for your letter of 14 June 2022, lodging an appeal against the above Final Appraisal Document (FAD).

Introduction

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

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

**Appeal point 1.1 NICE has failed to act fairly because “The Committee recognises that clinical uncertainties are inherent to clinical trials in mental health but provides no explanation of how (if at all) this situation has been taken into account in its decision making”**

This point is presented in your appeal letter as two sub points, as follows.

**Appeal point 1.1(a) NICE has failed to act fairly because “The Committee is required to take into account the clinical uncertainties “inherent” to clinical trials in mental health”**

I understand your primary point to be that while the Committee’s overall conclusions in relation to the cost-effectiveness of esketamine at paragraph 3.36 of the FAD focus on the uncertainty of the estimates, the Committee provides no explanation of precisely how its recognition (at para 3.17) that some clinical uncertainties are “inherent to clinical trials in mental health” has been taken into account in this appraisal.

On careful consideration, I do not regard this as a valid appeal point. That is because there is clear evidence in the FAD that the committee discussed and considered the uncertainties relating to trial design and that its response to the uncertainty was to engage in significant theoretical modelling. This is consistent with NICE’s Guide to the methods of technology appraisal 2013 (the “**Methods Guide 2013**”), in particular paragraph 6.2.16 of the Methods Guide 2013, which explains that:

“*When the evidence on key parameters used to estimate cost effectiveness (for example, clinical effectiveness and effect on health-related quality of life) has serious limitations and/or when a variety of assumptions have been necessary in the cost-effectiveness modelling, the additional uncertainty this generates is a key factor in underpinning the judgements of the Committee. The Appraisal Committee is likely to consider more favourably technologies for which evidence on cost effectiveness is underpinned by the best-quality clinical data than those for which supporting evidence is dependent to a large extent on theoretical modelling alone. However, the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases.”*

The Committee clearly understood all of this in the present appraisal and took into account the uncertainties by way of theoretical modelling and sensitivity analyses. In my view this was a proper approach to take and there is no confusion (as suggested in your appeal) as to “the approach to be followed by the Committee when assessing the clinical and cost effectiveness of an innovative new treatment and, in particular, how it takes account of the recognised difficulties “inherent” in mental health”.

You also state under point 1.1a that “*to the extent that the Committee may be relying on the remit from the Department of Health and Social Care to justify an approach which does not take into account the inherent challenges in developing new treatments in mental health, this would be inconsistent with NICE’s processes.”* Having considered the extract of paragraph 3.38 quoted in your appeal letter, I consider the Committee’s reference to equity of access relates to a different question of whether the committee was required to deviate from NICE’s normal published processes in order to seek to mitigate the impact of the inherent clinical uncertainties identified. I do not read the FAD as suggesting that the Committee was relying on the remit from DHSC to “justify an approach which does not take into account the inherent challenges in developing new treatments in mental health”, and I see no evidence the Committee took such an approach (rather it responded to these inherent challenges through the modelling).

I am not minded to refer this appeal point 1.1(a).

**Appeal point 1.1(b)** **NICE has failed to act fairly because “The Committee is also required to provide reasons for its conclusions in relation to the difficulties “inherent” in clinical trials for mental health”**

I understand that you consider paragraphs 6.1.4 and 6.1.9 of the Methods Guide 2013 and general standards of transparency as an element of procedural fairness require the Committee to “*explain its assessment of the evidence and provide reasons for its conclusions, including, in this case, the “inherent” difficulties in conducting research on technologies for the treatment of mental illnesses*.”

In summary, you say: “*in the context of the Committee’s conclusions at paragraphs 3.17, 3.36 and 3.38 of the FAD and its recognition of the “inherent” clinical uncertainties in conducting research in treatments for mental health, the Committee is required to explain how this situation has been taken into account when reaching its conclusions on the use of esketamine NS, in accordance with procedural fairness and section 6 of the Methods Guide, in view of the inevitable clinical uncertainties associated with research in this area. Its failure to do so in the FAD is inconsistent with rigorous decision making and precludes any determination of whether the approach followed by the Committee in this respect is fair and reasonable*.”

I do not regard this as a valid appeal point. That is because I consider it clear that the committee addressed the inherent clinical uncertainties identified through the modelling. I note that there has been ample opportunity for comment during consultation on the first and second ACDs in January and August 2020 and no point has been taken previously as to the committee’s approach in response to the inherent uncertainties in this area. In my view the FAD is well reasoned around the clinical uncertainty and the evidence taken into account by the Committee and its views on that evidence. I see no arguable point that paragraphs 6.1.4 and 6.1.9 of the Methods Guide 2013 or indeed that the principle of transparency requires more on this issue. I am therefore not minded to refer this appeal point 1.1(b).

**Appeal point 1.2 NICE has failed to act fairly because “Conducting an appraisal of esketamine NS using a procedure which fails to take into account the particular challenges investigating new treatments for depression, discriminates against people with this condition”**

A valid appeal point; however I consider this properly falls under ground 1(b) (not ground 1(a)) as it goes to alleged unlawfulness. So as to assist in preparing for the appeal, this appeal point 1.2 is limited to whether the committee’s application of NICE’s procedures in this particular appraisal discriminates against people with TRD.

**Appeal point 1.3 NICE has failed to act fairly because “The Committee has failed to take into account the broader social considerations in the appraisal of esketamine NS”**

You summarise this point as follows:

*“In summary, despite recognising the very substantial difficulties associated with development of new mental health treatments, the societal burden associated with TRD and the huge clinical need for new treatment options, the Committee has seemingly failed to comply with its obligation to take into account the broader societal benefits associated with treating TRD and the requirements of NICE’s own Principles Document in its decision making. Alternatively, if the Committee has taken such matters into account, it has failed to explain its reasoning and how they have influenced the Committee’s conclusions relating to esketamine NS, given the importance of mental health treatments and the fact that the current provision of mental health services is accepted to be inadequate. This omission is contrary to NICE’s processes and is procedurally unfair.”*

In particular, you refer to paragraphs 6.2.21 and 6.3.3 of the Methods Guide 2013. Paragraph 6.3.3 provides that “*Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of ... [inter alia] whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured...[and] Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21).”*

In turn, paragraphs 6.2.20-21 provide that in general the Committee uses the most plausible ICER as the primary consideration when making judgements about the acceptability of technologies as a cost-effective use of NHS resources but will take non-health objectives of the NHS into account by considering the extent to which society may be prepared to forego health gain in order to achieve other benefits that are not health related. Paragraph 6.2.20 notes the Committee’s conclusions will be *“affected by the following additional considerations:*

1. *Whether or how its judgements have a bearing on broader social considerations to the extent that these are covered by NICE's principles on social value judgements and*
2. *Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services, or are associated with significant benefits other than health, only when requested specifically by the Department of Health as part of the remit.*”

I am not persuaded by your view that “there is no evidence from the FAD that such benefits have been taken into account by the Committee or, if they have been taken into account, how such matters are reflected in the overall conclusions set out in the FAD”. In particular:

With regard to “NICE’s principles on social value judgements”, I note that (in line with para 6.2.20 quoted above) para 1.4.4 of the Methods Guide 2013 provides that “the Appraisal Committee will...take into account the Institute's guidance on social value judgements described in the Institute's document, Social value judgements: principles for the development of NICE” [[1]](#footnote-1). You refer to Principle 9. Paragraph 30, Principle 9 is worth quoting in full:

*230. Some conditions, such as sexually transmitted diseases and drug dependency are associated with stigma. We do not consider this a reason to alter our normal approach to developing advice and guidance. However, stigma may affect people’s behaviour in a way that changes the effectiveness of an intervention and routine quality of life assessments may not capture the benefits of treatment. Our advisory committees should take both these factors into account.”*

I note that SANE (patient organisation) referenced stigma associated with administration of esketamine at a mental health facility in its submission contained in the January 2020 committee papers.[[2]](#footnote-2) However no evidence was provided by the company for the committee to consider how stigma would impact either effectiveness or routine quality of life assessments. In the circumstances and in the absence of evidence that the committee ignored submission evidence indicating that its assessment of the change in the quality of life inadequately captured the health gain, I am not persuaded that there is any arguable unfairness here.

To the extent your appeal point relies on (2) above (that the committee should have considered whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services, or are associated with significant benefits other than health), this is expressly only when requested specifically by the Department of Health and Social Care as part of the remit.

In light of the above, I see no arguable point that the Committee departed (in paragraph 3.37 of the FAD of otherwise) from NICE’s procedures under paragraphs 6.2.21 or 6.3.3 of the Methods Guide 2013 as suggested in your appeal letter.

I am therefore not minded to refer this appeal point.

**Ground 1b: in making the assessment that preceded the recommendation, NICE has exceeded its powers**

**Appeal point 1.4 NICE has exceeded its powers because “The Appraisal Committee’s conclusion that it is very uncertain whether esketamine NS with an SSRI or SNRI is more effective than placebo with an SSRI or SNRI assumes the role of the regulator and conflicts with the marketing authorisation for the product”**

A valid appeal point; however I consider this properly falls under ground 2 (not ground 1(b)) as it goes to alleged unreasonableness in the Committee’s conclusion. So as to assist in preparing for the appeal, this appeal point 1.4 is limited to whether the committee’s conclusion that the evidence is “very uncertain” is reasonable in light of the evidence (in particular the evidence from the licensing authority). I do not consider it arguable that the Committee exceeded NICE’s powers by reaching a conclusion as to effectiveness, notwithstanding that that conclusion is arguably inconsistent with the view of the EMA’s CHMP in the licensing context. Therefore I am not minded to refer this point under 1(b) but will do so under ground 2.

**Appeal point 1.5 NICE has exceeded its powers because “The Committee conducted an assessment of the safety of esketamine NS, despite recognising that this falls outside the remit for the appraisal”**

You state (in high level summary) that “*The Appraisal Committee have carried out a detailed assessment of the safety of esketamine NS assuming the role of the regulator and...taking into account irrelevant issues in the context of their remit.” You also suggest “that the Committee gave extensive consideration to the safety profile of esketamine NS, both at the Committee meeting and in the FAD, raises a strong inference that such matters were taken into account by the Committee when reaching its conclusions regarding the technology. These concerns are not removed by the fact that the slide deck presented to the Committee was modified after the Committee meeting and that the FAD recognises (after describing the Committee’s concerns in detail) that they should not be taken into account by the Committee because it is then unclear why this assessment is included in the FAD at all*.”

You present this as two sub points, which I consider as follows.

**Appeal point 1.5(a) Consideration of safety at the fourth Committee meeting**

A valid appeal point; however I consider this properly falls under ground 1(a) (not ground 1(b)) as it goes to alleged procedural unfairness. So as to assist in preparing for the appeal, this appeal point 1.5(a) is limited to whether it was unfair for the Committee not to explain why the words “Is the safety profile acceptable?” were removed from slide 24 of the slide deck and the impact of this change (if any).

I do not consider it arguable that the Committee exceeded NICE’s powers by considering the safety profile of esketamine during the public part of the meeting, as I disagree with your view that the discussion around safety was unrelated to quality of life or costs. Conversely I consider it appropriate for committees to consider the impact of safety considerations when evaluating on health related quality of life and costs. Therefore I am not minded to refer this point under 1(b) but will do so under ground 1(a).

**Appeal point 1.5(b)** **Consideration of safety in the FAD**

I do not regard this as a valid appeal point. That is because I disagree with your view that the discussion at paragraph 3.18 of the FAD is entirely unrelated to associated quality of life or costs. In my view the matters discussed at 3.18 do go to QALY and cost impact and I see no procedural unfairness or overstepping of the remit of the Committee or the powers of NICE. Therefore I am not minded to refer this point.

**Appeal point 1.6 NICE has exceeded its powers because “The recommendations for research included in section 4 of the FAD relate to depression and treatments for depression in general, rather than specifically to esketamine NS”**

A valid appeal point; however I consider this properly falls under ground 1(a) (not ground 1(b)) as the substance of your argument is that NICE has not followed its own procedures, namely paragraph 6.4 of the Methods Guide 2013, in providing the recommendations for research at section 4 of the FAD.

In order to assist your preparation for the hearing, this point should focus on whether the committee acted in accordance with NICE’s procedures. I do not consider it relevant that “no research recommendations (general disease related or otherwise) were made in relation to vortioxetine (TA367) (the only health technology indicated for a depression indication where NICE has issued technology appraisal guidance) and, while NICE’s Clinical Guideline on Depression (CG90) does, quite properly, include various recommendations for disease area research, none of these recommendations reflect those suggested in the FAD for esketamine NS” as you have identified no relevant procedural requirement for the Committee to align with the vortioxetine or CG90.

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

**Appeal point 2.1: “The Committee’s conclusions in relation to the health state costs relevant to this appraisal are unreasonable”**

You present this as two sub points, as follows. Both relate to para 3.32 of the FAD.

**Appeal point 2.1(a)** **The Committee unreasonably characterises skewed data as resulting in uncertainty**

On careful consideration, I do not regard this as a valid appeal point. That is because it is perfectly possible to consider that data comprising “average" or “mean” costs is the best data on cost to the NHS while also noting that within that data set there is a patient population driving those averages such that – depending on the relevant patient population - the dataset will be more or less relevant in determining the impact of a particular use of a particular drug in NHS. It appears to me the Committee’s approach is consistent with paragraph 5.5.6 of NICE’s Methods Guide 2013, which notes that “data based on HRGs may not be appropriate in all circumstances (for example, when ... the mean cost does not reflect resource use in relation to the new technology under appraisal).”

As to your argument that “The assertion that skewed data are necessarily uncertain is also inconsistent with conclusions reached in other appraisals and therefore arbitrary and unreasonable”, while I accept that where two committees are considering analogous facts, it is likely that, acting reasonably, they will come to analogous decisions, there is no rule of precedent that a previous FAD must be followed. Rather NICE must exercise discretion in its decision making, with each decision being taken on its own facts. In the absence of further details, I can see no basis for an argument that the recommendations in the FAD cannot reasonably be justified from the evidence presented to the committee. I am not minded to refer this point to an appeal panel.

**Appeal point 2.1(b)** **The committee has unreasonably questioned the generalisability of the TRD costing study**

I understand this point is that “*In summary, the Committee has concluded (at 3.32) that the results of the TRD costing study may not be generalisable to UK clinical practice, even though they were obtained from UK NHS practice and are supported by two other NHS databases. The apparent rejection of these data by the Committee in circumstances where they represent the best data available to the Committee is unreasonable*.”

I do not consider this is a valid appeal point. Paragraph 3.32 is in my view well-reasoned on this point, as it explains (at very high level) that the data in the costing study represents a skewed distribution of costs in TRD as most healthcare resource is used by a proportionally small number of people (which the committee understood was mostly through a small number of people needing hospitalisation), that the same people who are hospitalised may not necessarily have esketamine (because there are precautions for its use for people with certain psychiatric comorbidities) and there was no evidence that esketamine would be beneficial in the group of people for whom hospital costs are largest. I see no arguable unreasonableness in the committee’s resulting view that further research is needed to fully understand the costs associated with TRD and hospitalisations.

I am not minded to refer this point to an appeal panel.

**Appeal point 2.2 “The Committee’s concerns that the clinical trials of esketamine may not have been adequately blinded are based on speculation only and conflict with the available evidence”**

On careful consideration, I do not regard this as a valid appeal point.

That is because as I understand it this point ultimately goes to the reasonableness of the Committee’s conclusion (at para 3.13 of the FAD) that “It is not appropriate to adjust the efficacy estimates of the placebo arm in the trials” on the basis you consider the Committee was wrong to have concerns as to the adequacy of the blinding.

I understand your arguments regarding TRANSFORM-2 that (1) patients in both groups were commenced on a new SSRI or SNRI at the same time as esketamine or placebo and these oral treatments could also produce treatment effects supporting blinding of randomisation; (2) an unusually high response in patients receiving OAD + placebo does not suggest negative expectations in these patients; and (3) data from Chen G et Al provided with the company’s initial evidence submission demonstrated that patients who experience dissociative symptoms achieve outcomes that are not significantly better than patients who do not experience such symptoms and that dissociative symptoms were experienced by patients on OAD + placebo as well as those on OAD + esketamine NS. I also understand your arguments relating to the SUSTAIN-1 trial, and that “*The Committee has not seemingly considered the views of the CHMP in relation to adequacy of blinding and has provided no reasons for disagreeing with the conclusions of the regulators in this respect.*.”

However, the Committee’s discussion that “blinding could be an issue” must be read in its context within paragraph 3.13 of the FAD. That paragraph notes that the company suggested a post-hoc adjustment of the TRANSFORM-2 data to account for higher efficacy estimates for the placebo arm compared with other studies. It then discusses possible reasons for the high placebo response rate (including, among other things, that blinding could be an issue) justifying its conclusion it was not appropriate to adjust the efficacy estimates of the placebo arm in the trials as suggested by the company. It’s clear from the papers and the FAD that the committee documented and considered a number of reasons that the results from a placebo arm should not be adjusted in isolation and that potential for unblinding was only one aspect of their decision making. I note this discussion is supported by more detail in the committee papers, slides and first Appraisal Consultation Document. I consider the FAD is well reasoned on this point.

I disagree with your view that “It is unreasonable for the Committee to speculate that trial results may be unreliable in the absence of any supporting evidence to that effect and in the face of a different conclusion by regulators”, as in my view it was appropriate for the Committee to consider these matters as one possible issue in response to, and in order to assess the suitability of, the proposed adjustments to the efficacy estimates of the placebo arms in the trials.

I am not minded to refer this point to an appeal panel.

**Appeal point 2.3 “The Committee’s conclusion that it is difficult to separate any effect of new oral antidepressants administered in the clinical trials from the effects of esketamine is unreasonable”**

For reasons aligned to those set out in response to appeal point 2.2, I do not regard this as a valid appeal point. Again this point challenges the reasonableness of the Committee’s conclusion that “It is not appropriate to adjust the efficacy estimates of the placebo arm in the trials”. Again I consider the Committee’s reasoning as to why they viewed it not to be appropriate is well articulated and explained in the FAD, particularly when read alongside the first Appraisal Consultation Document. The Committee’s conclusion is not an attack on the “standard trial design” that you describe and justify in your appeal letter, but rather it takes account of the impact of that trial design on the proposed adjustment to the placebo arm. I see no arguable unreasonableness here and am therefore not minded to refer this point to an appeal panel.

**Appeal point 2.4 “The Committee’s conclusions regarding potential uncertainty and generalisability of relapse rate data and long-term outcomes of depression are unreasonable in light of the available evidence”**

This point is presented in your appeal letter as two sub points, as follows.

**Appeal point 2.4(a)** **Consideration of relapse rate data**

A valid appeal point.

**Appeal point 2.4(b)** **Long-term outcomes of depression**

A valid appeal point.

**Appeal point 2.5 “The Committee’s conclusions regarding treatment changes conflict with NICE’s Clinical Guideline on Depression and are therefore unreasonable**

I do not regard this as a valid appeal point. That is because the Committee is not bound to accept CG90 as evidence of clinical practice; rather the CG90 is a broader guideline on depression that makes recommendations for ideal practice. It is a relevant factor for NHS bodies but does not have mandatory status and is not conclusive as to the practice in fact adopted in the NHS. I am not currently persuaded me that there is arguable unreasonableness here so am not minded to refer this point to an appeal panel.

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, **no later than 5 July 2022**, 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 13 July 2022.

Yours sincerely

Dr Mark Chakravarty

Lead Non-executive Director for Appeals

National Institute for Health and Care Excellence

1. <https://www.nice.org.uk/about/who-we-are/our-principles> [↑](#footnote-ref-1)
2. <https://www.nice.org.uk/guidance/gid-ta10371/documents/committee-papers> [↑](#footnote-ref-2)