NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on esketamine for treatment-resistant depression [ID1414]: Decision of the panel

Introduction

1. An appeal panel was convened on 27 July 2022 to consider an appeal against NICE's final appraisal document, to the NHS, on esketamine for treatment-resistant depression [ID1414].

2. The appeal panel consisted of:

• Professor Alan Silman	Chair
• Alina Lourie	Non-Executive Director of NICE
• Professor Peter Groves	Health service representative
• Dr Paul Robinson	Industry representative
• David Chandler	Lay representative

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered appeals submitted by Janssen (the company) and the Royal College of Psychiatrists.

5. Janssen was represented by:

• Amanda Cunnington	Senior Director Patient Access

- Nicola Trevor — Head of Health Economics Market Access and Reimbursement (HEMAR)
- Sarah Richards — Senior HEMAR Manager
- Jordan Talbot — Medical Lead Neuroscience
- Dr Adela Williams — External Legal Counsel

6. The Royal College of Psychiatrists was represented by:

- Dr Rupert McShane — Consultant Psychiatrist

7. NICE does not require appellants to declare any interests as they will have a clear interest in the technology that is subject of the appeal, often as the manufacturer, or bodies advocating the technology. However, at the hearing Dr McShane was incorrectly asked to declare any conflicts of interest. His declaration is accordingly not recorded and played no part in the panel's consideration.

8. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

- Dr Megan John — Chair, Technology Appraisal Committee D, NICE
- Helen Knight — Interim Director, Medicines Evaluation, NICE
- Jasdeep Hayre — Associate Director, NICE
- Adam Brooke — Health Technology Assessment Adviser, NICE
- Giles Monnickendam — Member, Technology Appraisal Committee D, NICE

9. The appeal panel's legal adviser, Alistair Robertson of DAC Beachcroft LLP, was also present.

10. The following members of the appeal panel for technology appraisals and highly specialised technologies were present as silent observers throughout the hearing and panel discussions.

- Catherine White — Lay Representative
- Professor Bee Wee — Non-Executive Director of NICE

11. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

12. There are two grounds under which an appeal can be lodged:

- Ground One: In making the assessment that preceded the recommendation, NICE has:

  (a) Failed to act fairly; and/or

  (b) Exceeded its powers.

- Ground Two: The recommendation is unreasonable in light of the evidence submitted to NICE.

13. Dr Mark Chakravarty, NICE Lead non-executive director for appeals, in preliminary correspondence had confirmed that:

- Janssen had potentially valid grounds of appeal as follows: Grounds 1a, 1b and Ground 2
- The Royal College of Psychiatrists had potentially valid grounds of appeal as follows: Ground 2

14. The appraisal that is the subject of the current appeal provided advice to the NHS on esketamine for treatment-resistant depression (TRD).

15. Esketamine is an N-methyl-D-aspartate receptor antagonist that is administered as a nasal spray and used in people with TRD (which is defined as a major depressive disorder that has not responded to at least 2 different treatments in the current depressive episode).

16. The numbering of appeal points in this letter reflects those that were used during the hearing. Reference is also made to their corresponding number in the original appeal letters. The text of this letter does not represent a verbatim account of the proceedings nor a documentation of the order of events that took place but rather, provides a brief summary of the appellant and committee submissions for the points that were discussed.

17. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Amanda Cunnington on behalf of Janssen, Dr Rupert McShane on behalf of the Royal College of Psychiatrists and Dr Megan John on behalf of the appraisal committee.

Appeal by Janssen

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

Appeal Ground 1a.1(a) (Original Appeal Point 1.1) 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.

18. Nicola Trevor, for Janssen, stated that while NICE had acknowledged in the Final Appraisal Document (FAD) that it recognised the inherent challenges associated with obtaining evidence and undertaking research in mental health, as well as the resulting uncertainties that ensue, it had not made sufficient provision for these in its decision-making. Furthermore, she expressed the view that NICE Technology Appraisal Methods and Processes appear to have a foundation in physical rather than mental health and that the higher levels of uncertainty resulting from mental health research appears to 'raise the

bar' for achieving a successful outcome when these methods are applied during a NICE Technology Appraisal.

19. Nicola Trevor explained that during the course of the appraisal, Janssen had demonstrated flexibility by changing the targeted treatment population for esketamine, in order to reduce the financial risk to the NHS, but that she had seen no suggestion that NICE had compromised its approach to assessing the evidence. She concluded that, in this appraisal, in Janssen's view NICE had been too negative and had adopted an approach that was insufficiently pragmatic or flexible in dealing with the uncertainties in the evidence that result from the inherent challenges in undertaking research in mental health.

20. Following questioning from the appeal panel, Sarah Richards, for Janssen, explained the measures that had been undertaken by Janssen in attempting to resolve the uncertainties in the evidence. This had included the submission of 'real-world' evidence from France and Spain on the longer-term use of esketamine as well as UK costing data to address uncertainties about non-pharmacological healthcare resource use costs in patients with TRD. Furthermore, extensive sensitivity analyses had been undertaken and the results of these were shared with NICE.

21. Megan John, for NICE, explained that the committee had given transparent consideration to the uncertainties that were encountered in the evidence during this appraisal, in line with the NICE Methods Guide. She told the hearing that the committee had been looking for ways to reach a positive recommendation for the use of esketamine in TRD but insufficient evidence was presented to them by Janssen during the appraisal to be able to do so. She explained that uncertainties in the evidence are often encountered during Technology Appraisals and that the onus of responsibility is with the Company and not NICE to provide sufficient evidence and analysis to be able to satisfactorily overcome these.

22. Megan John explained that during Technology Appraisals it is important for the committee to identify situations where uncertainties could potentially be resolved, for example through undertaking additional research, as opposed to when they are inherently unresolvable. She also explained that broadly speaking, the greater the uncertainty, the greater the risks of making a positive recommendation but despite this, a positive outcome is still possible even in the presence of some unresolvable uncertainty.

23. Megan John went on to describe how this appraisal had been unusually protracted and that this had provided an opportunity for Janssen to provide additional data to help resolve the uncertainties. Furthermore, the possibility of agreeing a Managed Access Scheme for the use of esketamine in TRD had been explored with NHS England in order to facilitate additional data acquisition with clinical usage, but no feasible means to achieve this were arrived at.

24. Jasdeep Hayre, for NICE, explained that the NICE Social Value Judgements make it clear that treatments should not be recommended if there is insufficient evidence to make a decision; that the Methods Guide indicates that committees need to be fully aware of uncertainties associated with both clinical and cost effectiveness; that there is no mandated or structured decision-making framework but that discretion can be applied by committees in their decision-making. He made it clear that these factors are applicable to the consideration of treatments for all conditions whether they be due to mental or physical illness.

25. Adam Brooke, for NICE, further explained the importance of the distinction between those uncertainties in the evidence that are potentially resolvable and those that are not in the context of this appraisal. He described how exceptionality can sometimes be taken into account by NICE when considering rare diseases. It is estimated, however, that 130,000 people in the UK suffer from TRD meaning that there is a substantial population in which further research on

esketamine is possible. Indeed, he went on to highlight that Janssen is sponsoring an on-going study, ESCAPE-TRD, which includes patients that are more aligned to those who would be likely to receive esketamine in the NHS and the results of which will therefore be an important addition to the current evidence base.

26. Adam Brooke went on to describe other challenges that were encountered in assessing the current evidence for esketamine in TRD for the population selected, some of which are resolvable. These included the small number of patients in the studies who were in the sub-group that were relevant to the appraisal; the submitted evidence mostly relating to people who had failed treatment with 2 rather than 3 oral anti-depressants (OAD); the 4 week treatment phase of the RCTs TRANSFORM-1 and TRANSFORM-2 being short with longer treatment phases both feasible and applicable in a currently ongoing trial (ESCAPE-TRD); and the restricted inclusion criteria for the relevant studies that limits the generalisability of the results to a wider 'real-world' population of patients with TRD who would be likely to receive esketamine in the NHS. Furthermore, he explained that the increased potential for a placebo-effect in trials in people with mental illness is not unique to this clinical scenario and that uncertainty could be reduced in future studies through the use of novel trial design, for example using the concept of 'safer interview'. Adam Brooke did acknowledge, however, that it is not feasible to design studies that compare OADs with psychological therapies.

27. Helen Knight, for NICE, explained that NICE have a responsibility to the wider NHS in ensuring that they make positive decisions only when there is sufficient confidence that a treatment offers good value for money. She explained that while there proved to be uncertainties in this appraisal that could not be resolved during the time of this Health Technology Assessment, this does not mean that they were not considered, for example by undertaking scenario and sensitivity analyses.

28. The appeal panel concluded as follows. In regard to this appeal point, it was clear that its role is to judge the fairness of the committee's actions during the appraisal, as it applied to the provisions of the NICE Methods and Process Guides, and not to judge the fairness of those methods and processes *per se.* The appeal panel was satisfied that during the course of this appraisal, the committee were aware of, had considered and had taken into account the inherent challenges associated with undertaking research in mental illness, and the uncertainty in the evidence that results from these. From the verbal evidence presented, the appeal panel was satisfied that NICE had also considered the areas of uncertainty which were potentially resolvable and those that were unresolvable. The appeal panel was satisfied that Janssen acknowledged the areas of uncertainty in the evidence available and was given sufficient opportunity to provide additional data and to undertake additional analyses to address some of these uncertainties. The appeal panel was also satisfied that NICE had fairly considered the additional data that was submitted by Janssen in its decision-making. The appeal panel accepted that these data were insufficient to resolve important areas of residual uncertainty in regard to the clinical and cost effectiveness of esketamine for TRD. In coming to this conclusion, the appeal panel did not accept that the committee had unfairly 'raised the bar' in regard to thresholds of certainty and evidence required to reach a positive decision for this treatment for patients with TRD. The appeal panel concluded that NICE had acted fairly in taking into account the clinical uncertainties inherent to clinical trials in mental illness.

29. The appeal panel therefore dismissed the appeal on this point.

Appeal Ground 1a.1(b) (Original Appeal Point 1.1): NICE has failed to act fairly because the committee is also required to provide reasons in relation to the difficulties inherent in clinical trials for mental health.

30. Nicola Trevor, for Janssen, explained that while NICE outlined in the FAD the challenges associated with undertaking research in mental illness, as well as the inequity of care provision that exists for patients

with mental rather than physical illness, it did not provide a clear and transparent explanation as to how these had been taken into account in committee decision-making.

31. Adela Williams, for Janssen, also claimed that despite the committee recognising inherent difficulties in undertaking research in mental illness, there was, from a legal perspective, insufficient evidence in the FAD about how this was reflected in its reasoning. She submitted that a fair procedure requires that the committee needs to not just be aware of and take into account the inherent difficulties, but also provide a clear explanation of their decision-making including the extent to which some inherent difficulties may have been disregarded. Furthermore, she expressed the view that NICE should explain in the FAD its conclusions about the uncertainties in the evidence that were either resolvable or unresolvable.

32. Helen Knight, for NICE, accepted that while the committee did balance different uncertainties that were presented to them in their decision-making, this was maybe not made clear enough in the FAD. She also explained that the NICE Methods Guide does not require the committee to define uncertainties that are resolvable and those that are unresolvable.

33. The appeal panel had regard to the NICE Methods Guide and concluded as follows: It was satisfied that NICE had identified and outlined in the FAD the clinical uncertainties that are inherent in clinical trials in mental illness as well as the difficulties in designing, recruiting to and interpreting results of trials in this disease area. It was also satisfied, from the verbal evidence presented, that the committee had taken these into account in their decision-making and had also considered how uncertainties were resolvable or unresolvable. It did not consider, however, that sufficient explanation was provided in the FAD about how the specific inherent difficulties in clinical trials and the uncertainties that result from them, had been taken into account in their reasoning and decision-making, or the

extent to which they had or had not been disregarded. Furthermore, the appeal panel considered that the committee should have explained in its conclusions about which uncertainties were, in its opinion, potentially resolvable and those that were unresolvable, since these might inform future trial design in this important disease area.

34. The appeal panel therefore upheld the appeal on this point.

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

Appeal Ground 1b.1 (Original appeal point 1.2): NICE has exceeded its powers by 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.

35. Adela Williams, for Janssen stated that the Equality Act 2010 requires fair and equal treatment for individuals with protected characteristics, including disability. She submitted that people with TRD fall within this cohort. She noted that the Equality Act 2010 prohibits direct discrimination, and that it can require adjustments to be made to the way in which people with protected characteristics are treated, to avoid discrimination. She observed the fine distinction between considering whether NICE procedures *per se* may potentially lead to discrimination under the Equality Act 2010, as opposed to whether, in this appraisal, the application of those principles had been discriminatory. She confirmed that Janssen's challenge was solely focused on the application of those principles in this appeal.

36. Adela Williams noted that the FAD showed that the committee had considered equality issues in relation, for example, to geographical challenges of accessing treatment with esketamine or ensuring that people in the criminal justice system have access to treatment. She submitted, however, that whilst the committee had recognised the inherent difficulties associated with undertaking research in mental illness, it had not adjusted sufficiently for those inherent difficulties

and had not shown or described in the FAD sufficient flexibility in its approach to uncertainty. She submitted that the committee had fallen into error by treating people with TRD in the same way as it would treat those with physical illness and that it should not have applied the same hard-edged endpoints and populations. Adela Williams noted that many of the people who will receive treatments appraised by NICE do suffer from disabilities, but she submitted that the difference in this case is that the particular disability is associated with challenges that make carrying out trials more difficult. This raises a question of how the disability interacts with the processes and the extent to which that requires adjustments. She submitted that the committee should have adjusted the standard procedures to reflect the inherent difficulties.

37. Following questioning from the appeal panel, Adela Williams confirmed that similar challenges can also be encountered in people with physical as well as mental illness, for example in the assessment of health-related quality of life, and that the inherent challenges in mental illness are a key part of the condition. She indicated, however, that this still requires NICE to make adjustments for the difficulties in undertaking clinical trials in mental illness in their decision-making and to demonstrate how they had done so. She submitted that the committee should have explained what adjustments it had made and why it considered that they were reasonable.

38. Megan John, for NICE, explained that the committee was fully aware of its responsibilities under the Equality Act 2010 in undertaking this appraisal and in the description of the procedures undertaken. Equalities considerations were referred to in sections 3.37, 3.40, 3.17 of the FAD as well as in the Equality Impact Assessment form. She further explained that the committee had reached its conclusions on the basis of all the evidence available, which had included a wide range of views about the benefits of esketamine from patient and clinical experts, in addition to clinical trial evidence. The committee

had been particularly careful to take full account of the wider range of views, in recognition of the difficulties of collecting clinical trial data for this cohort.

39. Helen Knight, for NICE, explained that in undertaking Technology Appraisals, NICE has a legitimate aim to produce positive advice only for treatments that are demonstrably cost effective. She indicated that during this appraisal, the committee had been mindful of the inherent difficulties and noted that committees do seek to identify areas where they may need to make adjustments. She also noted that no adjustments had been proposed in this case. She further explained that the committee had balanced the challenges of doing research in TRD with the evidence of cost effectiveness for esketamine that was available to them. In doing so, they had exercised their function as an independent professional advisory committee in making value judgements.

40. Adela Williams, for Janssen, reiterated Janssen's concern that a consequence of the disability shared by people with TRD is that it is more difficult to collect certain data, and that if guidance is based on the certainty of data alone then that would be discriminatory. In this case, she continued, the committee has concluded that there are inherent difficulties that cause uncertainties, and it is those that give rise to the need to make adjustments.

41. Jasdeep Hayre, for NICE, stated that the committee were well aware of the clinical uncertainties inherent to trials in mental illness and these were detailed in section 3.17 of the FAD. He went on to explain that some of these relate to protected characteristics while some do not, for example how trials are conducted or the effectiveness of a drug, and that some can be resolved but some cannot. Overall, however, having taken account of all the evidence presented to the committee, there was insufficient information presented for the uncertainties described, to be addressed sufficiently to lead to a positive recommendation.

42. Following questioning by the appeal panel, Megan John confirmed that the committee, in reaching its decision, had regard to the fact that the patient group may be disadvantaged because of the challenges of obtaining data, and that having taken that into account, the committee was still unable to make a positive recommendation. Helen Knight, for NICE, also confirmed that, in its decision-making, the committee had regard to the disability challenges that are faced by people with TRD, including those impacting upon research in mental illness. She accepted, however, that this could have been laid out more explicitly in the FAD.

43. The appeal panel concluded as follows: In regard to this appeal point, it was clear that its role was to determine whether the manner in which NICE methods and processes were applied in this appraisal led to discrimination under the Equality Act 2010, rather than to consider whether the NICE methods or processes *per se* were in anyway discriminatory. The appeal panel was satisfied that the committee had been aware of their responsibilities under the Equality Act 2010 in their application of NICE methods to a group of patients sharing the protected characteristic of disability (TRD). Furthermore, the appeal panel was satisfied that the committee pursued a legitimate aim to only recommend a treatment that is demonstrably cost effective, and that uncertainties in this regard prevented them from doing so. The appeal panel was satisfied that the committee were aware of and had adequately taken into account the clinical uncertainties inherent to clinical trials in mental illness, and that it had taken reasonable steps to adjust for those uncertainties, for example by considering wider information in addition to clinical data.

44. The appeal panel therefore dismissed the issue on this point.

45. Although it did not change the appeal panel's decision, the appeal panel did consider, however, that the committee ideally could have been clearer in the FAD, about how the uncertainties it identified were

related to the patient group's protected characteristic, and to explain how it had sought to adjust for these.

Appeal Ground 1b.2 (Original 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.

46. Adela Williams, for Janssen, described how the role of a regulator is to determine standards of safety and efficacy for new treatments and to make its judgements about market authorisation on the basis of a balance of benefits and risks. In contrast, she explained that the role of NICE is to determine clinical and cost effectiveness of new treatment. She acknowledged that consideration of safety issues may be relevant to this role but only in so much as they impact on health-related quality of life (HRQOL) and costs. Taking consideration of safety outside of these parameters, she submitted, would assume the role of a regulator.

47. Adela Williams submitted that the committee had exceeded its powers by allowing undue considerations of safety to influence its decision-making. To substantiate this claim, she explained that at the 4th meeting of the committee on 7 April 2022, slide 24 had concluded with a question about esketamine for the committee: 'is it safe?' She submitted that NICE did not recognise this to be improper but later removed the question from the slide prior to publication of the slide presentation on the NICE website. She submitted that this was an unacceptable procedural flaw.

48. Adela Williams went on to describe how there is a detailed description of the relevant safety issues associated with esketamine in section 3.18 of the FAD that extends to a whole page and then concludes with a final sentence acknowledging that the committee is not a safety committee and should not, therefore, make recommendations about safety. She concluded that there had been an undue influence of safety issues on the decision-making process meaning that the

committee should be asked to reconsider the evidence with a greater focus placed this time on clinical efficacy rather than safety *per se*.

49. Jordan Talbot, for Janssen, explained that the company had continued to collect safety data and that this covered, in total, more than 3,500 patient years of treatment which was submitted to the 4th committee meeting. Despite this and the fact that the safety of esketamine had already been established through the granting of market authorisation, he questioned the validity of the detailed consideration of safety issues at the 4th committee meeting which he recalled had extended to an hour. He also went on to state that some of the safety concerns detailed in section 3.18 are unsubstantiated by the evidence submitted.

50. Following questioning by the appeal panel, Adela Williams, for Janssen, clarified that esketamine had received full market authorisation and that this was not conditional, while Jordan Talbot, for Janssen, explained that a Register of usage had been established in collaboration with MHRA to minimize the risks associated with drug abuse.

51. Megan John, for NICE, agreed that NICE committees do have a clearly defined remit for their consideration of safety and submitted that the committee's consideration of the safety of esketamine was well within that remit since it focused on consequences for cost, disutility, treatment discontinuation and generalisability of use in broader populations. She emphasised, however, that a safety review was not undertaken by the committee. She also noted that the safety considerations detailed in section 3.18 had not been included in the appeal submitted by Janssen.

52. Megan John went on to explain that the wording of the question posed about esketamine on slide 24 at the 4th committee meeting: 'is it safe?' was an error, in terms of what was relevant for the committee to consider. This error in wording had been identified as such by one

of the committee members in the meeting who drew it to the attention of the committee. She described how the error, having been identified as such, was corrected prior to publication of the slide presentation on the NICE website.

53. Jasdeep Hayre, for NICE, confirmed that the question on slide 24 was an error and that the statement should have read: 'Have all safety issues been taken into consideration?' He corroborated the fact that this error was highlighted by a committee member and that, at this point, the committee were instructed not to discuss the question on the slide. He went on to provide additional context in explaining that it is commonly the case that errors and factual inaccuracies appear on slides presented to Technology Appraisal committee meetings; that these may range in importance from typographical errors to more substantial ones; that there was another error identified on slide 8 of the same presentation; and that identified errors are always corrected prior to publication. He noted that Janssen had not raised concerns about this error prior to the appeal process and stated that it would be wrong for NICE to publish information that it knew to be incorrect.

54. Jasdeep Hayre disputed the claimed length of the discussion by the committee on matters of safety and declared that it had lasted no more than 5 to 10 minutes. In a meeting of approximately 4 hours duration and with a presentation comprising 39 slides, he considered it implausible that the committee would dwell for an hour on a discussion about safety that was presented on only 2 slides.

55. Sarah Richards, for Janssen, said that the committee had had a mixed discussion about the safety and clinical efficacy of esketamine for 1 hour and claimed that the meeting had extended to 3.5 to 4 hours because of the safety considerations. She also acknowledged that the appropriateness of the discussion around safety had indeed been questioned by a committee member.

56. Megan John, for NICE, confirmed that the evidence on safety and clinical efficacy were considered together by the committee and that the reason why the committee meeting was protracted was because the committee was eager to arrive at a positive decision if it proved possible.

57. The appeal panel concluded as follows: It was satisfied that the committee had considered the issue of the safety of esketamine appropriately and within its remit given the potential impacts that this may have on important other issues such as cost and health-related quality of life. It is agreed by Janssen and NICE that a lengthy discussion took place at the 4th committee meeting about the evidence of safety and efficacy together and the appeal panel considered that there was insufficient evidence to conclude that the committee had given undue attention to the issue of safety in arriving at its negative decision. The question posed on slide 24 relating to the safety of esketamine at the 4th committee meeting: 'Is it safe?' is acknowledged as an error by NICE but the appeal panel considered that the action to correct this prior to publication was appropriate. The appeal panel concluded that NICE did not exceed its powers by considering safety issues during this appraisal.

58. The appeal panel therefore dismissed the appeal on this point.

Appeal Ground 1b.3 (Original 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.

59. Adela Williams, for Janssen, explained that NICE Technology Appraisals are directed at individual products and not the management of diseases. She referenced the NICE Methods Guide that outlines in section 6.4 that an appraisal committee can recommend that a technology is used only in the context of research or, while the technology is recommended as an option, research is also conducted. She highlighted that the 3 research

recommendations that were included in section 4 of this appraisal were generic; none related specifically to esketamine; and that they were therefore outside of the control of Janssen. On the other hand, by including them in the FAD, the implication is that the failings that are represented in the need for these generic research recommendations influenced the committee in their decision-making. Furthermore, she claimed that their inclusion means that NICE are setting an unfairly high hurdle for research on esketamine. In making these generic research recommendations, she claimed that NICE had exceeded its powers.

60. Sarah Richards, for Janssen, noted that in the explanation of why the committee had made its recommendations in Section 1 of the FAD, further research to address some of the uncertainties in the evidence was recommended. The research recommendations that were proposed in section 4, however, were generic and did not refer to esketamine. In this regard, there appeared to be inconsistency and she agreed with Adela Williams that NICE had exceeded its powers since addressing the stated research recommendations was unattainable for Janssen.

61. Megan John, for NICE, stated that the research recommendations in section 4 were formulated with the best intentions in mind in the knowledge that public-funded research can be stimulated by such advice. She made it clear that the nature of the research recommendations had not influenced the committee's decision-making but had been a consequence of it. She expressed the view that it would have been inappropriate for the committee to have made specific research recommendations for esketamine.

62. Helen Knight, for NICE, stated that committees do not necessarily make research recommendations when they undertake Technology Appraisals and that when they do, the recommendations can be directed at stakeholders as well as the company involved. During this appraisal, a range of views were received from stakeholders about

the need to consider the wider clinical area and the committee considered that it would be helpful to reflect these in their research recommendations. She added that NICE processes do allow for this and that they do not state that research recommendations should be solely linked to the technology under consideration.

63. Adam Brooke, for NICE, explained that the approach taken in this appraisal is not unprecedented. He cited TA320, which had appraised Dimethyl fumarate for treating relapsing-remitting multiple sclerosis, in which research recommendations were made that included the need for a more comprehensive synthesis of available evidence on the underlying disease progression of multiple sclerosis in the UK context, to better inform future models of cost-effectiveness. He agreed that it would have been inappropriate to have made specific research recommendations for esketamine and that it was clear from the FAD and some knowledge of the Janssen research programme that they are already aware of what research needs to be done to resolve residual evidence uncertainties.

64. Rupert McShane for the Royal College of Psychiatrists, stated that in his opinion the research recommendations in section 4 had been made by the committee with the best intentions in mind. Nonetheless, he expressed the view that the recommendation in section 4.1 of the FAD, for research into how clinical data from regulatory trials in depression could appropriately be used in health technology assessment and decision modelling, is unresolvable.

65. Jasdeep Hayre, for NICE, said that it was not unprecedented for NICE to issue research recommendations in the FAD for an appraisal that had had a negative outcome. He cited TA556, that appraised Darvadstrocel for treating complex perianal fistulas in Crohns disease, as a case in point. He went on to explain that the approach that can be taken by committees in making research recommendations is governed not just by the NICE Methods Guide but also by the NICE Process Guide which provides more latitude and wider powers.

66. To provide wider context, Jasdeep Hayre explained that when the NIHR undertake calls for research, the availability of research recommendations in Technology Appraisal FADs may be helpful and provide a useful reference point. Furthermore, if some of the recommendations are acted upon by the wider community then the results may assist in any future assessment of esketamine. Finally, he corroborated the fact that the research recommendations were discussed and agreed by the committee after it had made its decision.

67. Helen Knight, for NICE, clarified that the recommendation for research in section 1 of the FAD was in the lay summary which outlined in general terms the reasons why the committee had made its recommendations.

68. The appeal panel concluded as follows: It was satisfied that the committee was not precluded from making general research recommendations in a FAD when there has been a negative decision and that there is no obligation that these should be restricted to the technology under consideration. The appeal panel was persuaded that the research recommendations had been made by the committee with their best intentions in mind in order to be helpful and to stimulate awareness in the wider community of the need for further research into TRD in areas that go beyond the role of esketamine. It concluded, therefore, that it had not exceeded its powers in doing so.

69. The appeal panel therefore dismissed the appeal on this point.

70. The appeal panel noted that while the lay summary in section 1 is not a substantive part of the FAD decision, the reference that is made to the nature of the research that is required does appear to be inconsistent with the research recommendations in section 4. Whilst this did not affect the appeal panel's decision on this appeal point, the appeal panel did note that this may lead to confusion in the minds of the reader and could be resolved by the inclusion in section 4 of a duplicative statement from section 1 stating the need to also

undertake research into the uncertainties that remain about the clinical and cost-effectiveness of esketamine, and confirming that the remainder of the recommendations in section 4 are not directed specifically at Janssen.

Appeal by the Royal College of Psychiatrists

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

Appeal Ground 2.1: The recommendation is unreasonable because of the committee's approach to uncertainty in long-term data for modelling.

71. Rupert McShane, for the Royal College of Psychiatrists, explained that the main concern that is reflected in this appeal point is the approach to uncertainty. He summarised the clinical uncertainties in the evidence that he thought are important and highlighted those that he considered unresolvable including the exclusion from studies of people with an imminent suicide risk and the numerous different treatment lines for people with depression. He expressed the view that there was nothing new to learn from studies of 8-week treatment duration as opposed to 4 weeks; that the 1-year safety data available for esketamine was good; and that treatment withdrawal data suggests that the number of subsequent suicides is extremely small in a high-risk population. He explained that there is currently no infrastructure for routine data collection in patients with TRD and that this had proved to be the main challenge in attempting to agree a Managed Access Scheme for esketamine. Nonetheless, he described how, following advice from the Royal College of Psychiatrists to the MHRA, a Register of the usage of esketamine has been established by Janssen to help resolve concerns about potential abuse of esketamine. Finally, he explained the challenges associated with acquiring long-term data in people with depression that relate to the loss of motivation associated with the illness resulting in a high rate of drop-out in data collection.

72. Having acknowledged these uncertainties and their impact on the assessment of the cost-effectiveness of esketamine, Rupert McShane considered that it was unreasonable for the committee not to have attempted to arrive at an ICER value based on the ERG's most conservative estimates.

73. Megan John, for NICE, clarified that the committee were not involved in the discussions around the possibility of establishing a Managed Access Scheme for esketamine but that this had been a discussion between NICE and NHSE.

74. Megan John went on to explain that only a few of the multiple uncertainties identified could be expressed as issues with cost effectiveness and so included in the ICER modelling. She noted further that, had all of the uncertainties been included, the associated assumptions would have been unacceptable to the committee. She also highlighted that some of the plausible ICERs that were presented by the ERG exceeded the NICE range of acceptability. She commented that the company's estimates of the long-term benefit and cost reduction with esketamine were based on an assumption of a reduction in costly interventions such as hospitalisation, for which there was no evidence.

75. Giles Monnickendam, for NICE, further discussed some of the uncertainties in the company's value proposition and cost modelling including the generalisability of the short-term trial data as well as the absence of data on the natural history of TRD and the long-term effectiveness data of esketamine beyond 1 year.

76. Giles Monnickendam went on to describe the structural uncertainties that had proved challenging with cost modelling and cited where these had individually been described in the FAD. He noted that (i) section 3.16 discusses the challenges associated with the generalisability to NHS clinical practice of data from the TRANSFORM-2 and SUSTAIN-1 studies; (ii) section 3.20 describes

the difficulties in determining remission and relapse rates with esketamine in view of the short 4 weeks treatment phase in the trials; (iii) section 3.21 outlines the concerns that relapse rates come from different sources with the potential introduction of bias; (iv) section 3.22 describes the changes to the cost model that were made and the concerns that the committee had expressed about the plausibility of the best model; (v) section 3.23 refers to structural uncertainties in the model that result from uncertainty about the natural history of TRD and the data that was considered to address this; (vi) section 3.24 reflects on the lack of sufficient data to populate a model that extends to 20 years; (vii) Section 3.27 discusses the uncertainty associated with the lack of data about the impact of treatment of TRD on the care burden; (viii) section 3.29 refers to the uncertainty about the impact of stopping esketamine for reasons other than lack of efficacy; (ix) section 3.30 discusses the issue of stopping therapy in real-world clinical practice; and (x) section 3.32 explains the implication on costs of the uncertainty in the time that people with TRD spend in a major depressive episode (MDE) state. He also explained that structural model uncertainties cannot be assessed quantitatively and there is no framework available to do so.

77. Giles Monnickendam, for NICE, went on to describe that all of these uncertainties and their potential impact on overall ICERs had been considered by the committee, while the ERG had undertaken a variety of scenario analyses, which are not described in full in the FAD, to assist them in this process. The committee noted that the outputs of these analyses resulted in ICERs that were substantially higher than those presented by the company and that all of these were above the acceptable NICE thresholds of £20,000 per QALY and some were considerably above £30,000 per QALY. Consequently, the committee concluded, after due deliberation, that it was unable to arrive at a plausible ICER.

78. Giles Monnickendam, for NICE, made clear that although a range of uncertainties in the evidence were encountered, the ones that were most impactful in leading to uncertainty in the ICER range were those that impacted on the long-term modelling. These included uncertainty about relapse rates, remission duration, whether people remain on esketamine with or without remission, whether relapse is managed with esketamine and, if so, what the response would be and the likely impact of all of these on costs. He also explained that the cost of a MDE was particularly influential to the output of the cost modelling and that the uncertainty was not just the cost of MDE state but also the extent to which esketamine does or does not impact on this. He further described that healthcare use data are often skewed but that in this case it was notably so and that the potential overall reduction in costs with esketamine were largely driven by a small number of patients who had received costly interventions such as hospitalisation.

79. Sarah Richards, for Janssen, expressed the view that the company's base case had not been sufficiently discussed in the FAD; that the 1-year data for esketamine that is available is unusually robust; and that while the natural history of TRD is poorly documented, the company, in collaboration with the ERG had done a variety of scenario analyses to assist the committee in their decision-making.

80. Adam Brooke, for NICE, explained that all of the clinical uncertainties were included in the ICER calculations and that these are described in section 3.17 of the FAD. He also described how the time horizon of the cost model was shortened from 20 years to as low as 1 year to try and address some of the uncertainties. Finally, he noted that section 3.41 in the FAD makes it clear that the range of ICERs presented are likely to under-estimate the true cost-effectiveness of esketamine, but that this remains highly uncertain.

81. Giles Monnickendam, for NICE, further explained that shortening of the time horizon in the model was undertaken to try and address the uncertainties in the data surrounding the natural history of TRD as

well as the possible impact of esketamine on this. He described that as the time horizon in the model was shortened, the ICERs increased significantly.

82. Sarah Richards, for Janssen, explained that the company had initially modelled a time horizon of 5 years but had extended this to 20 years at the request of the committee. Janssen had submitted data on a range of time horizons and the resulting ICERs were all in a range that NICE would normally consider acceptable. She also expressed the opinion that the FAD did not pay sufficient reference to the time horizon that is modelled, in its recommendations.

83. Jasdeep Hayre, for NICE, responded that section 3.24 of the FAD describes the approach that was taken in considering a range of time horizons but that reducing the time horizon did not appear to resolve uncertainties about the possible costs and benefits of esketamine.

84. The appeal panel concluded as follows: It was satisfied that the committee had considered and discussed extensively the range of uncertainties in the evidence, including the long-term data available, that informed the cost modelling. It was persuaded that the committee had noted the impact that long-term outcomes had had on the results of the cost modelling and the appeal panel considered that it was legitimate that they had concerns about the uncertainty of the impact of esketamine on these, in view of the data available. The appeal panel noted that actions had been taken to mitigate the uncertainties in the evidence through the undertaking of a variety of scenario analyses and through the shortening of the time horizons considered. The appeal panel was satisfied that a range of ICERs had been presented to the committee for their consideration, some of which exceeded the thresholds deemed acceptable by NICE and concluded that the committee had acted reasonably in deciding that they were unable to determine which of these was most appropriate and plausible.

85. The appeal panel therefore dismissed the appeal on this point.

Appeal Ground 2.2: The recommendation is unreasonable because of inconsistencies between technology assessments in approach to extrapolating evidence to more resistant illness.

86. Rupert McShane, for the Royal College of Psychiatrists, explained that in this appraisal, it was considered that the extrapolation from the trials in which esketamine was used as a 3rd line treatment to a scenario in which it was used as a 4th line treatment introduced uncertainty. Nonetheless, he submitted that in a previous Technology Appraisal, TA367 vorioxetine for treating major depressive episodes, a precedent had been set by accepting data extrapolation from studies that included vortioxetine as a 2nd line treatment to its consideration as a 3rd line treatment.

87. Rupert McShane went on to claim that in TA367, it was accepted that treatment with vortioxetine would be stopped in all patients after 2 years in the context of stable remission, whereas in the present appraisal, the proposal that 60% of patients would stop treatment with esketamine after 2 years was deemed unacceptable. He considered that the stated requirement for more data to inform the introduction of stopping rules was unnecessary in view of the available results from the SUSTAIN studies. Furthermore, he expressed the opinion that the introduction of treatment stopping rules in mental illness is an acceptable means of resolving uncertainty in the evidence.

88. Rupert McShane concluded that in his view the failure to maintain consistency with the approaches adopted in the previous appraisal TA367 was, in these regards, unreasonable.

89. Megan John, for NICE, explained that the previous appraisal TA367 considered a different drug, using a different approach to cost modelling to the present appraisal and that vortioxetine and esketamine have very different cost profiles. She went on to explain that the claim that was made around the inclusion of stopping rules

with vortioxetine and the inconsistency, in this regard, with the current appraisal, was a misunderstanding. She outlined that the time horizon that was considered for treatment with vortioxetine in TA367 was up to 2 years which was consistent with the episodic nature of major depression. While the cost modelling did not, therefore, extend beyond 2 years in the appraisal, this did not mean that it was assumed that all patients will have stopped treatment with vortioxetine at 2 years. In contrast, with TRD, which is a more chronic and severe condition than major depression, it was appropriate to consider a longer time horizon. The introduction of stopping rules would have mandated clinicians to stop treatment even if people were experiencing benefit. This concept appeared to be contrary to the preferences expressed by patients with TRD, who stated a need to control the duration of their treatment, rather than be subjected to a seemingly arbitrary stopping point.

90. Giles Monnickendam, for NICE, confirmed that in TA367, the original time horizon of 1 year had been extended to 2 years for the purposes of undertaking sensitivity analyses. In addition to differences in the patient population considered, he highlighted the significantly lower cost of vortioxetine as compared with esketamine and explained how this has implications not just for the cost of treating the index episode but also for the cost of treating subsequent relapses, if the same agent is used again. The higher cost of esketamine means that the cost differences between treatment with esketamine and placebo are much higher than between vortioxetine and placebo.

91. In regard to the issue of introducing stopping rules, Giles Monnickendam explained that the committee had expressed concern about the high rates of relapse that were reported after stopping treatment with esketamine in the SUSTAIN-1 study. Furthermore, no consensus had emerged from the opinions of clinical experts on the appropriateness of this strategy. Meanwhile, patient experts expressed fear and concern about the consequences of imposing

treatment discontinuation with esketamine and there was also uncertainty as to how any subsequent relapse may be managed in regard to the possibility of the repeated use of esketamine.

92. Giles Monnickendam confirmed that the stopping guidance that was proposed by the company was a major driver of the ICERs and that the removal of the stopping rules from the model led to a substantial increase in the ICER values.

93. Following questioning from the appeal panel, Helen Knight, for NICE, explained that the application of stopping rules to cancer treatments undergoing Technology Appraisal by NICE is not analogous to the present appraisal. In addition to the different modes of actions of immunotherapies as compared with esketamine, the populations under consideration are quite different. There are particular risks associated with stopping treatment in people with TRD and were this to be included, modelling of 'no further benefit' as well as the stopping costs would need to be undertaken.

94. Adam Brooke, for NICE, pointed out that the use of vortioxetine as 3rd line as opposed to 2nd line treatment could be overseen in primary care while the use of esketamine as 4th line treatment as opposed to 3rd line treatment would necessitate a move from primary to secondary care at this point in the patient pathway. This would have important resource consequences.

95. The appeal panel concluded as follows: It was satisfied that significant differences had been identified by the committee between this appraisal and the previous TA367 in regard to the nature of the drugs, population and diseases under consideration; the cost of the drugs; and the need for treatment in primary or secondary care at different points in the care pathway. It was satisfied in light of those differences that it was reasonable to adopt a different approach in the two appraisals in regard to the acceptability of data extrapolation from studies of treatment earlier in the care pathway. The appeal panel

considered that the committee had given appropriate consideration to the introduction of stopping rules into the cost model and that it had reached a reasonable conclusion in not allowing this. In any event, and for completeness, it saw no evidence in this regard of inconsistency with TA367 since the circumstances of the two appraisals were not analogous (see above).

96. The appeal panel therefore dismissed the appeal on this point.

Appeal by Janssen

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

Appeal Ground 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.

97. Jordan Talbot, for Janssen, explained that this appeal point is related to the previous one (2.2). He described how additional targeted evidence generation was undertaken by Janssen in order to submit data to the 4th committee meeting on 7 April 2022. The aim was to assist the committee in resolving uncertainties about the natural history of TRD and the generalisability of clinical trial data available.

98. He explained that the evidence generation included a prospective analysis of 49 UK patients as well as a retrospective analysis of more than 9000 patients with TRD. This had included an analysis of the DISCOVER dataset that had defined a depression duration of approximately 6 years in patients with TRD, in addition to a targeted literature review. He submitted that these data, from different sources, showed matched characteristics with patients included in the clinical trials and that they provide reproducible evidence to corroborate the relapse rates that had been considered in people with TRD in the UK. He claimed that the conclusion by the committee that

there was no long-term outcome data available in TRD to inform their decision-making is inaccurate.

99. Megan John, for NICE, explained that the residual uncertainty about the disease course of TRD is explained in detail in section 2.23 of the FAD and that this was not appealed by Janssen. She stated that there was no long-term evidence presented for each of the patient sub-groups considered and no evidence about their different long-term health states. Scenario analyses had been undertaken and considered but this did not satisfactorily resolve the uncertainties about generalisability and bias that remained in the minds of the committee.

100. In discussing the approach that was taken to assessing relapse rates, Giles Monnickendam, for NICE, explained that the company had used data from SUSTAIN-1 for the esketamine arm and data from the STAR*D trial for the placebo arm. While it was deemed appropriate not to have used relapse rates from SUSTAIN-1 for both arms, the comparison of data from 2 different trials led to concerns about the loss of the ability of the committee to legitimately judge relative treatment effect. He noted that the previously discussed TA367 had applied identical relapse rates to both arms of the model to address this issue. While the comparison made in this appraisal also introduced concerns about the generalisability of the data (the STAR*D trial had been done in the USA), he explained that the introduction of bias was of greater concern.

101. Following questioning by the appeal panel about the submission of real-world data by Janssen to address the concerns about bias, Giles Monnickendam explained that techniques can be used to adjust for the mixing of data sets from clinical trials and real-world data studies but that the concerns about bias do not go away.

102. Adam Brooke, for NICE, explained that concerns that the withdrawal design of SUSTAIN-1, which included people whose depression was

in stable response or stable remission, could introduce bias were explained in Section 3.15 of the FAD and that this had not been appealed by Janssen.

103. Giles Monnickendam, for NICE, explained that in the context of long-term outcomes, understanding the MDE health state, which leads to a significant reduction in quality of life and is a high-cost driver in the ICER calculations, is an important factor. He stated that no data was available from clinical trials about this to inform the modelling. The DISCOVER data provides insights into the duration of a single episode of depression but there is no data to understand the pattern of remission and relapse over time that determines the proportion of that time people with TRD are in the MDE health state. While data from DISCOVER could be used to validate the model, data collected over a period of up to 5 years in regard to remission and relapse is needed to accurately populate a Markov model. These data are not currently available.

104. Adam Brooke, for NICE, described how section 3.23 of the FAD outlines the uncertainties that exists with the disease course of TRD and how these related to the modelling that was undertaken. He explained that input from clinical experts had suggested that there were elements of the model that deviated from standard clinical practice, for example the short 4-week treatment cycle that was used which was said to be considerably shorter than the time period of up to 6 months that is not unusually required to determine treatment efficacy.

105. Giles Monnickendam, for NICE, confirmed that attempts had been made to validate the model with clinical experts but no consensus was seen on important issues, for example how to define the start and finish of episodes of depression. The absence of consensus appeared to reflect a general lack of a clear understanding of the natural history of TRD amongst the experts. He went on to explain

that this was the rationale behind the research recommendations that were proposed by the committee in section 4.

106. Rupert McShane, for the Royal College of Psychiatrists, explained that while it might take 6 months to determine if a treatment works, with esketamine, clinicians may be prepared to make decisions at earlier time points because the treatment response appears to be rapid and binary.

107. The appeal panel concluded as follows: It recognised that Janssen had attempted to forward an understanding of the natural history of TRD and justify the assumptions that it had made in the cost modelling about long-term outcomes through the undertaking of additional targeted evidence generation prior to the 4th committee meeting on 7 April 2022. The appeal panel was satisfied that the committee had considered the new submitted data appropriately and noted that the committee had identified legitimate and significant residual uncertainties in regard to long-term outcomes in patients with TRD, the likely benefits of esketamine, and the legitimacy of the cost model outputs. The appeal panel concluded that the committee had acted reasonably in this regard.

108. The appeal panel therefore dismissed the appeal on this point.

Appeal Ground 2.6 (Original 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 market authorisation for the product.

109. This appeal point was originally made under ground 1(b), but was accepted for appeal under ground 2, 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).

110. Adela Williams, for Janssen, explained that this appeal point relates to the content of section 1 of the FAD. In the text that describes why the committee had made its recommendations, it was stated that when used in patients who had had treatment with at least 3 OADs, the clinical trial evidence suggests that esketamine may be more effective than placebo but that this was very uncertain. She further explained that esketamine had been granted market authorisation by MHRA, EMA and the FDA and submitted that this statement was therefore at odds with the judgements of the regulators. She also clarified that although only a subset of patients included in the regulatory trials were considered in this appraisal, this group were nonetheless covered by the wider regulatory approval.

111. Adela Williams also re-iterated the points that she had previously made during the consideration of appeal point 1b.2, namely that while regulators are responsible for assessing safety, quality and efficacy for a technology, it is the role of NICE to assess its clinical and cost effectiveness as well as the magnitude and acceptability of any benefits.

112. She therefore concluded that NICE had acted unreasonably by making this statement in section 1 of the FAD.

113. Megan John, for NICE, stated that the committee had not ignored the regulatory process undertaken by MHRA in making this statement. She explained that the section in which this sentence appears is a summary that is intended for a lay reader and which provides the rationale for the committee's decision-making in language that is simple and easy to understand. The intention is that this section is seen in context of the entirety of the clinical evidence considered and the whole of the FAD and does not refer to all of the details of the committee's conclusions. The section is intended to convey that the evidence overall is uncertain, not the regulatory conclusion that the drug is more efficacious than placebo within its marketing

authorisation. She stated that she would be happy to accede to a re-wording of this section.

114. Adam Brooke, for NICE, confirmed that this rationale section of the FAD is crafted in a clear and concise way according to a defined editorial structure. He made the point that had the dissatisfaction with this text been raised by Janssen during the consultation process then NICE would have altered it.

115. Adela Williams, for Janssen, made the point that just because this section is directed at lay readers, does not mean that it should not be accurate. Furthermore, she explained that this is an early part of the FAD and may, therefore, be very influential in the minds of the reader.

116. Helen Knight, for NICE, said that she would consult with the editorial team at NICE to ensure that committees have control of the wording of this section of the FAD in the future. She also expressed the view that this is a matter that could have been reasonably raised by Janssen during the consultation process and that the process of an appeal is not the only route to resolve such an issue.

117. The appeal panel concluded as follows: It accepted the explanation that was given by NICE about the statement in section 1 of the FAD that refers to uncertainty about the totality of evidence for effectiveness of esketamine for people with TRD. The appeal panel accepted that this section is directed at lay readers and summarises the reasons why the committee had made its recommendations in language that is concise and easy to understand. The appeal panel was satisfied that the statement had not been intended to question the judgement of the regulators in regard to the efficacy of esketamine and it noted and accepted the proposals that had been made by NICE to alter the wording accordingly.

118. The appeal panel therefore dismissed the appeal on this point.

119. The appeal panel support the proposal made by NICE to re-word the lay summary component of section 1 in order to remove any doubt about their focus on assessing the clinical and cost effectiveness of esketamine in this appraisal rather than its efficacy.

Conclusion and effect of the appeal panel's decision

120. The appeal panel therefore upholds the appeal of Janssen on appeal point 1a.1(b) that NICE failed to act fairly in not providing sufficient explanation of how the uncertainties in the evidence that are inherent to clinical trials in mental health were taken into account in its decision-making. The appeal is dismissed on all other grounds.

121. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to explain more clearly how the uncertainties in the evidence inherent in clinical trials were taken into account in their reasoning and decision-making or the extent to which they were or were not disregarded. Furthermore, the appeal panel consider that it would be helpful for the committee to explain its conclusions about which uncertainties are potentially resolvable and those that are not since this might inform future trial design in this important disease area.

122. The appeal panel draws to the attention of NICE paragraphs 45, 70 and 119 of this letter in which specific areas are discussed where re-wording of the FAD might be considered.

123. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within 3 months of NICE publishing the final guidance.