

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease

Appeal by the Alzheimer's Society, Age Concern, Counsel and Care, the Dementia Care Trust and the Royal College of Nursing

Decision of the Appeal Panel

1. Introduction

- 1.1. The Appeal panel convened a hearing on 13 and 14 July 2006 to consider an appeal against the Institute's Guidance to the NHS on the use of donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease, as set out in the Final Appraisal Determination produced by the Appraisal Committee ("**the FAD**").
- 1.2. The Appeal Panel comprised Dr Susanna Lawrence (Chair of the Appeal Panel and Vice Chairman of the Institute's Board), Mr Frederick George (non-executive member of the Institute's Board), Ms Jean Gaffin (Patient Representative), Mr Roy Luff (non-executive member of the Institute's Board) and Professor Peter Stonier (Industry Representative).
- 1.3. The appeal was lodged by the following appellant: the Alzheimer's Society, Age Concern, Counsel and Care, the Dementia Care Trust and the Royal College of Nursing.
- 1.4. The following individuals involved in the appraisal were present to answer questions from the Appeal Panel: Professor Andrew Stevens (Chair), Dr. Carole Longson (Director, Centre for Health Technology Evaluation), Mr Andrew Dillon (Chief Executive, National Institute for Health and Clinical Excellence), Mr. Meindert Boysen (Technical Lead, National Institute for Health and Clinical Excellence), Alec Miners (ex- Technical Lead), Dr Karl Claxton (Committee Member), Dr John Geddes (Committee Member) and Mr Julian Gizzi (legal representative)

1.5. The three grounds on which the Appeal Panel can hear an appeal are:

- (1) The Institute has failed to act fairly and in accordance with its procedures;
- (2) The Institute has prepared guidance which is perverse in the light of the evidence submitted; and
- (3) The Institute has exceeded its powers.

1.6. Over the course of the two day hearing, the Panel heard a large volume of information regarding Alzheimers disease, the technologies under appraisal, the lengthy process that had taken place since the scope for the appraisal was first identified in January 2004, and the deliberations of the Committee in reaching their conclusions.

1.7. The Panel were aware of the devastating nature of Alzheimer's disease, and the severe distress and difficulty caused to patients, carers, and family members. They were informed of the specific nature of the technologies, namely that some treatment benefit for some patients was established, but that this was small and time limited, and served to ameliorate the symptoms of the disease rather than prevent deterioration.

1.8. They recognised the dilemma facing the Appraisal Committee, in that they were charged with assessing the costs and benefits of a wide range of technologies across the whole disease spectrum, affecting the population as a whole. The Appeal Panel understood that the Committee had to be fair to the entire population in assessing cost effectiveness. They were advised that, in relation to other technologies, the cost of treating all patients with Alzheimer's disease was great, given the limited clinical benefit, and that they were unable to recommend the technologies for all patients for this reason. The Panel recognised the efforts of the Appraisal Committee in attempting to identify the groups of patients who would respond best to treatment. The Panel heard that the Committee had been able to identify a group of patients with Alzheimer's disease who would achieve most benefit from the treatment, and that the FAD recommended treatment for this group, namely people with moderate and moderately severe disease. The Panel recognised that this was an important development from the earlier draft guidance, where the cost/benefit ratio had precluded recommending treatment for ANY people with Alzheimer's disease.

1.9. The Panel heard the view of the Appraisal Committee, reflected in the FAD, that targeting treatment for people with moderate disease would result in about 40% of people with Alzheimer's disease being eligible for

treatment. In the earlier guidance, where initial responders were the subgroup targeted for treatment, the projected figure was also 40% of people with Alzheimer's disease. The Appraisal Committee judged that the current FAD better identified the patients likely to receive most benefit from the treatment.

2. Ground 1

1a The institute has failed to act fairly in that the FAD failed to provide adequate reasoning for a number of statements potentially affecting the final outcome.

1ai The FAD fails to give clear reasoning for the Committee's decision that "it was not convinced that inclusion of an element of harm in the economic analysis from further prescribing of antipsychotics as a result of their recommendation was appropriate" (paragraph 4.3.10.4 of the FAD).

2.1. The Appeal Panel questioned the Appraisal Committee Chairman as to why neuroleptic-related harm had not been included in the economic analysis. The Chairman responded that the Committee had decided that it was appropriate to factor in the benefits to behavioural symptoms in the economic analysis. They were mindful of the need to avoid 'double counting', and so had not included harm as a further factor in the economic analysis.

2.2. The Appeal Panel considered that paragraph 4.3.10.4 contained sufficient reasoning to explain the Appraisal Committee's deliberations concerning the inclusion of the effect of neuroleptic use within the economic model. The Committee is not required to give very detailed explanations in the FAD, bearing in mind that the FAD must be relatively concise and of practical use.

2.3. Appeal point 1ai was therefore dismissed.

1aii The FAD fails to give clear reasoning as to why the responder analysis ... has been disregarded and why the Committee was not persuaded that the responder definition would result in cost effective use of the drug treatments (paragraph 4.3.10.7 of the FAD).

2.4. Paragraph 4.3.10.7 states the reasons why the responder definition was rejected: it was retrospective, could plausibly lead to selection bias and related uncertainty in the interpretation of clinical effectiveness. It also describes the placebo effect and refers to the wide range of cost-

effectiveness estimates that might result from modelling the 'responder' data.

2.5. The Panel considered that the paragraph explained sufficiently the reasoning behind the Committee's decision to reject the responder analysis in assessing cost effectiveness. This point is also considered under Ground 2 (point 2diii).

2.6. Appeal point 1aii was therefore dismissed.

1b NICE have failed to act fairly because they have failed to explain how they have taken into account clinical need of people in mild stages and late stages of Alzheimer's disease and the clinical priorities of the Department of Health.

1bi The FAD contradicts priorities set out within Government policy on dementia care, as it will discourage the early diagnosis of Alzheimer's disease.

2.7. The Committee is not required expressly to consider the broad clinical priorities of the Secretary of State and the National Assembly for Wales in the FAD. The Appeal Panel ascertained that the Committee had considered the wider context outlined in the NSF for older people and the DH policy document 'Everybody's business: integrated mental health services for older people'.

2.8. The Appeal Panel was satisfied that there was no procedural unfairness with regard to this point. The point concerning discouraging early diagnosis is considered specifically under Ground 2 (point 2ai).

2.9. Appeal point 1bi was therefore dismissed.

1bii The current FAD denies access to drug treatment in the mild and late stages of Alzheimers Disease, thus ignoring the clinical need of people in these stages of the illness.

2.10. The Appeal Panel heard that the Appraisal Committee were very aware of the severity of the symptoms of Alzheimer's Disease and the high levels of distress and difficulty they caused both patients and carers. However, they emphasised that their role was not to consider the severity of the clinical need, but to what extent the clinical need could be ameliorated by the technology.

2.11. The Appeal Panel did not consider there had been procedural unfairness in this respect. The point was also considered under Ground 2.

- 2.12. The Panel questioned the Appraisal Committee members regarding the differential benefits in the mild and moderate groups, and heard that, although there was a statistically significant improvement in both the mild and the moderate group, the subgroup analysis demonstrated a greater magnitude of response in the moderate group, as outlined in points 4.1.2.12, 4.1.3.10, and 4.1.4.11 of the FAD. The Appraisal Committee Chairman addressed the assertion outlined in appeal point 1bii, that treatment was more meaningful in early dementia. The Committee's role was to assess the evidence. The Panel heard that there was no evidence of a differential effect in respect of the impact of treatment, and evidence of no differential effect, as described in Technical Report 1.
- 2.13. Although there was no evidence that treating patients with mild symptoms achieved greater benefit, the Committee acknowledged that they had heard anecdotally that improvement in the mild phase of the disease was more meaningful. The Committee did not accept that the benefit in the moderate group was a phenomenon created by the non-linearity of the MMSE with the course of the disease. Patient welfare, or quality of life, as measured by utilities, did have a linear relationship with MMSE (or ADAScog), as described in Technical Report 1.
- 2.14. The Committee agreed that the drugs are still clinically effective at the mild stages, but were less so, thus generating a higher cost/QALY. The Committee had a responsibility to consider the wider benefits and costs of NHS resources, and considered that the cost effectiveness of the treatment for people with mild symptoms would be an unfair use of NHS resources.
- 2.15. The Appeal Panel concluded that the deliberations and decisions of the Appraisal Committee had been logical, and that they had not behaved perversely.
- 2.16. Appeal point 1bii was therefore dismissed under Grounds 1 and 2.

1c The FAD has failed to have regard to the Secretary of State's Directions to 'attach particular importance to equal opportunities issues...in relation to the guidance it issues'

- 2.17. The Appeal Panel questioned the Appraisal Committee members as to whether and how they had taken account of the limitations of the MMSE tool. The Appraisal Committee had recognised the limitations of the MMSE scores (paragraph 4.3.13 in the FAD): the MMSE test is a screening tool and is difficult to apply for certain groups, including people with learning difficulties, people whose first language is not English, and people with a particularly high IQ. The Appraisal Committee had heard

from their clinical members of the importance of flexibility in interpreting MMSE scores.

- 2.18. The Chairman confirmed that it was the intention that people with equivalent disabilities due to Alzheimer's disease should receive equivalent treatments.
- 2.19. People with learning disabilities were excluded from the evidence base, and therefore specific recommendations were not made for this group. The intention of the Committee was to recommend that learning disability specialists should use their judgment in interpreting or applying MMSE scores (paragraph 4.3.13). It was the express intention of the Committee that people with learning disabilities were treated differently from the population as a whole and that a greater degree of discretion should be exercised.
- 2.20. Regarding people whose first language was not English, the Committee agreed that clinical judgment and 'common sense' should be exercised in applying the Guidance. Like all other guidance issued by NICE, this guidance was not binding, and application had to be in the context of the whole range of clinical and social issues affecting each patient.
- 2.21. People with high IQ were included within the validation of the MMSE index, since trials were based on an average taken from the whole population.
- 2.22. The Appeal Panel questioned the Appraisal Committee Chairman as to whether the Committee believed there was ever a situation where treatment might continue in a patient whose MMSE score was less than 10. The Chairman acknowledged that this was possible, and suggested that, in these instances, it was a matter of individual clinical judgment to continue treatment when appropriate. Such flexibility in applying the guidance was covered by the 'context' statement present in all guidance published by NICE: 'guidance does not...override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.'
- 2.23. The Appeal Panel considered that the guidance was written so as to give a clear recommendation, but that the 'context' statement allowed for individual cases to be assessed, and the guidance overruled, where necessary.

2.24. The Appeal Panel concluded that the Appraisal Committee had taken into account the particular needs of the different groups potentially adversely affected by MMSE scores.

2.25. However, they did believe that 4.3.13 was not worded accurately so as to reflect the intended meaning of the Committee in respect of both the particular recommendations for people with learning disabilities and the AChE inhibitor licence. Consequently, they referred point 1c to the Guidance Executive for further consideration.

1d In the case of memantine, the FAD has failed to follow the remit of the scope which lists health related quality of life for carers as an outcome and states that where evidence allows combination treatment should be considered.

2.26. In response to questioning, the Appraisal Committee Chairman confirmed that all evidence relating to drugs within their license was considered by the Committee, including, specifically, the two trials mentioned in point 1d. No evidence had been ignored. Regarding carer time, the manufacturers of memantine had submitted their own economic model, and had therefore had the option to include considerations of carer time, but had chosen not to do so.

2.27. A related point is also raised under Ground 2 (point 2I).

2.28. The Appeal Panel concluded that the Committee had acted fairly in considering all trials submitted, and the economic model submitted.

2.29. Appeal point 1d was therefore dismissed.

1e. The reliance of the Appraisal Committee on incremental cost per QALY is perverse.

2.30. This point was considered under Ground 1 and Ground 2.

2.31. This point is also related to point 1b under Ground 1.

2.32. The Appeal Panel questioned the Appraisal Committee Chairman regarding the use of QALYs. Whilst stating that QALYs were used in order to provide a common outcome measure to allow comparisons of cost effectiveness to be made across all morbidities, he accepted that QALYs were particularly difficult to measure in this patient group. Because of this difficulty, the Committee had not relied solely on the Assessment Group's analysis, but had tested the data using the EQ-5D health state tariff methodology, the cost utility analysis used in the

augmented base case, described in Technical Report 1, and the LASER-AD study (Livingstone et al 2004).

- 2.33. The Panel heard that the Committee had used figures reflecting a more optimistic interpretation of the data in relation to the transition from pre full time care to full time care, in order to accommodate remaining doubts regarding the estimates.
- 2.34. Furthermore, the Panel heard that the final reworkings produced results very close to those in the three industry submissions.
- 2.35. The Chairman of the Appraisal Committee acknowledged that modelling around the two health states (pre full term care and full term care) was difficult, and that the AHEAD model used by SHTAC in the Assessment Report was the best available. The Panel also noted that the AHEAD model was used by one of the manufacturers. In recognition of the imperfections of the model, the Committee had repopulated the model with alternative data so as to provide a more optimistic scenario. They had directed the NICE secretariat to explore the model in a variety of different ways (see FAD paragraph 4.2.6.1) in order to ascertain whether more optimistic cost estimates could be assumed. As outlined in Technical Report 1, the AHEAD model and the donezepil model were reconciled using an amended starting utility of 0.69 instead of 0.6 for the pre full time health state.
- 2.36. The Appeal Panel considered that the uncertainties inherent in the the QALY estimates and the economic model had been addressed, by testing the model against others, by moving data to a more optimistic scenario, and by augmenting the model as described in the FAD. They recognised that the original model rendered the technologies cost-ineffective, and that amendments to the model had served to bring the costs down to a utilisable level, for the moderate and moderately severe subgroups.
- 2.37. The Appeal Panel considered that the Committee had utilised the best available model, and had taken extensive measures to eliminate the negative effects of uncertainty, and define a cost effective subgroup. Without this reworking the technologies would have been cost-ineffective for all people with Alzheimers disease. The Panel concluded that there was no perversity in the behaviour, reasoning or decisions of the Committee regarding the use of QALYs or the economic model.

1ei The use of the QALY derived only from carer proxies as a decision making tool is both unacceptable and totally inappropriate.

- 2.38. This point was considered under Ground 1 and Ground 2

2.39. The appellants raised the difficulty in measuring health related quality of life in people with Alzheimer's disease, and in particular the use of data derived from the Health Utilities Index 2 (HUI 2, Neumann et al 1999 and 2000).

2.40. The Appeal Panel asked why the Committee had used a scale not evaluated in dementia, and reliant on proxy measures, and were informed that it was the best available, given that there were no reliable methods of directly assessing patient wellbeing. The measures described previously (testing the model and upward adjustment of all parameters to provide the most optimistic scenario) sought to address the shortcomings. The model had been tested against other methodologies, including the EQ5D, and it had been established that the QALY provided a fair comparison.

2.41. Furthermore, the (HUI2) questionnaire and the AHEAD model were used in one of the manufacturers submissions.

2.42. The Panel were satisfied that the Committee had behaved fairly and not acted perversely in selecting the HUI2 to assess quality of life, and had taken steps to eliminate the potential negative effects of the uncertainties surrounding the index.

2.43. Appeal point 1ei was therefore dismissed under Grounds 1 and 2.

1eii Four of the six subscales in the Health Utility Index Mark 2 (HUI2) do not change substantially between mild and severe dementia.

2.44. This point was considered under both Ground 1 and Ground 2

2.45. The Appeal Panel enquired of the Committee Chairman whether they had considered removing the subscales that did not alter substantially between mild and severe dementia, ie pain and emotion. They were advised that the HUI2 index was used in a range of morbidities, not just dementia, and that removing subscales would have the effect of exaggerating the extent of the change experienced in people as they moved from the mild to the severe disease state when comparing Alzheimer's disease against other conditions.

2.46. The Appeal were satisfied that the approach of the Committee was fair and reasonable.

2.47. Appeal point 1eii was therefore dismissed under Grounds 1 and 2.

1f NICE have been unreasonable in their interpretation of comments from the Alzheimer's Society on the behavioural subgroup.

2.48. The appellants asserted that their comments had been taken out of context in paragraph 4.3.17 of the FAD. The Appeal Panel first sought and received confirmation that the 'other consultees' referred to in paragraph 4.3.17 were those represented by the joint appeal from Alzheimers Society et al. The Appraisal Committee Chairman asserted that it was the view of the Committee (and others) that there was a well established, distinct subgroup of people with agitation. The appellants' comments had been correct in seeking to delineate a difference in response to memantine between those with psychosis and those with agitation. However, the appellants had disagreed with this interpretation of their comments. The Chairman proposed that the wording should be changed so as better to reflect the impression of the Committee, namely that the manufacturers categorisation of people as behaviourally disturbed was neither specific enough to be workable nor consistent with the definition proposed by others in general.

2.49. The Appeal Panel concluded that the Committee had not been unreasonable or perverse.

2.50. The Panel referred point 1f to the Guidance Executive for further consideration.

3. **Ground 2**

2a It is perverse to promote bad practice rather than clinical excellence. The FAD does this in two key ways:

2ai The FAD discourages early diagnosis and treatment, which is recognised to be best practice in dementia care.

3.1. The Appeal Panel heard that the Committee had received comments regarding the improved package of care for people with dementia as a result of TA 19 (4.3.5 in the FAD). On questioning, the Committee members were in full agreement with the appellants that the continuation of memory clinics and other interventions was paramount in offering care to people with Alzheimer's disease. A Guideline Development Group was currently in the process of writing the Guideline for managing people with dementia, and would be defining the packages of care.

3.2. The Appeal Panel decided that any potential negative effect of the guidance on referral patterns was speculative, and that it was just as likely that referral would continue as now, as most clinicians recognised that any pharmacological intervention was only part of the package of care delivered by specialist services.

- 3.3. The Panel enquired of the Appraisal Committee members why they had not recommended treatment with AChE inhibitors for people with mild disease. The Appraisal Committee Chairman explained that the original model, without adjustments, had produced CQG figures approaching UK£100,000, for all eligible patients, ie those with mild, moderate and moderately severe disease. It was only through identifying subgroups that a group of patients were identified for whom treatment would be cost effective. Any further manipulation that moved resources back towards the mild group would render treatment for both groups cost-ineffective.
- 3.4. The Panel ascertained that the Committee had investigated subgroups in order to ascertain whether there was a subgroup of patients for whom the technologies were more cost effective, thus enabling the Committee to recommend the technologies for this subgroup. The Committee Chairman emphasised that, without the subgroup analysis, the technologies would NOT be recommended for people with mild and moderate Alzheimer's disease, because they were not cost effective for the group as a whole. Thus, identifying the greater benefit (and thus improved cost effectiveness) of the moderate disease group enabled the Committee to move from recommending no treatment to recommending treatment for those with moderate and moderately severe Alzheimer's disease.
- 3.5. The Panel ascertained that differentiation of the subgroups defined as mild, moderate, and moderately severe reflected clinical practice and was possible to implement.
- 3.6. The Panel formed the view that, in identifying the moderate and moderately severe subgroups as the groups that would benefit most from the technologies, the Committee had ensured that the technology was 1) available 2) targeted most effectively, and 3) delivered acceptable cost effectiveness. The Panel was advised that any resource shift from the moderate to the mild group rendered treatment for both groups cost-ineffective.
- 3.7. The Panel therefore concluded that the Committee had reasoned cogently and logically in reaching their conclusions, and that these conclusions were not perverse.
- 3.8. Appeal point 2ai was therefore dismissed.

2aii It is well established that neuroleptic use should be minimised. However, the FAD works against this principle.

- 3.9. In response to questioning, the Appraisal Committee Chairman confirmed that, though the Committee were aware that neuroleptics might be used inappropriately in this patient group, the scope did not cover the use of

neuroleptics in Alzheimer's disease. All consultees had had an opportunity to determine what went in the scope, and the use of neuroleptics had not been raised. The FAD therefore made no comment (in either direction) regarding the use of neuroleptics in Alzheimer's disease. The dementia Guidelines Development Group would consider the issue, and guidance would be provided in that context. The Appeal Panel noted that, in fact, the Appraisal Committee had little alternative but to adopt this approach, particularly given that had been unable to recommend memantine on grounds of clinical effectiveness.

3.10. The Appeal Panel were satisfied that this conclusion was not perverse.

3.11. Appeal point 2a_{ii} was therefore dismissed.

2b The decision to base access to anticholinesterase treatment on MMSE score is perverse in light of the evidence of the unsuitability of the MMSE tool for this purpose.

3.12. The Appeal Panel questioned the Appraisal Committee Chairman as to why the Committee had chosen MMSE scores for defining the mild, moderate and severe subgroups. The Chairman acknowledged that the MMSE was an imperfect tool. He explained that MMSE had been chosen because it linked evidence to practice. In trials, both ADAScog and MMSE had been used extensively in measuring primary outcomes, but ADAScog was not practical to use in a clinical setting. MMSE was the only system that met both criteria. Furthermore, the MMSE was recommended for use in TA 19, and was accepted by all parties in that instance.

3.13. The MMSE score was the best tool available to define the subgroups, and the alternative was to not define the subgroups at all, rendering the technology cost-ineffective for all people with Alzheimer's disease.

3.14. The Committee had deliberated as to whether to soften the subgroup thresholds by including words such as 'normally' and 'usually' but concluded that the guidance would not benefit from lack of precision. The Committee had noted that under the current guidance (TA19), which had used such terminology, audit showed that approximately 70% of people with Alzheimer's disease were prescribed the technologies, whilst the evidence base suggested the responder group was likely to be around 40%. They had concluded that the 'softened' wording of that guidance had led to a failure to apply it rigorously and consequent systematic use of the technologies outside the guidance.

- 3.15. The Committee concluded it was more appropriate to maintain precise guidance, whilst dropping the lower end of the moderate subgroup from 12 to 10 in order to accommodate the necessary flexibility required in a clinical setting.
- 3.16. The appellants raised the concern that the MMSE varied over time. The Appeal Panel noted that the FAD did not specify how often the MMSE should be applied determining an individual's position in relation to the threshold. The Committee stated that this was a matter for the Guidelines Development Group to consider. The Panel believed this to be appropriate, and noted that there was nothing in the FAD to suggest that clinical decisions should be made on a single assessment using the MMSE.
- 3.17. The Appeal Panel's interrogation regarding different groups (people with high or low premorbid ability, sensory difficulties or who are being tested in a second language) for whom the MMSE might be misleading is reported in point 1c under Ground 1.
- 3.18. The Appeal Panel formed the view that the Committee had acknowledged and addressed the limitations in application and interpretation of MMSE scores. The Panel concluded that the Committee had not made perverse recommendations in the FAD in this regard.
- 3.19. Appeal point 2b was therefore dismissed.

2c As the FAD stands, individuals with an MMSE of below 20 who respond well to treatment are at risk of having effective treatment removed should their MMSE score increase to above 20. This is perverse.

- 3.20. The Appeal Panel noted that there was no reference within the FAD to discontinuing treatment should the MMSE score increase to above 20. They confirmed with the Appraisal Committee members that it was not the intention of the FAD that treatment should be discontinued when high improved scores.
- 3.21. The Panel concluded that this point was not substantiated by the FAD.
- 3.22. Appeal point 2c was therefore dismissed.

2d It is perverse to use inaccurate assumptions within the model of cost effectiveness for anticholinesterase drugs. Specifically

I. The model does not capture benefits to carers following effective drug treatment

- 3.23. The Committee had taken evidence from carers at the ACD meeting, and members of the Guideline Development Group were present at all Committee meetings.
- 3.24. The Panel heard that costs for informal carers are not normally included in assessing a technology's cost-effectiveness, but it was in recognition of the particular and important role that carers play in the care of people with dementia that a carer utility was included in the analysis for this technology.
- 3.25. The Appeal Panel heard that the Appraisal Committee was mindful of the need to avoid 'double counting', and therefore needed to use either carer time or QOL gain as a measure of the effect on carers of the technology. As their brief was to develop guidance that took account of PSS/NHS costs, they used the index most able to be converted into monetary terms, namely QOL gain. (Had they been required to assess services, it might have been more appropriate to choose carer time.)
- 3.26. For this reason, references to carer time saved had been removed in the FAD. It was pointed out that in paragraph 4.1.3.7 there was reference to carer time saved with galantamine treatment. The Chair of the Appraisal Committee stated that, in the interests of fairness, this reference should be removed from the FAD.
- 3.27. The Panel heard that the studies considered showed no difference in carer quality of life across the disease spectrum. In other words, the impact of the disease on the carer was similar whether the patient had mild, moderate or severe disease. If anything, there was a possible improvement to carer utility as the patient moved into full time care. There was some evidence to suggest no difference in utility between mild and moderate disease. On this analysis, the most appropriate carer utility would have been 0. However, the Committee were uncomfortable with this scenario, and so wished, once again, to put the most optimistic figure into the analysis. As explained in Technical Report 1, the augmented base case contained a utility loss of 0.01(from Neumann, 1999) from the beginning of care until the person they cared for required full time care. This was the most favourable possible interpretation of the data regarding the change in impact on carer QOL that could be brought about by using the technology.
- 3.28. The Panel heard that the appellants would have preferred carer time to be the identified parameter, as they believed it would more accurately reflect the wider costs to the carer – for instance the burden of

caring and associated depression. The Panel were very sympathetic to the notion that the carer burden was great, and needed to be acknowledged. The Committee members emphasised that they had wished to be as generous as possible in terms of assessing carer impact, and had looked at all the evidence submitted to them. However, the cost effectiveness analysis required them to identify only what proportion of the burden of caring is avoided by employing the technology.

3.29. The Panel were satisfied that the Committee had made considerable efforts to identify carer benefits of the technologies, and had included a factor that was optimistic given the data. They concluded that the Committee had been fair in this respect.

3.30. The Panel heard that the Committee readily recognised the imperfections and inaccurate assumptions within the model, and noted the effort of the Committee to manage these assumptions by employing the most optimistic interpretations reasonably available.

3.31. The Appeal Panel did not believe the Committee had acted perversely in reaching their conclusions.

3.32. In its central respects, therefore, appeal point 2di was therefore dismissed

3.33. However, the Appeal Panel believed that there was merit in the suggestion from the Chairman of the Appraisal Committee to omit references to carer time in paragraph 4.1.3.7, and accordingly refer this point to the Guidance Executive.

II. The model ignores savings resulting from reduction in neuroleptic use

3.34. The Appeal Panel enquired as to why an element of harm saving had not been factored into the model. The Committee members explained that the benefits arising for the amelioration of behavioural disturbances as a result of using AChE inhibitors had been taken into account (paragraph 4.3.10.4)

3.35. The Chairman advised that the scope of the current FAD did not include the use of neuroleptics, and this issue would be addressed in the dementia guideline currently under consideration by the Guidelines Development Group. Although aware that neuroleptics might sometimes be prescribed inappropriately, it was not possible to factor in savings in relation to prescribing that should not be occurring in the first place. It was not the role of the FAD to address this problem.

3.36. Appeal point 2dii was therefore dismissed.

III. The model fails to use the results of the responder analysis, which provides the most realistic assessment of costs and benefits

3.37. The Panel questioned the Committee members as to why they had not recommended initial responders as the desired subgroup, particularly since this was the group targeted for treatment in TA 19. The Committee had rejected responders as the target treatment group because they were difficult to identify clinically. (Both those treated and those on placebo had apparent cognition gains at six months, and amongst the 'non-responders', those on the drug benefited relative to 'non-responders' on placebo.) Further, like any post hoc analysis, the responder analysis was difficult to interpret owing to selection bias. Regression to the mean and the inclusion of those non-responders with slowly progressing disease made identification of the responder group difficult. They concluded that this level of uncertainty precluded initial responders from being the appropriate subgroup to treat.

3.38. The Panel also heard that, although the evidence suggested that 40% of people with Alzheimer's disease were responders, audit performed in the NHS suggested that 70% of people with Alzheimer's disease were treated. This supported the assertion that the group was difficult to identify clinically.

3.39. The Panel heard that the Committee had deliberated between the two possible subgroups for treatment, and had concluded that treating 'responders' (as defined in TA19) was less likely to target those who would benefit most, and more likely to lead to the treatment of greater numbers of people who would not benefit.

3.40. The Panel concluded that the Appraisal Committee had deliberated on the merits of the various subgroup possibilities in attempting to identify maximum cost effectiveness, and had outlined their conclusions in paragraph 4.3.10.7 of the FAD, as well as outlining the process leading to their conclusions in paragraphs 4.2.6.5 and 4.2.6.6.

3.41. Appeal point 2diii was therefore dismissed.

IV. The model underestimates the costs of care

3.42. The Appeal Panel questioned why the figure of UK£355/week had been used, and heard that this was the average (NHS/PSS) cost estimate for full time institutional care. In response to comments from the Alzheimer's Society and others following the Assessment Group Report,

the figure of UK£520/week was inserted into the model, but this made no difference to outcome in the sensitivity analysis. The Committee had not merely accepted the Assessment Group's costs, but had moved the cost of full time care up and pre full time care down to assess the outcome cost: there was no difference. The base case remained the best case, leading to the recommendation to treat the moderate group. If the base case were adjusted, the incremental cost effectiveness reduced in the mild group, but not sufficiently to bring it within the bounds of acceptable cost-effectiveness.

3.43. The Panel concluded that, in taking the average costs, the figure used in the model was reasonable. Furthermore, if a higher figure was used, there was no difference in outcome, and the recommendations in the FAD would have stayed the same.

3.44. Appeal point 2div was therefore dismissed.

2e The conclusion that there is insufficient evidence to determine the clinical efficacy of memantine is perverse in light of the evidence.

3.45. The appellants asserted that one pivotal trial (TARIOT 2003) had been excluded. The Appraisal Committee Chairman stated that the trial had been considered (paragraph 4.1.6.3 and 4.3.15 of the FAD), although the results had been treated with caution.

3.46. The Appeal Panel noted that it would not be realistic to expect the Committee to explain their judgments regarding individual studies in the FAD. However, in this case, it was clear from the FAD that the trial had been considered, and was integral to the conclusions reached by the Committee.

3.47. Regarding the subgroup of people with agitation or psychosis, the Committee gives their reasons for rejecting the data relating to this subgroup in paragraphs 4.3.17 of the FAD.

3.48. Appeal point 2e was therefore dismissed.

2f The failure to consider reduction in neuroleptic use following treatment with memantine is unreasonable.

3.49. The Appraisal Committee Chairman stated that the scope had been fully and openly debated, and the decision had been not to include neuroleptics. There was no evidence regarding the use of memantine

versus neuroleptics, thus it was not possible for the Committee to assess the relative benefits.

2g Excluding benefits of memantine treatment to carers is perverse in light of the evidence.

3.50. The Appeal Panel questioned the Appraisal Committee Chairman as to whether the Committee had excluded the benefits of memantine treatment to carers. The Chairman explained that the Committee's first job was to establish the clinical effectiveness of a technology, before considering cost effectiveness. The Committee had concluded that memantine failed the clinical effectiveness test, on the basis of current evidence, and recommended further research. They had undertaken some cost effectiveness analysis in order to treat the different technologies with equivalences, but had not applied the same detailed analysis to memantine as to the AChE inhibitors as they had already formed the view that they were unable to recommend memantine for use in the NHS.

3.51. The Appeal Panel concluded that the Committee's reasons for not exploring the carer benefits derived from memantine were reasonable given that they judged memantine to fail the clinical effectiveness test.

3.52. Appeal point 2i was therefore dismissed.

4. Conclusion and effect of the Appeal Panel's decision

4.1. Subject to the points referred to the Guidance Executive for consideration, the Appeal Panel has dismissed the appeal on all points.

4.2. 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 or the issuing of the Guidance.

