NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Health Technology Appraisal

Appeal Hearing

Advice on adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a previous TNF-α inhibitor (sequential use).

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 29th September 2008 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a previous TNF-α inhibitor (sequential use).

2. The Appeal Panel consisted of Mark Taylor (chair of the Panel), Professor Patrick Morrison (non-executive director of the Institute), Sir Michael Rawlins (chairman of the Institute), Peter Sanders, (lay representative), Dr David Webster (industry representative). Dr Andrew Fairburn was present as an observer.

3. The Panel considered appeals submitted by:

    Abbott Laboratories
    Arthritis and Musculoskeletal Alliance
    National Rheumatoid Arthritis Society
    Royal College of Nursing
    Schering Plough
    Wyeth Pharmaceuticals

4. In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor David Barnett (chair of the Appraisal Committee), Dr Carole Longson (Director, Centre for

Health Technology Evaluation), Allan Wailoo (Decision Support Unit), Ms Zoe Garrett, and Ms Elisabeth George.

5. The Institute's legal advisor (Stephen Hocking, Beachcroft LLP) was also present.

6. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and a number of members of the public were present at this appeal.

7. There are three grounds on which an appeal can be lodged:

   The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process;

   The Institute has prepared guidance that is perverse in light of the evidence submitted;

   The Institute has exceeded its legal powers.

8. The chair of the Appeals Committee (Mr Mark Taylor), in preliminary correspondence, had confirmed that the appellants had potentially valid grounds of appeal as follows:

   Royal College of Nursing – grounds 2 and 3

   Abbott Laboratories – grounds 1 and 2

   Arthritis and Musculoskeletal Alliance – ground 2

   National Rheumatoid Arthritis Society – ground 2

   Schering Plough – grounds 1, 2 and 3.

   Wyeth Pharmaceuticals – grounds 1 and 2.

   (All references to appeal point numbers in this letter are taken from the respective appellant's appeal letter.)

Appeal Ground 1: The Institute has failed to act fairly and in accordance with its procedures

Abbot

Appeal points 3.6 to 3.8

9. The appellant alleged that the Institute had failed to provide a fully executable version of the economic model used in the appraisal. The Appellant argued that the effect of the Court of Appeal decision in R ota Eisai v NICE is that procedural fairness always requires the release of such models. The appellant stated that its ability to analyse the impact of proposed changes was significantly restricted in the absence of such a model.

10. The Panel noted that the Eisai judgement was currently under appeal to the House of Lords. The Panel noted that the Institute's position was that the Eisai judgement was incorrectly decided as a matter of law. The Panel was also aware that unless and until successfully appealed, a Court of Appeal judgement remains in effect. Finally the Panel noted that the Court of Appeal in Eisai had not ordered any disclosure of the economic model in that case at this time, pending resolution of the appeal to the House of Lords.

11. The Appeal Panel concluded that, notwithstanding the strict legal position that the Court of Appeal judgement remains in effect, there is currently uncertainty as to whether it will be found to have correctly stated the law. The Panel observes that, in a very similar situation, the Court of Appeal itself did not require the release of a fully executable model, pending resolution of that uncertainty. The Panel decided that this was the correct approach in this case also.

12. The Panel therefore makes no finding on this point. When the appeal in the Eisai case is concluded, the Panel will expect the Institute to consider what steps

may be necessary, if any, in connection with access to a fully executable version of the economic model used in this appraisal.

Schering-Plough

Appeal point 1.1

13. The appellant alleged that the process for this appraisal was unfair and contrary to the Institute's procedures. The appellant stated that the Institute regarded this present appraisal, on the sequential use of anti-TNFs, as a continuation of the previous appraisal published as TA130. The appellant claimed that the present appraisal departed, significantly, from the scope of the original one (November 2004) which covered first line, as well as subsequent, use of anti-TNF drugs in the treatment of rheumatoid arthritis. The current appraisal did not conform to the November 2004 scope and the Institute should have therefore invited consultees, including the appellant, to submit additional evidence and to have taken this into account in the present appraisal. Failure to do so had been unfair.

14. In response to questions from the appeal panel, the appellant indicated that it sought to submit a revised economic model as well the results of a new clinical study, but that it had been precluded from so doing.

15. Dr Longson indicated that the Institute had considered, at great length, whether the present appraisal constituted an extension of the existing appraisal (with its November 2004 scope) or whether it constituted a new appraisal. The Institute had concluded that the present appraisal was an extension of the existing appraisal and not a new one requiring a new scope. Nevertheless, this decision did not have the effect, necessarily, of preventing appellants from submitting significant new data.

16. Professor Barnett stated that the Appraisal Committee had discussed the totality of the available evidence on clinical and cost effectiveness. He

accepted, however, that this would not have included unpublished information of which the committee had been unaware.

17. The appeal panel considered that the present appraisal departed significantly from the original November 2004 scope. In particular, the present appraisal included comparisons with rituximab; and this could not have been reasonably inferred from amongst the comparators identified in the November 2004 scope[1]. The panel accepted that, in November 2004, rituximab had not been available for the treatment of rheumatoid arthritis. Rituximab, however, has now been recommended for use, in the NHS, for patients with rheumatoid arthritis who have failed to respond to an anti-TNF product. Moreover, rituximab has different biological properties to those of the anti-TNF drugs that are the subject of the present appraisal.

18. Furthermore, the appraisal committee appears to have identified and used a new data set (the US national databank for rheumatic diseases), and yet it has not given consultees an opportunity to submit any new data which they may have. The panel noted other changes between TA 130 and this appraisal, for example in discount rates.

19. The panel considers that the committee had a range of options open to it following the appeal in TA130. The Panel makes no criticism of the decision to split the appraisal at that time. The Panel's view is that it was not necessary to consult on that decision per se, as the effect of it was merely to issue guidance that was within the terms of the original scope, albeit that it did not discharge the whole of the original scope.

20. If the committee wished to analyse sequential use as part of that same appraisal, (which again would not be a decision requiring consultation) then it was incumbent on it to do so under the same scope, using the same evidence

[1] Had rituximab been used only as a cross check for broad consistency between different appraisals, this would have been acceptable without the need for further consultation or evidence. However the appraisal committee candidly admitted that the role played by rituximab in this appraisal went deeper than this.

base, and using the same methodology as applied to the guidance which had been published. Alternatively it was open to the committee to conclude that the scope, evidence base or methodology might be unsuitable for an appraisal of sequential use, in which case a new appraisal should have been begun, with the usual opportunities for consultation and submission of evidence. This last course of action would also require consultation as to whether it should be adopted at all.

21. In light of the fact that the committee had considered new evidence, introduced a new comparator, and introduced other changes, the panel concluded this could not be considered a continuation of TA130 and that the Institute should have consulted on, and then issued, a revised scope. The Institute's failure to do so had placed consultees, including the appellant, at a disadvantage, and was also a failure to adhere to published procedures. (Furthermore consultees should have been given the opportunity to argue that rituximab should not have been used as a comparator, and they were denied that opportunity.)

22. The appeal panel therefore upheld the appeal on this point. The appeal panel considered that the topic should be re-scoped and that the Institute's normal procedures and methods, for a multi-technology assessment, should then follow. This should include invitations to consultees for submission of evidence, re-modelling if necessary and the development of new draft guidance for consultation.

Appeal point 1.2:

23. The appellant alleged that the Institute had failed to provide a fully executable version of the economic model used in the appraisal. The Appellant argued that the effect of the Court of Appeal decision in R ota Eisai v NICE is that procedural fairness always requires the release of such models. The appellant stated that it was unable to test the model thoroughly without access to its source code.

24. The Panel noted that the Eisai judgement was currently under appeal to the House of Lords. The Panel noted that the Institute's position was that the Eisai judgement was incorrectly decided as a matter of law. The Panel was also aware that unless and until successfully appealed, a Court of Appeal judgement remains in effect. Finally the Panel noted that the Court of Appeal in Eisai had not ordered any disclosure of the economic model in that case at this time, pending resolution of the appeal to the House of Lords.

25. The Appeal Panel concluded that, notwithstanding the strict legal position that the Court of Appeal judgement remains in effect, there is currently uncertainty as to whether it will be found to have correctly stated the law. The Panel observes that, in a very similar situation, the Court of Appeal itself did not require the release of a fully executable model, pending resolution of that uncertainty. The Panel decided that this was the correct approach in this case also.

26. The Panel therefore makes no finding on this point. When the appeal in the Eisai case is concluded, the Panel will expect the Institute to consider what steps may be necessary, if any, in connection with access to a fully executable version of the economic model used in this appraisal.

Wyeth

Appeal point 1.1

27. The appellant alleged that the Appraisal Committee had been inequitable in its use of the data from the British Society of Rheumatology's Biologicals Register (BSRBR). In particular, it had been unclear as to why the committee had used data relating to the use of anti-TNF drugs, but not that for disease modifying anti-rheumatic drugs (DMARDs), from the BSRBR data. Furthermore, although the committee appeared to have been prepared to accept the data from the DMARD arm of the ReACT study it rejected the use of the anti-TNF arm of

this same study. This was unfair and contrary to the Institute's published procedures.

28. Professor Barnett explained that although the BSRBR data had been extraordinarily useful to the Appraisal Committee, in this appraisal, the data on the use of DMARDs were difficult to assess. The DMARDs that patients received was unclear; and, anyway, according to the BSRBR data there was no apparent response to them. This, in the committee's view, was implausible.

29. The appeal panel accepted that there had been a wide array of clinical data for the appraisal committee to consider. It also accepted that the committee had thoroughly explored the evidence available to it. Nevertheless, the panel did not consider that the FAD had described, with sufficient clarity, which of the available data the committee used in drawing its conclusions about the clinical and cost effectiveness of the sequential use of anti-TNF drugs. The panel felt it was possible that the fairness of consultation during the appraisal could have been affected as a result.

30. The appeal panel therefore upheld the appeal on this point. At the completion of the re-appraisal of the sequential use of anti-TNFs, the FAD should clearly indicate which data the appraisal committee uses to base its final conclusions on their clinical and cost effectiveness. The committee should consider whether and to what extent it also needs to give reasons for its choice of data, although the panel is mindful that it is legitimate to be concerned that the FAD should not become over-long.

Appeal point 1.2

31. The appellant claimed that in the appeal panel's decision letter of April 2007, on the use of anti-TNF drugs, indicated that the guidance on sequential use should be reconsidered. In the view of the appellant, that appeal panel had suggested that this should include a reassessment of the evidence for the cost effectiveness of a second anti-TNF drug with a more complete examination of

the minimum effectiveness that would be required for it to be marginally cost effective. This had not been conducted in a transparent way and, in the view of the appellant, the appraisal committee was not able to reach a robust and informed decision. The appellant had conducted their own analysis but this had not been accepted by the Institute for consideration by the committee.

32. In view of this appeal panel's findings in paragraphs 22 and 30 (above) the panel upheld the appeal on this point.

Appeal point 1.3

33. The appellant claimed that the failure to include offset costs (ie costs associated with joint replacements etc), although included in the original sensitivity analyses in TA130 as well as in the evaluation of the use of rituximab (TA126), introduced bias against the sequential use of sequential anti-TNF drugs.

34. Professor Barnett explained that the offset costs had not been included because they added little to the overall cost effectiveness of the sequential use of anti-TNF drugs.

35. The appeal panel did not accept this as a valid argument in this case. If, as argued by Dr Longson (paragraph 14), this was a continuation of the original 2004 appraisal then the consultees could have reasonably expected it to have been carried out in the same manner even if some elements, in retrospect, contributed little to the economic evaluation. (As noted above, the appeal panel does not agree that this was in substance a continuation of T130. Had that explicitly been the committee's intention, it might have been open to the committee not to have included offset costs. However, the committee's case was that it was seeking to carry out a continuation of TA130, and in that context the panel finds that it acted unfairly).

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

Appeal point 1.4

37. The appellant claimed that the use of different discount rates (FAD 4.3.15) in this appraisal, compared to that in T130, was a breach of the Institute's procedures and was unfair. On its own admission, the committee accepted FAD 4.3.15) that this would alter the estimates of incremental cost effectiveness.

38. Professor Barnett explained that sensitivity analyses had included changing the discount rates to 6% (costs) and 1.5% (benefits) without changing its conclusions about the cost effectiveness of sequential anti-TNF drugs.

39. Again, the appeal panel did not accept this as a valid argument. If this was a continuation of the original 2004 appraisal, the consultees could have reasonably expected it to have been carried out in the same manner even if some elements, in retrospect, contributed little to the economic evaluation. (As noted above, the appeal panel does not agree that this was in substance a continuation of T130. Had that explicitly been the committee's intention, it might have been open to the committee to change the discount rates. However, the committee's case was that it was seeking to carry out a continuation of TA130, and in that context the panel finds that it acted unfairly)

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

Appeal point 1.5

41. The appellant alleged that inclusion of rituximab as a comparator in this appraisal was unfair. At the time this appraisal started, in 2004, rituximab had not been licensed for this indication and could not have been considered to be a "current standard comparator".

42. The appeal panel, noting its conclusions in paragraphs 22 and 30(above), upheld the appeal on this point.

Appeal point 1.6

43. The appellant claimed that the cost effectiveness of rituximab, in comparison with anti-TNF drugs, had not been adequately established in accordance with the Institute's procedures and methods. In particular, the appellant had claimed to possess evidence that, in routine clinical practice, the treatment intervals for rituximab were more likely to be 7 months rather than 9 months. As a consequence, the cost per QALY of anti-TNF drugs compared to rituximab, were likely to be lower than those reported by the committee. The appellant had not, however, been permitted to submit this evidence.

44. The appeal panel, noting its comments and conclusions in paragraphs 22 and 30, upheld the appeal on this point.

Appeal point 1.7

45. The appellant alleged that, by including rituximab as a comparator in this appraisal, the November 2004 scope could no longer be considered to be relevant to the appraisal of the sequential use of anti-TNF drugs.

46. The appeal panel, noting its comments and conclusions in paragraphs 22 and 30, upheld the appeal on this point.

Appeal Ground 2 – The Institute has prepared a Final Appraisal Determination that is perverse in the light of the evidence submitted

Abbott

Appeal point 3.1 – 3.5

47. The appellant alleged that the Institute had acted unfairly by failing to give due consideration to the impact of joint replacement costs, costs of outpatient visits

and inpatient stays on estimates of the cost effectiveness of sequential ant-TNF drugs. This was particularly so, given that these were included in the appraisals of anti-TNF drugs for first-line use (TA130) and of rituximab (TA126).

48. The appeal panel noted its findings in paragraphs 33-36 (above). Whilst it has found that the failure to include these costs constituted unfairness given the procedural history of this appraisal, the appeal panel did not consider the appraisal committee to have been perverse in not including them. In the circumstances confronting them, the committee had exercised its judgement about the appropriateness of including or excluding certain costs in appraising the cost effectiveness of anti-TNF drugs for sequential use. In this situation the committee's approach could not reasonably be considered to have been perverse, even if it was unfair.

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

Appeal points 4.1-4.5

50. The appellant alleged that the data used in the modelling of the effectiveness of conventional DMARDs do not reflect the effectiveness of conventional DMARDs in clinical practice. In particular, the use of the HAQ multipliers in the BRAM model is perverse in the light of the evidence of the minimal impact of conventional DMARDs from the BSRBR, BROSG and US National Databank for Rheumatic Diseases.

51. Professor Barnett explained that the appraisal committee examined a number of sources of data about the effectiveness of DMARDs in patients who were unresponsive to a first-line anti-TNF. The committee considered that no response to DMARDS was implausible, and considered that the most plausible response was that in the placebo arm of the abatacept study. In response to questions from the panel he accepted that this would include an element of a "placebo" effect but that nevertheless, in the judgement of the committee this provided the least unreliable source of evidence.

52. The appeal panel accepted that this had, from a scientific standpoint, been an extraordinarily difficult appraisal; and that the committee had been required to select data from a variety of sources in order to reach its conclusions. In selecting the placebo arm of the abatacept study the committee had exercised its best judgement and the panel felt that the committee could not be regarded as having acted perversely albeit as noted above the FAD did not provide sufficient clarity about why the committee accepted some, and not other, data that it examined.

53. The appeal panel therefore rejected the appeal on this point but upheld it on unfairness.

Arthritis and Musculoskeletal Alliance

Appeal point 1:

54. The appellant alleged that the appraisal committee had been perverse in failing to apply critical assessment of the BRAM model; and accepting the conclusions of this model to the exclusion of other analyses. In particular, reliance on the HAQ data underestimates the clinical effectiveness because the HAQ correlates most closely with disease duration. The magnitude of benefit, as assessed from the HAQ data will therefore be limited but the improvement in quality of life in relation to pain and stiffness may be substantial. Furthermore, using the placebo response from the abatacept trial was inappropriate because of the inherent contribution of a "placebo effect". Finally the HAQ is a non-linear scale. Changes in high scores may be more important for quality of life than changes in low scores.

55. Professor Barnett stated that the appraisal committee had been fully aware of the problems inherent in using the HAQ score and fully accepted its limitations. The committee had also examined, carefully, other published models (including that by Brennan et al, Rheumatology 2007; 46: 1350). In response to

questioning by the panel, he also accepted that the HAQ might not necessarily capture significant elements of overall quality of life. The committee, however, had to form a judgement about which data it could most appropriately use in the assessment of clinical efficacy and had done so to the best of its ability.

56. The panel accepted (see paragraph 43 above) that the committee was entitled, indeed forced, to make a judgement about the most appropriate data and models that should underpin its conclusions. The panel did not consider the committee had been perverse in its judgement. Nevertheless, the panel considered that the FAD did not indicate, with sufficient clarity, which data the committee regarded as most appropriate and why it reached that conclusion. Whilst this did not constitute perversity, as noted above it did amount to unfairness to the consultees.

57. The appeal panel therefore rejected the appeal on perversity, but upheld it on unfairness.

Appeal point 3:

58. The appellant alleged that the appraisal committee's rejection of sequential use because of the lack of evidence (FAD 4.3.3) was perverse. The ReACT and BSRBR studies included 899 and 6,318 patients respectively. The BSRBR data included 446 and 496 patients who switched from their first anti-TNF therapy due respectively to either an adverse event or a lack of response.

59. Professor Barnett explained that the comment in FAD 4.3.3 related not to the numbers of patients but to the quality of the evidence from which the committee had to draw conclusions.

60. The appeal panel accepted that the appraisal committee had had to appraise the clinical and cost effectiveness of sequential use of ant-TNF drugs using data from a variety of sources. The fact that there were substantial limitations to the evidence base was a reasonable comment and not perverse.

61. The appeal panel therefore rejected the appeal on this point.

National Rheumatoid Arthritis Society

62. The appellant alleged that the guidance failed to take account of the interests of patients with sero-negative rheumatoid arthritis. Such patients had virtually no response to rituximab and so were left without any therapeutic alternative if anti-TNF drugs were unavailable to them. In response to questioning, the appellant stated that for sero-negative patients, who would probably derive little or no benefit from treatment, the risks of rituximab were too adverse to even contemplate a trial of this therapy in this patient sub-group.

63. Professor Barnett stated that the appraisal committee were aware that sero-negative patients had a poor response to rituximab (FAD 4.3.20). He accepted that, in estimating the cost effectiveness of rituximab, the committee had not distinguished between sero-positive and sero-negative patients. He pointed out, however, that to do so would not improve the cost effectiveness of rituximab versus a second anti-TNF drug.

64. The appeal panel, though acknowledging Professor Barnett's point, were concerned that the committee had not paid specific attention to patients with sero-negative rheumatoid arthritis. For such patients the evidence relating to rituximab would appear to be irrelevant, yet the FAD implied that rituximab had been considered in the context of all patients. This would amount to taking into account an irrelevant factor, and hence perversity, as regards sero-negative patients. In developing new guidance on the sequential use of anti-TNF drugs the appraisal committee should give special consideration to this group of patients, and in particular must not have regard to the availability of rituximab. However the panel stresses that whether or not this should result in any special guidance applying to these patients will be a matter for the committee in its discretion.

65. The appeal panel upheld the appeal on this point.

Royal College of Nursing

Appeal point 1-5:

66. The appellant alleged that the recommendations failed to take account of the offset cost in the analysis of the sequential use of anti-TNF drugs. In TA130 (para 4.3.9) the committee had concluded that the inclusion of benefits related to the reduction in hospitalisations and long-term requirement for joint replacement, although as yet based on unproven assumptions, was an important factor to be taken into account in the costs associated with the treatment of RA.

67. The appeal panel, noting Professor Barnett's previous comments, and its own conclusions, in paragraphs 33-36 (above) accepted that the failure to include these costs constituted unfairness but did not consider the appraisal committee to have been perverse. In the circumstances confronting them, the committee had exercised its judgement about the appropriateness of including or excluding certain costs in appraising the cost effectiveness of anti-TNF drugs for sequential use. In this situation the committee could not reasonably be considered to have been perverse even it was unfair of them to have do so.

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

Appeal point 6-10

69. The appellant alleged that the choice of which of the three drugs under consideration would be prescribed first for a patient was arbitrary. It was arbitrary which drug would be tried first, and arbitrary as to whether there may be a toxic reaction allowing the patient to try a second drug. Further guidance should be given as to the order in which drugs should be tried and/or when a patient may switch between drugs.

70. The appeal panel concluded that there was no good evidence that would justify a recommendation as to trying these drugs in any particular order, and further noted the committee's usual practice of appraising drugs as a class unless there were clear reasons not to do so. The panel felt that failure to recommend an order of treatment when there was no good evidence to support such a recommendation was not arbitrary. The panel also felt that it was not correct to describe the possibility of a toxic reaction as "arbitrary". No doubt it was uncertain which patients would experience such a reaction, but the recommendation that patients who were unable to complete treatment for six months because of a toxic reaction should switch to another anti-TNF could not be described as arbitrary. Switching was a response to an event. The panel rejected the argument that clinicians needed guidance as to what did or did not constitute a toxic reaction, as this should be well within their clinical ability to judge objectively.

71. The panel rejected the appeal on this ground.

Schering-Plough

Appeal point 2.1:

72. The appellant alleged that the use of the placebo arm of the comparison with abatacept study to demonstrate the effectiveness of DMARDs in sequential use of anti-TNF drugs was perverse. The appellant further claimed that this was likely to underestimate the incremental effect of anti-TNF drugs.

73. The appeal panel, noting Professor Barnett's comments as well as its own conclusions and findings in paragraphs 50-53 and 54-57 (above) considered that the appraisal committee had not been perverse.

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

Appeal point 2.2:

75. The appellant claimed that the appraisal committee had failed to take proper account of the fact that patients with rheumatoid arthritis who are sero-negative do not respond as well to rituximab as those who are sero-positive.

76. The appeal panel, noting Professor Barnett's comments as well as its own conclusions and findings in paragraphs 62-65, upheld the appeal on this point.

Wyeth

Appeal points 2.1 and 2.2:

77. The appellant alleged that the failure of the appraisal committee to base its estimate of the cost effectiveness of the anti-TNF products on the BSRBR was perverse. The appellant claimed that it would have been more appropriate for the effectiveness of DMARDs, after the failure of a first anti-TNF drug, to have been estimated from the BSRBR data rather than from the placebo arm of the abatacept study. If this had been done, the appellant considered that the incremental cost effectiveness ration would have been less than £30,000 per QALY. Moreover, given that the mean HAQ change across of the entire group of patients given DMARDs was zero, the claim in FAD 4.3.7 ignores the fact that some patients deteriorated on DMARDs.

78. The appeal panel, noting Professor Barnett's comments as well as its own conclusions and findings in paragraphs 50-53 and 54-57 (above), considered that the appraisal committee had not been perverse in its use of the evidence available to it..

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

Appeal point 2.3:

80. The appellant alleged that the failure to incorporate offset costs in this appraisal was perverse. The appellant considered that the fact that the offset costs had no significant impact on the ICERs for the first appraisal (TA130) did not justify their omission from this appraisal.

81. The appeal panel, noting Professor Barnett's previous comments, and its own conclusions, in paragraphs 33-36 (above) accepted that the failure to include these costs constituted unfairness but did not consider the appraisal committee to have been perverse. In the circumstances confronting them, the committee had exercised it judgement about the appropriateness of including or excluding certain costs in appraising the cost effectiveness of anti-TNF drugs for sequential use. In this situation the committee could not reasonably be considered to have been perverse even it was unfair of them to do so.

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

Appeal points 2.4 and 2.5:

83. The appellant claimed that the discount rates used in this appraisal, compared to that in TA126 and TA130, had the effect of giving undue weight to clinical effectiveness. This, in the view of the appellant, was perverse.

84. The appeal panel, taking account of Professor Barnett's comments and the panel's own conclusions in paragraphs 37-40 (above), considered that although the use of different discount rates in this appraisal constituted unfairness it did not amount to perversity by the appraisal committee. Although the committee was expected take account of the discount rates in the Institute's published methods there might be circumstances where these should be changed if, in the committee's judgement there was a valid reason for doing so.

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

Appeal point 2.6:

86. The appellant alleged that the appraisal committee had been perverse in failing to identify patient subgroups in whom sequential anti-TNF drugs might be cost effective. In particular, the committee had failed to give sufficient weight to the evidence from the ReACT study demonstrating that secondary failures showed greater effectiveness from the sequential use of anti-TNFs than primary failures.

87. The appeal panel considered that it was a matter for the appraisal committee to make reasonable judgements about the appropriateness of the available data to elucidate particular issues; but that it should explain its reasons for so doing. In this instance the panel did not consider that the committee had necessarily been perverse in not identifying subgroups, but it concluded that the committee had failed to provide sufficient justification for its decision. In dismissing the appeal on this particular point the panel nevertheless considers that the committee failed to provide sufficient reasoning for its decision. This constituted unfairness, and the appeal would be upheld on that ground.

Appeal point 2.8:

88. The appellant alleged that the failure of the appraisal committee to use the DMARD efficacy data from the BSRBR in combination with the ReAct data for the anti-TNF drugs was perverse. The appellant claimed that the selective use of the inputs, in this appraisal, had resulted in bias.

89. The appeal panel noted above that it is a matter for the committee which data it uses to base its conclusions on, provided its choices can be rationally justified. The appellant's preferred combination of data sets may be a rational alternative choice, but this did not lead the appeal panel to conclude that the choice made by the appeal panel was irrational.

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

Appeal point 2.9:

91. The appellant alleged that some HAQ improvements had been inappropriately extrapolated from the ReAct study. In particular, the evidence from the Assessment Groups indicated that the effectiveness of the sequential use of anti-TNFs differed between individual products. The approach used by the appraisal committee had resulted in an underestimate of the effectiveness of etanercept.

92. The appeal panel accepted that the appraisal committee had considered this issue carefully. Indeed FAD 4.3.15 specifically commented on the approach suggested by the appellant but, in the committee's judgement, the enrolment in the ReAct trial could have affected the effectiveness data. The panel did not consider that this was perverse.

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

Ground 3: The Institute has exceeded its legal powers

Royal College of Nursing

Appeal points 11-16

94. The appellant argued that a recommendation that drugs should be used only in the context of research was discriminatory and/or failed to take account of positive "due regard" anti-discrimination duties, in as much as persons with learning difficulties, and people from ethnic minorities, were less likely to participate in clinical trials.

95. The panel felt this argument was ill founded. It accepted that for certain forms of trials there would be certain populations who would undoubtedly be

less likely to participate. The reasons for this would vary. However it noted that there was no question of direct discrimination. Where the reason for exclusion related to eligibility for enrolment (for example, requirements as to informed consent might have the effect of excluding persons with severe learning difficulties from a trial) the panel took the view that any indirect discrimination there may be is justified in pursuit of the legitimate objective of obtaining valuable trial data, and the need to conduct on trials on an ethical basis. Where the reason for exclusion may be societal (as may be the case with some ethnic minority populations) the panel took the view that it was the responsibility of researchers to take all reasonable steps to ensure that participation in a trial was available to all on an equal basis. The possibility that this may not be achieved could not constitute illegality on the part of the committee, who are entitled to assume that trials will be well designed and conducted within the bounds of all relevant legislation. Given the very general nature of the recommendation, no specific advice could have been given on this point, and a general instruction to avoid unlawful discrimination would have added nothing of value to the guidance.

96. The panel also observes in passing that the argument assumes that participation in a trial is a benefit, which would not necessarily be the case for all forms of trial.

97. The panel therefore rejects the appeal on this point.

Schering-Plough

Appeal point 3.1

98. The appellant argued that in changing the scope of this appraisal the Institute had exceeded its powers.

99. The appellant indicated that this argument was in the alternative to its main point, which was that the appraisal as conducted was unfair in that a number of

changes had been made from the appraisal published as TA130 without consultation or a call for further evidence. As the panel has agreed that this was unfair, and has upheld the appeal on those ground, there is no need to make a finding on this point.

Conclusions

100. The appeal panel upholds this appeal on Grounds 1 and 2. In particular, the panel considers that the Institute should not have regarded this appraisal as a continuation of the one scoped in November 2004 and published, in part as TA130. Instead, especially in the light of the inclusion of rituximab as a comparator, which could not have been reasonably inferred from the November 2004 scope, the sequential use of anti-TNF should be restarted as a new appraisal. Advice from officials at the Department of Health should be sought as to whether a new formal referral from ministers is required.

101. The panel accepts that this appraisal is one of considerable complexity requiring the exercise of considerable judgement by the appraisal committee. The committee is well constituted to make such judgements but, when doing so, it should explain with greater clarity the reasons for its conclusions.

102. The Appeal Panel acknowledges the strenuous efforts of the Appraisal Committee to bring this assessment to a supportable conclusion. Nevertheless the complex and controversial issues involved have led to an unusually protracted process, with many patients no doubt awaiting the final outcome. The Panel therefore hopes that the Appraisal Committee and the Institute will take every responsible step to complete the re-appraisal now required as soon as reasonably possible

103. There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel and the Institute's decision to issue the Guidance may be challenged by an interested party through an application to the High Court for permission to apply for

judicial review. Any such application must be made promptly and in any event within three months of this Decision.