Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Clinical Excellence

HTA 09/87/01

FINAL PROTOCOL

November 2009

1. Title of the project:
The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111)

2. Name of TAR team and project 'lead'

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3. Plain English Summary

This project will review and update the evidence presented to the National Institute of Health and Clinical Excellence in 2004 of how good a number of drugs (donepezil, galantamine, rivastigmine and memantine) are for treating Alzheimer's disease. The assessment will also assess whether the reviewed drugs are likely to be considered good value for money for the NHS.

4. Decision problem

4.1 Purpose

Dementia is a chronic progressive mental disorder that adversely affects higher cortical functions including memory, thinking and orientation. Alzheimer's disease is the most common form of dementia. It is a degenerative cerebral disease with

characteristic neuropathological and neurochemical features. Alzheimer's disease is usually insidious in onset and develops slowly but steadily over a period of several years. It affects predominantly the elderly. Progression is characterised by deterioration in cognition (thinking, conceiving, reasoning) and functional ability (activities of daily living) and a disturbance in behaviour and mood. Changes in one or more of these domains and their effects on the person provide the basis for diagnosis and they are used to assess the severity and progression of the condition.

Population data (2005) for England and Wales show an estimated prevalence of 380,000 people with Alzheimer's disease.[1] The incidence rate for Alzheimer's disease for England and Wales in people aged of 65-69 years has been estimated in 2005 at 6.7 [95% CI 3.8-12.4] per 1000 years and 68.5 [95% CI 52.5-88.1] per 1000 years for those 85 years or older. This indicates there are approximately 163,000 [95% CI 96,000-272,000] new cases per year.[2]

People with Alzheimer's disease lose their ability to carry out routine daily activities like dressing, toileting, travelling and handling money and, as a result, many people require a high level of care. Often, this is provided by an elderly relative, whose own health and quality of life can be affected by the burden of providing care. Behavioural changes in the person, such as aggression, are particularly disturbing for carers.

Several different methods are used to assess the severity of Alzheimer's disease depending on the setting, for example research or clinical practice, and the type of outcome being assessed.

Global outcome measures include: the Global Deterioration Scale (GDS); Clinical Global Impression of Change (CGIC); Clinician's Interview-based Impression of Change (CIBIC); CIBIC-plus and Gottfries-Brane-Steen scale.

Functional ability and quality of life can be assessed using the Progressive Deterioration Scale (PDS), Disability Assessment for Dementia (DAD), the Alzheimer's Disease Cooperative Studies for Daily Living Inventory (ADCS/ADL) and the Instrumental Activities of Daily Living (IADL) scale.

Cognitive ability can be assessed using the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog – 70 points), the Severe Impairment Battery (SIB) or the MMSE (Mini Mental State Examination) (30 points). MMSE score, for example, denotes the severity of cognitive impairment as follows: mild Alzheimer's disease: MMSE 21–26, moderate Alzheimer's disease: MMSE 10–20, moderately severe Alzheimer's disease: MMSE 10–14, severe Alzheimer's disease: MMSE less than 10.

Management of Alzheimer's disease involves treatment of cognitive, behavioural and psychological symptoms. Non-pharmacological treatment is social support and increasing assistance with day-to-day activities. These include: information and education, carer support groups, community dementia teams; home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.

4.2 Interventions

This technology assessment report (TAR) will consider four pharmaceutical interventions. Three have marketing authorisations in the UK for the treatment of adults with mild to moderately severe Alzheimer's disease (measured by the MMSE 26-10). These are donepezil (Aricept, Eisai), rivastigmine (Exelon, Novartis), and galantamine (Reminyl, Shire). They are acetylcholinesterase (AChE) inhibitors, which work by increasing the concentration of acetylcholine at sites of neurotransmission.

The fourth drug, memantine (Ebixa, Lundbeck), has a UK marketing authorisation for the treatment of people with moderate to severe Alzheimer's disease (measured by the MMSE 20 or less). It is a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

4.3 Place of the interventions in the treatment pathway

NICE guidance (Technology Appraisal 111[3] and Clinical Guideline 42[4]) currently recommends the three AChE inhibitors donepezil, galantamine and rivastigmine as options in the management of patients with Alzheimer's disease of moderate severity only (for people with a MMSE score of between 10 and 20 points) and under the following conditions:

Only specialists in the care of patients with dementia should initiate treatment. Carers' views on the patient's condition at baseline should be sought.

Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers' views on the patient's condition at follow-up should be sought. The drug should only be continued while the patient's MMSE score remains at or above 10 points and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect.

When the decision has been made to prescribe an AChE inhibitor, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost (taking

into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical comorbidity, possibility of drug interactions and dosing profiles.

Memantine is not recommended as a treatment option for patients with moderately severe to severe Alzheimer's disease except as part of well-designed clinical studies.

Patients with mild Alzheimer's disease who were receiving donepezil, galantamine or rivastigmine at the time guidance was issued, and patients with moderately severe to severe Alzheimer's disease who were receiving memantine, whether as routine therapy or as part of a clinical trial, were permitted to continue on therapy (including after the conclusion of a clinical trial) until they, their carers and/or specialist considered it appropriate to stop.

4.4 Relevant comparators

For people with **mild** Alzheimer's disease the comparator will be best supportive care with or without placebo i.e. treatment without AChE inhibitors and without memantine. Best supportive care is considered to be social support and assistance with day-to-day activities. These include: information and education, carer support groups, community dementia teams; home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.

For people with **moderate** Alzheimer's disease the comparators will be donepezil, galantamine, rivastigmine, memantine and best supportive care (with or without placebo, as described above).

For people with **severe** Alzheimer's disease the comparator will be treatment without memantine.

4.5 Population and relevant sub-groups

The population will be adults with Alzheimer's disease. However, similar to TA 111, where trials include participants with mixed dementia; these will be included where the predominant dementia is Alzheimer's disease.

If evidence allows, the following subgroups will be considered: subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbidities (such as cerebrovascular disease).

4.6 Outcomes to be addressed

Evidence in relation to the following kinds of outcomes will be considered:

- Measures of severity and response to treatment
- Behavioural symptoms
- Mortality
- Ability to remain independent
- Likelihood of admission to residential/nursing care
- Health related quality of life of patients and carers (where data permit, analyses will be carried out separately for patients alone, and for patients and carers combined)
- Adverse effects of treatment
- Cost-effectiveness and costs (review of economic studies)

4.7 Other considerations

Treatments will only be assessed in accordance with their marketing authorisation.

If evidence allows, interventions will be compared with each other, in sequential use, or as combination therapy, within their licensed indications.

5. Methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of donepezil, galantamine, rivastigmine and memantine for Alzheimer's disease.

The review will be an update the previous review of clinical effectiveness undertaken in 2004 to inform NICE's TA 111 Guidance. The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination[5].

Population: Adults with Alzheimer's disease. However, similar to TA 111, where trials include participants with mixed dementia; these will be included where the predominant dementia is Alzheimer's disease.

Interventions: This technology assessment report (TAR) will consider four pharmaceutical interventions. Three have marketing authorizations in the UK for the treatment of adults with mild to moderately severe Alzheimer's disease (measured by the MMSE 26-10). These are donepezil (Aricept, Eisai), rivastigmine (Exelon, Novartis), and galantamine (Reminyl, Shire). They are AChE inhibitors, which work by increasing the concentration of acetylcholine at sites of neurotransmission.

The fourth drug, memantine (Ebixa, Lundbeck), has a UK marketing authorisation for the treatment of people with moderate to severe Alzheimer's disease (measured by

the MMSE 20-0). It is a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Comparators: For people with **mild** Alzheimer's disease the comparator will be placebo and/or best supportive care i.e. treatment without AChE inhibitors and without memantine. Treatment without AChE inhibitors or memantine is considered to be social support and assistance with day-to-day activities. These include: information and education, carer support groups, community dementia teams; home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.

For people with **moderate** Alzheimer's disease the comparators will be, donepezil, galantamine, rivastigmine, memantine and placebo and/or best supportive care (as above) i.e. treatments without AChE inhibitors.

For people with **severe** Alzheimer's disease the comparator will be treatment without memantine.

Outcomes: Data on the following kinds of outcomes will be extracted from included studies:

- Measures of severity and response to treatment
- Behavioural symptoms
- Mortality
- Ability to remain independent
- Likelihood of admission to residential/nursing care
- Health related quality of life of patients and carers (where data permit, analyses will be carried out separately for patients alone, and for patients and carers combined)
- Adverse effects of treatment

Search strategy

As this assessment is an update of TA 111 searches will be conducted from 2004. The search strategy will comprise the following main elements:

Searching of electronic databases using a comprehensive search strategy designed and executed by a highly experienced Information Scientist

Contact with experts in the field

Scrutiny of bibliographies of retrieved papers

Scrutiny of manufacturer and sponsor submissions to NICE

Databases:

Electronic databases: including MEDLINE (Ovid); PubMed; EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; NRR (National Research Register); Web of Science Proceedings; Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website.

Relevant studies will be identified in two stages. Abstracts and titles returned by the search strategy will be screened for inclusion independently by two researchers. Disagreements will be resolved by discussion. Full texts of identified studies will be obtained and screened in the same way.

Inclusion criteria

For the review of clinical effectiveness, in the first instance, only systematic reviews of randomised controlled trials (RCTs) and RCTs will be considered. However, if there are no RCTs which report one of the listed outcomes of interest or if there are no RCTs with over 12 months' follow up, we will extend our inclusion criteria to controlled clinical trials to search for studies with missing outcomes or longer follow up. The systematic reviews will be used as a source for finding further RCTs and to compare with our systematic review. These criteria may be relaxed for consideration of adverse events, for which non-randomised and observational studies may be included.

For the purpose of this review, a systematic review[5-7] will be defined as one that has:

- A focused research question
- Explicit search criteria that are available to review, either in the document or on application
- Explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest
- A critical appraisal of included studies, including consideration of internal and external validity of the research
- A synthesis of the included evidence, whether narrative or quantitative

Exclusion criteria

Studies will be excluded if they do not match the inclusion criteria, and in particular:

- Non-randomised studies (except for adverse events)
- Animal models

- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

Data extraction strategy

Data will be extracted by one reviewer using a bespoke database (Microsoft Access) with a standardised data specification and checked independently by another. Information extracted and tabulated will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events if reported. Where there is incomplete information on key data, we will attempt to contact the study's authors to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

Quality assessment strategy

Consideration of study quality will include the adequacy of reporting of the following factors in accordance with the NHS Centre for Reviews and Dissemination's criteria for assessing the quality of RCTs:[5]

1. Random sequence generation
2. Allocation concealment
3. Specification of inclusion criteria
4. Blinding
5. Numbers of participants randomised, excluded and lost to follow up
6. Outcome measures
7. Whether intention to treat analysis is performed
8. Methods for handling missing data

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, pairwise meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses. If appropriate and feasible, consideration will also be given to simultaneous comparison of treatments using Bayesian multiple treatment comparison methods in WinBUGS 1.4.1.

Meta-analysis will be carried out using STATA software, with the use of fixed- and/or random-effects appropriate to the assembled datasets. Heterogeneity will be

explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic. Small study effects (to which publication bias may contribute) will be assessed and quantified. We will investigate the likelihood of publication bias using funnel plots if there are sufficient included studies.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Systematic review of economic studies relevant to the decision problem

This systematic review aims to update the systematic review of cost-effectiveness studies which was conducted in 2004 as part of the review of evidence to inform the NICE's earlier guidance on these drugs (TA111).

The review will aim to summarise the main results of past studies, and identify any key economic costs and trade-offs relevant to the decision problem. It may also indicate the strengths and weaknesses of different modelling approaches in this treatment area.

Therefore, it will fully extract study data and assess study quality only for those economic evaluations or costing studies published since 2004 which are of relevance to the current decision problem.

Search strategy

The range of sources searched will include those for clinical effectiveness and extend to NHS EED and Econlit.

Study selection criteria and procedures

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness, except:

Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies.)

Full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data).

Standalone cost analyses based in the UK NHS will also be sought and appraised.

Based on the above inclusion/exclusion criteria, study selection will be made by one reviewer.

Study quality assessment

The methodological quality of the economic evaluations will be assessed according to internationally accepted criteria such as the CHEC list questions developed by Evers et al.[8] Any studies based on decision models will also be assessed against the ISPOR guidelines for good practice in decision analytic modelling.[9]

Data extraction strategy

For those studies which are of relevance to the current decision problem, data will be extracted by one researcher into two summary tables: one to describe the study design of each economic evaluation and the other to describe the main results.

In study design table: author and year; model type or trial based; study design (e.g. CEA, CUA or cost-analysis); service setting/country; study population; comparators; research question; perspective, time horizon, and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features.

For modelling-based economic evaluations a supplementary Study Design table will record further descriptions of: model structure (and note its consistency with the study perspective, and knowledge of disease/treatment processes); sources of transition & chance node probabilities; sources of utility values; sources of resource use and unit costs; handling of heterogeneity in populations; evidence of validation (e.g. debugging, calibration against external data, comparison with other models).

In the Results table: for each comparator, incremental cost; incremental effectiveness/utility and incremental cost-effectiveness ratio(s). Excluded comparators on the basis of dominance or extended dominance will also be noted. The original authors' conclusions will be noted, and also any issues they raise concerning the generalisability of results. Finally the reviewers' comments on study quality and generalisability (in relation to the TAR scope) of their results will be recorded.

Synthesis of extracted evidence

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base.

6.2. Economic Modelling

A new cost-effectiveness analysis may be carried out from the perspective of the UK NHS and PSS using a decision analytic model. Such a new analysis will be conducted if, in the TAR team's judgement, the existing published evidence (and/or the analyses submitted by manufacturers) is insufficiently relevant to the current decision problem. The evaluation will be constrained by available evidence.

Model structure will be determined on the basis of available research evidence and clinical expert opinion.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from sponsor submissions to NICE.

Resource use will be specified and valued from the perspective of the NHS and PSS. The resource use associated with different health states or clinical events will be obtained or estimated either from trial data, sponsor submissions, other published sources, or – where published sources are unavailable – relevant expert contacts or NHS Trusts. Unit cost data will be identified from national NHS and PSS reference cost databases for the most recent year, or, where these are not relevant, will be extracted from published work and/or sponsor submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Search strategies for additional information regarding model parameters or topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper 'Methods for establishing parameter values for decision analytic models' commissioned by the UK Dept. of Health and produced by InterTASC (January 2005). In addition to systematic reviews and RCTs other UK studies will be considered if appropriate.

ICERs estimated from Consultee models will be compared with the respective ICERs from the Assessment Group's model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Methods for measuring and valuing health effects

Ideally, the measurement of changes in health-related quality of life (HRQL) should be reported directly from patients. The value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D will be the preferred measure of HRQL for the purposes of estimating QALYs. In the absence of reliable EQ-5D utility data from relevant trials or patient groups, the use of alternative sources for utility weights for health states will be informed by the NICE Guide to the methods of technology appraisal (2009).

Time horizon, perspective and discounting

The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease.

The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.[4]

Further considerations

If evidence allows, the cost-effectiveness of the treatments in different relevant subgroups of patients will be explored, where appropriate with the estimation of sub-group specific cost-effectiveness ratios.

If evidence allows, non-reference case cost-utility analyses may include the quality of life impacts on the main carers of people with Alzheimer's.

If clinically appropriate and if evidence allows, modelling of the subgroup of people with behavioural disturbance may consider concomitant use of anti-psychotic medication.

7. Expertise in this TAR team

Name	Institution	Expertise
Mary Bond	**PenTAG, Peninsula Medical School, University of Exeter**	**Systematic reviewing and project management**
Gabriel Rogers	**PenTAG, Peninsula Medical School, University of Exeter**	**Systematic reviewing and economic evaluation and modelling**
Jaime Peters	**PenTAG, Peninsula Medical School, University of Exeter**	**Economic modelling**
Rob Anderson	**PenTAG, Peninsula Medical School, University of Exeter**	**Health economics and economic modelling**
Tiffany Moxham	**PenTAG, Peninsula Medical School, University of Exeter**	**Information science**
Mike Jeffreys	**Royal Devon and Exeter Foundation Trust**	**Clinical expert**
Alec Miners	**London School of Hygiene and Tropical Medicine**	**Health Economics and economic modelling**
Chris Hyde	**PenTAG, Peninsula Medical School, University of Exeter**	**Systematic reviewing and economic evaluation**

TAR Centre

About PenTAG:

The Peninsula Technology Assessment Group is part of the Institute of Health Service Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, systematic reviews and economic analyses for the NICE (Technology Appraisal and Centre for Public Health Excellence) and systematic reviews as part of the Cochrane Collaboration Heart Group, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Recent projects include:

- Systematic review of the effectiveness and cost-effectiveness of weight management schemes for the under fives (2009).

- Barriers to and facilitators for the effectiveness of multiple risk factor programmes aimed at reducing cardiovascular disease within a given population: a systematic review of qualitative research (2009).
- Population and community programmes addressing multiple risk factors to prevent cardiovascular disease: a qualitative study into how and why some programmes are more successful than others (2009)
- Barriers to and facilitators of conveying information to prevent first occurrence of skin cancer: a systematic review of qualitative research (2009)
- The Effectiveness and Cost-Effectiveness of Cochlear Implants for Severe to Profound Deafness in Children and Adults: A Systematic Review and Economic Model (2008)
- The Effectiveness and Cost-Effectiveness of Methods of Storing Donated Kidneys from deceased donors: A Systematic Review and Economic Model (2009)
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: A systematic review and economic model (2008)
- The Effectiveness and Cost-Effectiveness of Cinacalcet for Secondary Hyperparathyroidism in end stage renal disease patients on dialysis. Systematic Review And Economic Evaluation (2007)
- The effectiveness and cost-effectiveness of Carmustine Implants and Temozolomide for the treatment of newly-diagnosed High Grade Glioma**.** Systematic Review And Economic Evaluation (2007)
- The Effectiveness and Cost-Effectiveness of Cardiac Resynchronisation Therapy for Heart Failure. Systematic Review and Economic Evaluation (2007)
- Inhaled Corticosteroids and Long-Acting Beta2-Agonists for The Treatment of Chronic Asthma in Adults and Children Aged 12 Years and Over: a Systematic Review and Economic Analysis (2007)
- Inhaled Corticosteroids and Long-Acting Beta2-Agonists for The Treatment of Chronic Asthma an Children Under the Age of 12 Years: a Systematic Review and Economic Analysis (2007)
- The Cost-Effectiveness of testing for hepatitis C (HCV) in former injecting drug users. Systematic Review And Economic Evaluation. (2006)

Contributions of team members		
Rob Anderson	**Senior Lecturer in Health Economics**	**Will oversee the cost-effectiveness aspects of the analysis and report and advise on obtaining costs and utilities for the model, and contribute to writing and editing the report.**
Mary Bond	**Research Fellow in HTA**	**Will provide overall project management, Write the protocol, assess abstracts and titles for inclusion and exclusion, contribute to the clinical effectiveness systematic review, contribute to the design of the model and contribute to writing and editing the report.**
Chris Hyde	**Professor of Public Health**	**Will assess abstracts and titles for inclusion and exclusion, contribute to the writing and editing of the report and be overall Director of the project and Guarantor of the report.**
Mike Jeffreys	**Consultant Physician**	**Will provide clinical input into the design of the model, advise on clinical matters and contribute to the editing of the report.**
Alec Miners	**Health Economist**	**Will appraise industry submissions**
Tiffany Moxham	**Information Specialist**	**Will write and run the search strategies for clinical and cost-effectiveness.**
Jaime Peters	**Research Fellow in Modelling**	**Will lead the design, development and execution of the economic model and contribute to writing and editing the report.**
Gabriel Rogers	**Research Fellow in HTA**	**Will assess abstracts and titles for inclusion and exclusion, lead the systematic reviews of clinical effectiveness and economic evaluations, appraise the industry submissions, provide support in the design and execution of the economic model and contribute to the writing and editing of the report.**

8. Competing interests of authors

None

9. Timetable/milestones

Consultee information meeting	05/01/10
1st Appraisal Committee meeting	25/08/10

10. Appendices

10.1. Draft search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present

1	Alzheimer Disease/	50121
2	alzheimer*.tw.	63441
3	1 or 2	71807
4	Memantine/	1059
5	Memantine.mp.	1547
6	ebixa.mp.	15
7	axura.mp.	6

8	namenda*.mp.	20
9	or/4-8	1549
10	Galantamine/	998
11	galantamin*.mp.	1226
12	galanthamine.mp.	366
13	Epigalanthamin.mp.	0
14	Jilkon*.mp.	0
15	Lycoremin*.mp.	2
16	Nivalin*.mp.	102
17	Razadyne*.mp.	2
18	Reminyl*.mp.	49
19	or/10-18	1383
20	donepezil*.mp.	1901
21	donezepil*.mp.	12
22	aricept*.mp.	90
23	Memac*.mp.	0
24	Memorit*.mp.	1
25	Eranz*.mp.	1
26	or/20-25	1920
27	rivastigmin*.mp.	943
28	exelon*.mp.	53
29	prometax*.mp.	0
30	or/27-29	945
31	30 or 26 or 19 or 9	4732
32	3 and 31	2416
33	Randomized controlled trial.pt.	290718
34	randomized controlled trial/	290718
35	(random$ or placebo$).ti,ab,sh.	706213
36	((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.	122846
37	or/33-36	724845
38	clinical trial/	469646
39	"controlled clinical trial".pt.	82893
40	(retraction of publication or retracted publication).pt.	2813
41	37 or 38 or 39 or 40	940958
42	32 and 41	878
43	(animals not humans).sh.	3410297
44	42 not 43	873
45	limit 44 to (english language and yr="2004 -Current")	546

Reference List

(1) Albanese E, Banerjee S, Dhanasiri S, Fernandez J, Ferri C, Knapp M et al. Dementia UK: The full report. 2007. London, Alzheimer's Society.

(2) Matthews F, Brayne C. The incidence of dementia in England and Wales: findings from the five identical sites of the MRC CFA Study. PLoS Med 2005; 2(8):e193.

(3) Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess 2006; 10(1):iii-xi, 1.

(4) National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal. 2008. London, National Institute for Clinical Excellence.

(5) NHS Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. York: CRD University of York; 2009.

(6) Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339(jul21_1):b2535.

(7) Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. The Lancet 1999; 354(9193):1896-1900.

(8) Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International Journal of Technology Assessment in Health Care 2005; 21(1):240-245.

(9) Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C et al. Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practice: Modeling Studies. VALUE HEALTH 2003; 6(1):9-17.