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Abstract

Development of a core outcome set for disease modification trials in mild to moderate dementia: a systematic review, patient and public consultation and consensus recommendations

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Background: There is currently no disease-modifying treatment available to halt or delay the progression of the disease pathology in dementia. An agreed core set of the best-available and most appropriate outcomes for disease modification would facilitate the design of trials and ensure consistency across disease modification trials, as well as making results comparable and meta-analysable in future trials.

Objectives: To agree a set of core outcomes for disease modification trials for mild to moderate dementia with the UK dementia research community and patient and public involvement (PPI).

Data sources: We included disease modification trials with quantitative outcomes of efficacy from (1) references from related systematic reviews in workstream 1; (2) searches of the Cochrane Dementia and Cognitive Improvement Group study register, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, EMBASE, Latin American and Caribbean Health Sciences Literature and PsycINFO on 11 December 2015, and clinical trial registries [International Standard Randomised Controlled Trial Number (ISRCTN) and clinicaltrials.gov] on 22 and 29 January 2016; and (3) hand-searches of reference lists of relevant systematic reviews from database searches.

Review methods: The project consisted of four workstreams. (1) We obtained related core outcome sets and work from co-applicants. (2) We systematically reviewed published and ongoing disease modification trials to identify the outcomes used in different domains. We extracted outcomes used in each trial, recording how many used each outcome and with how many participants. We divided outcomes into the domains measured and searched for validation data. (3) We consulted with PPI participants about recommended outcomes. (4) We presented all the synthesised information at a conference attended by the wider body of National Institute for Health Research (NIHR) dementia researchers to reach consensus on a core set of outcomes.

Results: We included 149 papers from the 22,918 papers screened, referring to 125 individual trials. Eighty-one outcomes were used across trials, including 72 scales [31 cognitive, 12 activities of daily living (ADLs), 10 global, 16 neuropsychiatric and three quality of life] and nine biological techniques. We consulted with 18 people for PPI. The conference decided that only cognition and biological markers are core measures of disease modification. Cognition should be measured by the Mini Mental State Examination (MMSE) or the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog), and brain changes through structural magnetic resonance imaging (MRI) in a subset of participants. All other domains are important but not core. We recommend using the Neuropsychiatric Inventory for neuropsychiatric symptoms: the Disability Assessment for Dementia for ADLs, the Dementia Quality of Life Measure for quality of life and the Clinical Dementia Rating scale to measure dementia globally.

Limitations: Most of the trials included participants with Alzheimer's disease, so recommendations may not apply to other types of dementia. We did not conduct economic analyses. The PPI consultation was limited to members of the Alzheimer's Society Research Network.

Conclusions: Cognitive outcomes and biological markers form the core outcome set for future disease modification trials, measured by the MMSE or ADAS-Cog, and structural MRI in a subset of participants.

Future work: We envisage that the core set may be superseded in the future, particularly for other types of dementia. There is a need to develop an algorithm to compare scores on the MMSE and ADAS-Cog.

Study registration: The project was registered with Core Outcome Measures in Effectiveness Trials [www.comet-initiative.org/studies/details/819?result=true (accessed 7 April 2016)]. The systematic review protocol is registered as PROSPERO CRD42015027346.

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List of abbreviations

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive subscale
ADAS-Noncog	Alzheimer's Disease Assessment Scale-Non Cognitive scale
ADCS-ADL	Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory
ADFACS	Alzheimer's Disease Functional Activity and Change Scale
ADL	activity of daily living
ALOIS	Cochrane Dementia and Cognitive Improvement Group study register
AS	Alzheimer's Society
BADL	Bristol Activities of Daily Living
BEHAVE-AD	Behavioural Pathology in Alzheimer's Disease
BPRS	Brief Psychiatric Rating Scale
CCT	clinical controlled trial
CDR	Clinical Dementia Rating scale
CENTRAL	Cochrane Central Register of Controlled Trials
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CIBIC+	Clinician's Interview-Based Impression of Change plus Caregiver Input
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COMET	Core Outcome Measures in Effectiveness Trials
CSF	cerebrospinal fluid
DAD	Disability Assessment For Dementia
DEMQOL	Dementia Quality of Life measure
DSRS	Dementia Severity Rating Scale
EEG	electroencephalography
EQ-5D	EuroQol-5 Dimensions
HRQoL	health-related quality of life
IADL	instrumental activities of daily living
ICHOM	International Consortium for Health Outcomes Measurement Working Group
ISRCTN	International Standard Randomised Controlled Trial Number
JPND	European Union Joint Programme – Neurodegenerative Disease Research
LILACS	Latin American and Caribbean Health Sciences Literature
MCI	mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NIHR	National Institute for Health Research
NPI	Neuropsychiatric Inventory
NTB	Neuropsychological Test Battery
P-tau	phosphorylated tau
P-tau181	phosphorylated tau 181
PET	positron emission tomography
PiB	Pittsburgh compound B
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSMS	Personal Self-Maintenance Scale
PWD	person with dementia
QALY	quality-adjusted life-year
QOL-AD	Quality of Life in Alzheimer's Disease
RCT	randomised controlled trial
T-tau	total tau

Plain English summary

In the UK, around 850,000 people have dementia. If a treatment can change the underlying pathology of dementia this is called disease modification, although no trials have yet found effective disease-modifying treatments. Trials have used differing outcome measures to evaluate if a treatment works, making it difficult to compare and contrast results. To address this issue we aimed, in collaboration with the UK dementia research community and the Alzheimer's Society's Research Network, to develop a core set of outcome measures for use in future disease-modifying trials for mild to moderate dementia.

We looked at the outcomes used across completed and ongoing disease modification trials and found measures in six test areas: cognition, biological, behaviour, quality of life, activities of daily living and global. We used these findings to conduct a small consultation with people living with dementia and family carers. We presented all results at our consensus conference and discussed them to reach our conclusions.

We recommend that the core set of outcome measures should include a cognitive measure, namely the Mini Mental State Examination or the Alzheimer's Disease Assessment Scale – Cognitive subscale, and an optional magnetic resonance imaging scan looking at brain structure as a biological measure. We have specified measures for the other areas that are important but not core. The recommendations may change as new measures are developed, and, as most of the trials included participants with Alzheimer's disease only, recommendations need to be developed for different dementias. They apply only to mild to moderate stages of dementia.

Scientific summary

Introduction

In the UK, as in the rest of the developed and developing world, the prevalence of dementia is increasing, primarily driven by the ageing population. People living with dementia can currently only be offered management to improve their symptoms as no disease-modifying treatments that would halt or delay the progression of the underlying disease pathology are available. The G8 Dementia Summit in 2013 committed to find a disease-modifying treatment by 2025. If a treatment were found to slow disease progression of mild to moderate dementia, then this would reduce the number of people living with severe dementia in the future.

However, across both published and ongoing disease modification trials there is large variation in the outcomes used as end points, making it difficult to compare and contrast results. To improve future disease modification trials there is a need for harmonisation among the outcomes measured, as well as for outcomes to be appropriate, sensitive to change and clinically meaningful. An agreed core set of the best-available outcomes would enhance interpretation of data across trials, including the combination of results in meta-analyses.

There is, therefore, an urgent need for consensus from National Institute for Health Research (NIHR) dementia researchers in the UK on a core outcome set of measures to be used across future disease modification trials in mild to moderate dementia. This will ensure that new trials can be combined in systematic reviews and contrasted as to their effectiveness.

Review question

What are the core clinical health outcomes that should be used in all NIHR-funded trials of disease modification in mild to moderate dementia, and how should they be measured?

Methods

The project consisted of four workstreams.

1. First, we used overlapping core outcome sets and work from co-applicants.
2. At the same time we performed a systematic review to identify which outcomes are used in published and ongoing disease modification trials.
3. We then consulted with people living with dementia and carers about the outcomes found in the systematic review.
4. Finally, we held a conference where the synthesis of information from the previous workstreams was debated by a wider body of NIHR dementia researchers to reach consensus on a core set of outcomes.

Workstream 1: co-applicants core outcome sets and work

First, we considered overlapping core outcome sets that had been, or were currently being, developed by co-applicants of the project, as well as reference lists from co-applicants. This included:

1. an outcome set of what is most important to people living with dementia
2. an outcome set for psychosocial interventions in dementia
3. reference lists from a systematic review of non-pharmacological interventions previously conducted by a co-applicant
4. the Cochrane Dementia and Cognitive Improvement Group study register (ALOIS), a database of dementia studies run by the Cochrane Dementia and Cognitive Improvement Group, which was represented by a co-applicant.

Workstream 2: systematic review

Protocol

We registered the protocol with PROSPERO [CRD42015027346; www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027346 (accessed 7 April 2016)].

Searches

We conducted database searches (ALOIS, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, EMBASE, Latin American and Caribbean Health Sciences Literature and PsycINFO) on 11 December 2015. Additionally, we decided to search ongoing trials on clinical trials registries [International Standard Randomised Controlled Trial Number (ISRCTN) and clinicaltrials.gov) on 22 and 29 January 2016, respectively, to ensure that we had complete data about what measures are currently being used. We also hand-searched the reference lists of relevant systematic reviews found within the database searches.

Inclusion and exclusion criteria

We included trials that met all of the inclusion criteria:

1. The full text is written in English.
2. The trial is published in a peer-reviewed journal article or is an ongoing trial.
3. At least some of the participants have clinically diagnosed mild or moderate dementia.
4. The intervention aimed to modify the dementia disease.
5. It is a randomised controlled trial (RCT) or clinical controlled trial with:
   i. the intervention directed at the person with dementia
   ii. the control or comparator arm comprising treatment as usual, no intervention, sham therapy, other therapy or placebo.
6. At least one quantitative outcome measure related to disease modification in mild or moderate dementia.

We excluded studies in which all participants had severe dementia or mild cognitive impairment, and if the whole study was set in care homes, as very few people with mild to moderate dementia would be resident in care homes. We also excluded trials if the outcomes were only qualitative, economic or related only to carers or drug levels.

Data extraction

We extracted characteristics from each of the trials, including trial type, location, intervention, control group, participants and which outcomes were measured at what time points. Across the trials we calculated how many used each outcome and with how many participants. We also divided the outcomes into the domains that they measured, namely cognition, biological markers, activities of daily living (ADLs), global assessment, neuropsychiatric symptoms and quality of life.

Validation data

We searched separately for validation data for each outcome measure. This included information about any relevant populations that the outcome is validated for use with, minimal clinically important difference, reliability (inter-rater and test–retest), ceiling-and-floor effects, sensitivity to change and any risks associated with using the measure.

Workstream 3: patient and public involvement

We conducted three focus groups, one in each of Cambridge, London and Sheffield, in partnership with the Alzheimer's Society (AS) volunteer research network; consulting with people living with dementia and family carers about the acceptability of outcomes, which they felt were core and any difficulties in completing outcomes.

We conducted an e-mail consultation with focus group participants afterwards on a report of the main recommendations from across the three groups, to allow participants to comment on domains they had not discussed and to make sure the recommendations to be presented at the conference represented what had been said across the groups.

We also conducted a second e-mail consultation after the consensus conference with the wider AS research network who had not attended the focus groups, to gain further feedback on a report of the main recommendations made at the conference.

Workstream 4: consensus conference

We invited all co-applicants and collaborators of the project to the conference, thus including the wider body of NIHR dementia researchers and additional people who had been involved during the project. Twenty-seven people attended the conference from a wide range of specialties within dementia research.

The conference began with an overview of the project, the systematic review results and recommendations from the focus group consultations. We had previously selected champions with expertise within each of the domains and asked them to synthesise the results of the systematic review and validation data to present recommendations for that domain at the conference. The conference attendees discussed their opinions after each presentation. After this was finished the whole group agreed on overall recommendations.

Results

Systematic review results

Included studies

We found 22,918 original references from database searches and additional references from workstream 1, and included 149 references referring to 125 trials.

Of the 125 included trials, 95 were published completed studies, three were published protocols and 27 were ongoing trials listed on trial registries. Most were RCTs ($n = 124$), and all tested the efficacy of pharmacological interventions.

Outcomes

There were 81 different outcomes used across the trials; 72 questionnaire-/interview-based measures and nine biological techniques used to measure biomarkers. We categorised outcomes by the domain they measured. The domains were:

- cognition (31 outcome measures)
- quality of life (three outcome measures)
- ADLs (12 outcome measures)
- neuropsychiatric symptoms (16 outcome measures)
- global assessment (10 outcome measures)
- biological markers (nine biological techniques).

Patient and public involvement results

Participants

Overall, 18 people participated in patient and public involvement (PPI). The focus groups comprised 12 people: three people living with dementia, two current family carers, six former family carers and one PPI group member.

Five of the focus group participants replied to the first e-mail consultation. Six people replied to the second e-mail consultation: one person with dementia, three current family carers and two former family carers.

Main recommendations

The participants made general recommendations around completing outcomes, as well as recommendations specific to the domains.

Questionnaires' content and delivery

Questioning should be clear, as participants may give different answers depending on the wording of the questions, and too many questions and fast delivery can cause anxiety.

Time and travel

The maximum time for a meeting without a break is 1.5 hours, although researchers should aim for shorter periods. Being able to participate in research locally, rather than having to travel far to a specific centre, would encourage and help with participation.

Carers' participation

Volunteers highlighted the probable disparity between the answers given by people with dementia and carers, although they also thought that this could provide additional data. Volunteers also highlighted that not all people with dementia will have a defined carer and, in the case of those who do, carers should be involved in decisions around participating in research if their time and availability is needed.

Engagement

Many participants thought that clear restatement during the study of the reasons why they were completing particular measures would aid continued engagement in the trial.

Activities of daily living

Volunteers had differing opinions about the use of ADL measures, but generally judged that instrumental ADLs, rather than basic ADLs, were more relevant in mild to moderate dementia. Volunteers suggested that questions should ask about the reasons for impairment, as this is not included in ADL measures.

Biological markers

Volunteers generally thought that biomarkers should be core, viewing them as being the most reliable, objective measures, although carers questioned the value of the data collected, particularly from blood tests.

Some volunteers particularly liked cerebrospinal fluid (CSF) measures, even though they were aware of possible side effects, but they thought that misconceptions about what the procedure involves might discourage participation. Those who had experienced CSF tests did not like the need to have it done in a specific location.

Most volunteers thought that imaging could be core, as it can provide objective data, and that many would consent to scans as giving biological data can make a person with dementia feel that they are contributing useful information. Practical issues around travel were raised, and volunteers agreed that scanning may be difficult for some people with dementia.

Cognition

Overall, volunteers agreed that cognition should be core. People with dementia described the distress of seeing their score worsen, and a tendency to try to prepare for tests to prevent this from happening. Some people preferred the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) to the Mini Mental State Examination (MMSE) as it is more detailed.

Neuropsychiatric symptoms

Some participants said that behaviour is core because it is a significant aspect of dementia and seems more sensitive to illness than ADLs; others thought that behaviour should not be considered in isolation, as it may be less applicable in mild to moderate stages and does not measure the reasons behind behaviour changes.

Quality of life

Volunteers had different opinions over the inclusion of quality-of-life measures as core. One volunteer thought that quality of life is core, as it can give a summary of an individual's experience of dementia. Others were unsure about the sensitivity of quality-of-life measures. It was suggested that comparing carer and patient responses would give the most accurate account of quality of life.

Global

Volunteers had differing opinions about global rating scales. Some approved of the breadth of the measures. However, others suggested that global measures are superficial, depending too much on the individual's experience on the day, and not meaningful.

Consensus conference results

Core domains

Cognition

Cognitive impairment is the core symptom of dementia, and it was therefore judged to be a core domain. The conference recommended the use of either the ADAS-Cog or MMSE, as both are the best available of the included tests based on psychometric properties and are the most commonly used. It would be helpful for a future study to formulate an algorithm to be able to compare scores on both the ADAS-Cog and MMSE.

Biological markers

The conference concluded that structural magnetic resonance imaging (MRI) currently offers the best biological marker of disease progression, although it is not a perfect biomarker. The conference recommends MRI as a core outcome, but only as an optional part of the study, as it would not require as many participants as a cognitive outcome for satisfactory power. This would enable people who are unable or unwilling to undergo MRI to participate.

Non-core domains

The conference judged that the other four domains are important but not core. It was thought that they will frequently be measured in studies and, therefore, we have made recommendations as to which to use on the basis of their frequency of use and psychometric properties.

Activities of daily living

We recommend using an informant-rated measure as people with dementia can underestimate their functional impairment. We recommend the use of the Disability Assessment for Dementia (DAD), a dementia-specific ADL measure that has acceptable psychometric properties in this domain.

Neuropsychiatric

Within this category we recommend the Neuropsychiatric Inventory (NPI), the only measure being used in ongoing disease modification trials and with satisfactory psychometric measures in this population.

Quality of life

We recommend the Dementia Quality of Life Measure (DEMQOL), as it is a dementia-specific measure with acceptable psychometric properties and because it is possible to collect data for it from both the person with dementia and an informant.

Global

For global outcomes we recommend the Clinical Dementia Rating (CDR) scale, a staging instrument specific to dementia with adequate psychometric properties. We recommend using the global CDR score, as using the sum of boxes score makes the scale a multidomain instrument rather than a staging one.

Conclusions

Recommendations

The main recommendations are that cognition and biological markers are the only core outcome domains, and should be measured by the ADAS-Cog or MMSE, respectively, and structural MRI. MRI can be conducted on a subset of trial participants and so MRI findings are an optional outcome. We have also made recommendations for the important, but non-core, domains of ADLs, global, neuropsychiatric and quality of life, recommending the DAD, CDR, NPI and DEMQOL, respectively. As the recommended measures are currently the best available, we expect that additional or alternative outcome measures may supersede the current core set, particularly biological markers, which are the subject of considerable ongoing research.

Future research

As we recommend using either the ADAS-Cog or MMSE for cognition, it would be useful to develop an algorithm to directly compare the scale scores. It would also be useful to conduct further detailed qualitative research with PPI and trial staff, such as clinical research nurses.

Study registration

The project was registered with Core Outcome Measures in Effectiveness Trials [www.comet-initiative.org/studies/details/819?result=true (accessed 7 April)]. The systematic review protocol is registered as PROSPERO CRD42015027346.

Funding

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Chapter 1 Introduction

It is estimated that 850,000 people in the UK are currently living with dementia (> 1% of the entire UK population),[1] and one-third of people born in the UK in 2015 will develop dementia during their lifetime.[2] Dementia care currently costs in excess of £23B per annum,[1] with costs expected to triple in the next 30 years as the number of older people increases. Dementia affects not only the person with the illness, but also their family and wider society, and with the current absence of a preventative treatment, the number of people with dementia is projected to reach > 1 million by 2020 and double again in the subsequent 20 years.[1] However, some recent population studies[3,4] have suggested that the prevalence of dementia among those now reaching 65–75 years of age may be slightly lower and, therefore, the rate of increase, primarily driven by the ageing of the population, may not be as great as once thought. These new data increase the optimism about potential primary prevention of dementia and of finding a disease-modifying treatment[5] that would either halt or delay underlying pathology.

There have been huge strides forward across dementia research, in particular with early diagnosis, information, advanced decision-making, psychological therapies, management of neuropsychiatric symptoms, strategies for family carers and cholinesterase inhibitors in Alzheimer's disease (AD). There have also been positive changes in attitudes, including highlighting personhood and living well with dementia. There is, however, currently no cure or disease-modifying treatment for the common dementias. This may be partly because our research knowledge and funding of dementia lags behind that of other major diseases, such as cancer or heart disease.[6]

Following the successful expansion of NHS Memory Services, the number of people diagnosed with dementia has increased dramatically in England.[7] Currently, dementia sufferers can be offered only symptomatic treatments, as well as access to social and psychological treatment, education, support and advice.[1,8] The NHS thus has a huge potential to use effective disease course-modifying treatments (which may be pharmacological or non-pharmacological, and aimed at dementia in general or individual subtypes) and provides a large and highly motivated group of affected patients and their families who would want to support research and developments in this area.

The National Institute for Health Research (NIHR) has identified this as an important area of research and, through the Efficacy and Mechanism Evaluation programme, is supporting two large drug-repurposing disease modification trials of AD. The first of these, the RADAR trial (Reducing pathology in Alzheimer's Disease through Angiotensin TaRgeting),[9] is a Phase II randomised controlled trial (RCT) evaluating the effect of losartan on brain tissue changes in AD, with magnetic resonance imaging (MRI) brain volume change over 12 months as a primary outcome measure. Second, the MADE study (Minocycline for Alzheimer's Disease Trial),[10] looking at the efficacy of minocycline in AD, measures change in cognition at 24 months with the Mini Mental State Examination (MMSE) and function with the Bristol Activities of Daily Living (BADL) scale. These trials were developed, funded and set up without any liaison between the trial teams. Indeed, both had been funded for almost 2 years before the chief investigators found out about each other's trials and began to communicate about progress and difficulties. The completely different nature of the designs and choice of outcome measures for these trials, together with the lack of co-ordinated activity of the trial teams, illustrate starkly just how much more the UK dementia research community could do at this early stage to strategically develop a co-ordinated approach to developing research in an effective and cost-efficient way, particularly with the outcomes used across trials. Demonstrating efficacy in AD modification has so far defeated the resources and efforts of the global pharmaceutical industry, and it is unlikely that individual academic and NHS organisations will do any better if we cannot agree a unified approach that will allow us to co-ordinate resources and integrate findings.

Delivering high-quality research in dementia is fundamentally important to the NHS and, since May 2013, the NIHR has made good progress towards the target of recruiting 10% of dementia patients into clinical trials. Working in partnership with the Alzheimer's Society (AS) and Alzheimer's Research UK, the NIHR

launched 'Join Dementia Research' to provide 'ready' cohorts of patients consenting to be approached about research. In addition, it has established ENRICH (Enabling Research in Care Homes), a network to support an increase of dementia research in care homes. In February 2015, the UK prime minister announced plans for a further £300M investment in dementia research. The UK has an experienced cadre of dementia triallists with a track record of designing and delivering studies of pharmacological, psychological, educational and other complex interventions, the results of which have often had an international impact on practice. The NIHR has intimated that prospective investigators' testing of putative disease modifiers should very seriously consider the use of adaptive trial designs to improve the efficiency of trials.

Between 1998 and 2012, 101 new potential pharmacological treatments for AD entered trials internationally, but only four drugs have received regulatory approval, all of which were symptomatic treatments rather than disease modifying;[11] these included cholinesterase inhibitors (donepezil, rivastigmine and galantamine). Memantine, the last new drug to receive regulatory approval, was approved more than 10 years ago.[12] Since then, many promising disease-modifying drugs have been proposed, but all have failed at the point of Phase III trials or at earlier stages of development.[13] As a consequence, the number of pharmaceutical companies with drug development programmes in neurodegeneration is shrinking. One suggested explanation for the failure of so many new drugs for AD has been that by the point of clinical presentation the burden of neurodegeneration may already be too great for disease-modifying interventions to have efficacy. Another is that the majority of new drugs target just one of the numerous pathological mechanisms (e.g. inflammation, hypoxia and oxidative stress, reduced energy metabolism) that are active and probably contribute to disease severity and progression. It is predicted that if a treatment that could slow the progression of mild to moderate dementia by 50% became available in 2020, this could reduce the numbers of people living with severe dementia from 14% to 2% by 2050.[14] At the G8 Dementia Summit held in London in December 2013, a commitment was made to find a disease-modifying treatment by 2025.[15]

To improve the possibility of identifying a disease-modifying treatment, it is important that the outcomes measured in trials are appropriate, sensitive and clinically meaningful.[16–18] It is also essential that there is a harmonisation of the outcome measures being used across trials to combat the large variance of measures currently used.[19] In 2015, the NIHR commissioned a call for the development of a core set of outcomes to be used in future disease modification trials, particularly in mild to moderate dementia. Developing standardised outcome sets is now being recognised as important across medical research, so that there should be a commitment to measuring minimum sufficient sets of outcomes for every major medical condition.[20] An agreed core set of outcomes would improve the efficiency and effectiveness of trials, and enhance interpretation of data across disease-modifying trials. This applies to both drugs and non-pharmacological interventions so that the efficacy of, for example, exercise, diet changes and new drugs can be compared. It is also important to consider the acceptability of measurement packages and the burden that they put on patients and their families. The priorities of patients in disease-modifying trials may not be the same as those of researchers, and patients in focus groups appear to be less concerned about stigma and other negative effects of diagnoses but wish to unambiguously know their disease status and accept biological and possibly invasive tests.[21] These may include quality-of-life and related outcomes that people with dementia and their families report as being important to them, and can inform cost-effectiveness analysis, as well as more symptom-related scales, such as cognition. Finally, a standardised core outcome set would aid meta-analysis and thus enable the combination of small data sets to better inform practice. Therefore, there is an urgent need for a consensus from dementia researchers in the UK about the core outcomes that should be used in future disease modification trials in mild to moderate dementia.

This has led to the current project, which intends to produce a consensus within the dementia community about the core outcomes for disease modification trials. It is funded by the NIHR Health Technology Assessment programme, and brings together as co-applicants and collaborators, a large multidisciplinary team of experts who are co-authors of the report and the AS, which has led the public involvement of experts by experience arm of the study. The aims of the project are detailed in *Chapter 2*.

In workstream 1 we gathered possible relevant references that had been identified by other related systematic reviews. These came from co-applicant Louise Lafortune, who led a systematic review on non-pharmacological interventions for people living with dementia. We also searched the Cochrane Dementia and Cognitive Improvement Group study register (ALOIS), which is maintained by the Cochrane Dementia and Cognitive Improvement Group, represented by co-applicant Jenny McCleery. The use of additional references from workstream 1 is detailed in *Chapter 3*. In addition, we looked at other core sets being developed by members of the group, including an AS and European Union Joint Programme – Neurodegenerative Disease Research (JPND)-funded study about outcomes used in psychosocial interventions in dementia, led by co-applicant Gail Mountain, and a review of measures which are important to patients with dementia funded by the International Consortium for Health Outcomes Measurement Working Group (ICHOM) led by co-applicant Charlotte Roberts.

In workstream 2, we conducted a systematic review of the outcome measures that have been, and are currently, used in disease-modifying trials of dementia; to our knowledge this is the first systematic review of outcomes used in disease modification trials, the methods and results of which are detailed in *Chapters 3* and *4*.

We considered the frequency of outcome use and validation, and discussed these outcomes with people living with dementia and their carers. This patient and public involvement (PPI) consultation method and results are detailed in *Chapters 5* and *6*.

We then brought all of the systematic review information together, with each potential domain being presented by a champion, as well as presentation of the PPI focus groups results. This expert body debated the questions and came to conclusions. Summaries of these presentations and the conference discussion are detailed in *Chapter 7*. The discussions and conclusions are in *Chapters 8* and *9*.

Chapter 2 Research question and objectives

The research question we set out to answer was 'what are the core clinical and patient-relevant health outcomes that should be used in all NIHR-funded trials of disease modification in mild to moderate dementia, and how should they be measured?'.

Objectives

1. To appraise existing research into outcome sets being developed for use in psychosocial interventions (funded by the AS and JPND) and around what is most important to patients (measured by the ICHOM), in the light of the goals of this study.
2. To update and add to the existing body of work by a systematic search of the outcomes used in pharmacological and non-pharmacological studies of disease modification.
3. To appraise the outcomes identified through this systematic search, either using the existing research as above or through the literature.
4. To synthesise the evidence to identify important, valid, reliable and acceptable outcome measures in mild to moderate dementia.
5. To ensure by consultation that these outcome measures are acceptable and relevant to patients, carers, clinicians and the research community, and that they would be practical to include in NIHR trials and other studies.
6. To produce updated, evidence-based recommendations on the best outcome measures for disease modification in mild to moderate dementia research and practice.
7. To validate these recommendations through a consensus conference.
8. To set out these results in a research paper and report for the *Health Technology Assessment* journal.
9. To enable the NIHR to specify an agreed set of core outcomes to be used for all funded trials of disease modification in mild to moderate dementia.

Core Outcome Measures in Effectiveness Trials

We registered the project with Core Outcome Measures in Effectiveness Trials (COMET), a database of planned, ongoing and completed core outcome sets. The project's COMET record is accessible at www.comet-initiative.org/studies/details/819?result=true (accessed 7 April 2016).

Chapter 3 Systematic review methods

Protocol

We created the protocol for the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[22] and registered it with PROSPERO [no. CRD42015027346; accessible at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027346 (accessed 7 April 2016)].

Search strategy

Database searches

As specified in the protocol, we searched Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, MEDLINE, Latin American and Caribbean Health Sciences Literature (LILACS) and PsycINFO.

The search terms within the protocol were originally adapted from another systematic review being carried out by a member of the group.[23] These search terms, however, resulted in an unacceptably high number of irrelevant results, with > 85,000 references identified in a search of MEDLINE alone. Therefore, in consultation with the project steering group, we adapted the search terms to reduce irrelevant references being picked up. The full search strategy for MEDLINE (via OvidSP) is shown in *Appendix 1*, with the same strategy used for EMBASE and PsycINFO (via OvidSP), and modified for searches in CENTRAL (via The Cochrane Library), CINAHL (via EBSCO*host*), and LILACS [via the Virtual Health Library (VHL) Regional Portal]. As we are interested in outcome measures available in English, we limited database searches to English language where possible (CINAHL, EMBASE, LILACS, MEDLINE and PsycINFO).

As part of workstream 1 we also searched ALOIS and added these references to the ones found in the other database searches. We used the advanced search for intervention studies, with a combination of search terms: ('outcome' OR outcome OR outcomes OR 'instrument' OR instrument OR instruments OR 'measure' OR measure OR measures) AND (intervention OR therapy OR therapeutic OR trial OR trials) AND (control OR controlled), selecting 'Treatment dementia' as the study aim, all study designs, <any> interventions, and <any> if included in Cochrane.

Additional databases

In order to ensure that we picked up all outcomes that are currently being used, we adapted the protocol to include searches of the International Standard Randomised Controlled Trial Number (ISRCTN) and ClinicalTrials.gov trial registries for ongoing disease modification trials in dementia. To search the ISRCTN database we selected the trial status as 'ongoing' and the condition as 'dementia'. To search ClinicalTrials.gov we combined 'dementia' AND '(control OR controlled)', and limited the search to 'open studies'.

Hand-searches

We hand-searched the bibliographies of relevant systematic reviews that were found within the database searches. We then also searched additional references collected in workstream 1, from a systematic review of non-pharmacological interventions for dementia.

Search dates

Searches were conducted on 11 December 2015 (for ALOIS, CENTRAL, CINAHL, EMBASE, LILACS and PsycINFO), 22 January 2016 (for ISRCTN) and 29 January 2016 (for ClinicalTrials.gov). All of the searches were conducted from database inception, with no limit on the end date.

Study inclusion

Inclusion criteria

We defined a disease modification trial as one where the intervention aims to change the underlying pathology of the dementia disease. This is as opposed to trials that aim solely to treat the symptoms of dementia, but not affect the underlying illness.

We included trials if they met all of the following criteria:

1. The full text is written in English.
2. The trial is published in a peer-reviewed journal or is an ongoing trial.
3. At least some of the participants have clinically diagnosed mild or moderate dementia.
4. It is a trial that aimed to modify the dementia disease.
5. It is a RCT or clinical controlled trial (CCT) with:
   i. the intervention directed at the person with dementia
   ii. the control or comparator arm comprising treatment as usual, no intervention, sham therapy, other therapy or placebo.
6. At least one quantitative outcome measure related to disease modification in mild or moderate dementia.

Exclusion criteria

We excluded studies where:

1. all participants had severe dementia (according to the study inclusion criteria, including a MMSE score of < 12 or equivalent)
2. the whole study was set in care homes, as the commission call specified a review of outcome measures that modify the disease of mild to moderate dementia and very few of whom would be resident in care homes
3. all participants had mild cognitive impairment (MCI)
4. the outcomes were only:
   i. qualitative
   ii. related to carers
   iii. economic
   iv. related to drug levels.

Screening titles and abstracts, and full texts

We screened titles and abstracts found across the searches for relevance. Two reviewers (DG and LW) piloted this procedure by independently screening the first 20 titles and abstracts and then compared their decisions. There were no disagreements, confirming the reliability of the first screening.

Three raters (AGS, DG and LW) also piloted the screening of full texts for inclusion criteria. They screened the first 10 papers independently, comparing answers and discussing, and then repeating the process with the next 10 papers. The three raters agreed on 80% of the first 20 papers, with no decision to exclude a paper that was eventually included. The raters disagreed regarding whether or not four papers should be excluded (see *Appendix 2*). The disagreements were whether or not the intervention was aiming to modify the underlying pathology of the disease of dementia. We agreed to solve this by examining in detail how the intervention is described in the background section, as well as the aim of the intervention within the trial. We also agreed to discuss any trials where we were unsure if the aim was to modify the disease between the raters and Gill Livingston if necessary. If a trial seemed to fulfil the inclusion criteria but we needed extra information about it, we contacted the authors to ask for this.

Data extraction

We extracted data about trial location, trial type, dementia type and severity, how the dementia diagnosis was made, participants' sex and age, description of the intervention (number of participants; *n*), description of the comparator group (*n*), outcomes related to disease modification (primary or secondary if reported) and when outcomes were measured. To assess the accuracy of extracted data, Derek Groskreutz and Lucy Webster independently extracted data from the same subsample of five trials and compared their answers. There were no differences between the raters' extracted data. We used this exercise, and an additional five papers, to pilot the data extraction tool and ensure that all relevant data from trials were captured. After piloting the tool, we created a second data extraction tool, which included the time period from baseline when each outcome was measured for each study, as within trials different outcomes were measured at different time points.

Data synthesis

For each outcome measure we listed how frequently it was used (i.e. number of trials) with how many participants there were across the trials. We searched Google Scholar (Google Inc., Mountain View, CA, USA) to find a copy of each outcome measure in English, either the manual or a key paper relating to its development. We divided all outcomes into domains [specifically cognition, activities of daily living (ADLs), biological markers, neuropsychiatric symptoms, quality of life and global]. Initially we had not planned to consider global outcomes, but we added it as a separate outcome category as we found relevant measures.

Quality assessment

As our aim was to synthesise the outcomes used across trials, rather than to report results, we did not consider it necessary to assess the quality of studies.

Outcome validation

We conducted separate iterative searches on Google Scholar using the name of the measure and psychometric terms, and consulted within our expert group for each outcome measure to find information on the measures' psychometric properties relevant to people living with dementia. Specifically, we sought information about:

- if the measure is validated in people with mild to moderate dementia for the outcome in which it is used as a measure
- if there are any relevant populations in which the measure is validated (e.g. mild to moderate dementia, ethnic groups, languages)
- unit of measurement
- sensitivity to change
- minimal clinically important difference
- reliability (inter-rater and test–retest)
- acceptability
- ceiling-and-floor effects
- average time taken to complete
- who fills in the questionnaire (i.e. researcher through patient, family carer, paid carer or observation, or self-complete)
- any risks identified of use of the measure.

Chapter 4 Results of the systematic review

Details of included and excluded studies

Figure 1 shows a PRISMA flow diagram with the results of the searches. Altogether we found 22,918 original references from searches of databases and workstream 1 (ALOIS and another systematic review of non-pharmacological interventions for dementia). From the screening of all titles and abstracts, we excluded 22,021 references and sought the full texts of 897 abstracts. From the full texts, we excluded 748 papers; a list of excluded studies and reasons for exclusion is in *Appendix 3*. We included 149 reports of 125 trials.

The 125 trials included 95 published trials, three published protocols and 27 ongoing trials, the characteristics of which are available, respectively, in *Tables 1–3* in this chapter. One trial was a CCT, with the other

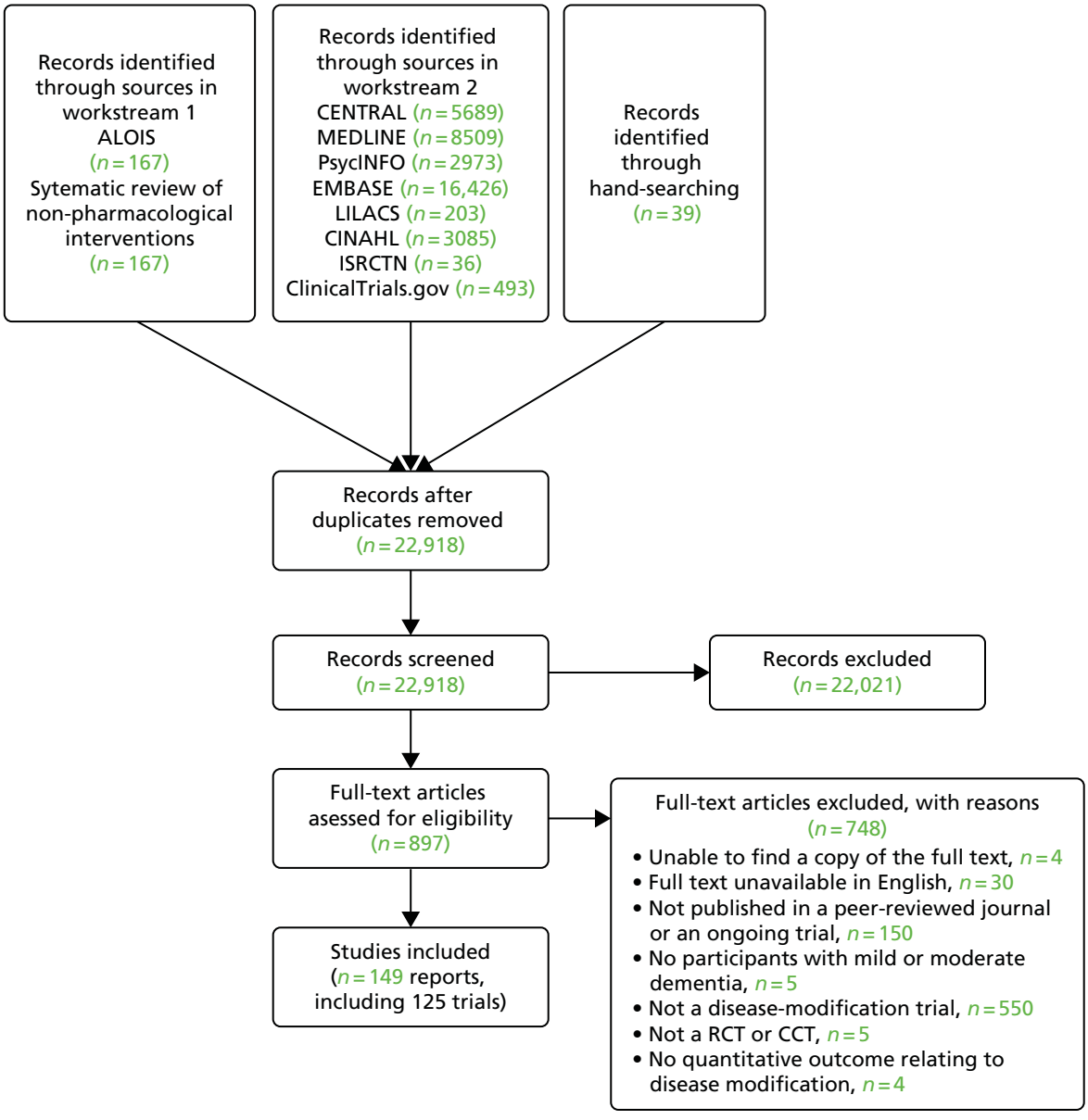

FIGURE 1 The PRISMA flow diagram.

124 trials being RCTs. Trials were carried out in Australia ($n = 2$), Austria ($n = 1$), Canada ($n = 1$), China ($n = 2$), Denmark ($n = 1$), France ($n = 2$), Germany ($n = 5$), Iran ($n = 2$), Italy ($n = 4$), Japan ($n = 1$), Korea ($n = 1$), the Netherlands ($n = 2$), New Zealand ($n = 1$), Poland ($n = 2$), Russia ($n = 1$), Spain ($n = 3$), Sweden ($n = 4$), Taiwan ($n = 1$), the UK ($n = 6$) and the USA ($n = 46$); 37 were multicountry studies.

Across the trials, most participants had only AD; 16 studies included only patients with mild AD (seven of which specified early AD), six included patients with moderate AD, 84 involved patients with mild to moderate AD, two included patients with mild to severe AD, two studies included patients with moderate to severe AD and in one study all participants had AD of unspecified severity but were living at home. Eight trials also included participants with MCI, alongside mild ($n = 5$) or mild to moderate AD ($n = 3$). Three trials combined participants with AD and vascular dementia, two included patients with mild to moderate AD or vascular dementia, and one comprised patients with mild to moderate AD, with or without vascular dementia. Two trials included participants with vascular dementia only, one included patients with mild to moderately severe vascular dementia and one included patients with mild to moderate subcortical ischaemic vascular dementia. One trial included participants with mild to moderate primary degenerative dementia or vascular dementia.

Outcomes found in the review

An overview of the findings of the systematic review is available in *Box 1*.

BOX 1 Overview of findings of the systematic review

Findings (number of trials)

Cognitive outcomes (117 trials measured at least one cognitive outcome; 31 different outcomes)

Global: Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) ($n = 92$); Mattis Dementia Rating Scale ($n = 1$); MMSE ($n = 83$); Modified Telephone Interview for Cognitive Status ($n = 1$); and Vascular Dementia Assessment Scale Cognitive subscale ($n = 1$).

Batteries: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD)'s Neuropsychological Test Battery ($n = 2$); Cogstate Alzheimer's Battery ($n = 6$); Computerised Neuropsychological Test Battery ($n = 1$); Frontal Assessment Battery ($n = 1$); Mental Deterioration Battery ($n = 1$); Neuropsychological Test Battery ($n = 7$); Severe Impairment Battery ($n = 1$); Syndrome Short Test ($n = 2$); Wechsler Adult Intelligence Scale – Revised ($n = 1$); Wechsler Memory Scale ($n = 5$); and Western Aphasia Battery ($n = 1$).

Individual tests (either used in combination or to supplement the ADAS-Cog or MMSE): Buschke Selective Reminding Test ($n = 3$); Benton Visual Retention Test ($n = 1$); clock drawing test ($n = 2$); controlled oral word association test ($n = 2$); digit span test ($n = 2$); digit symbol ($n = 3$); dot counting *n*-back task ($n = 1$); fluency tests ($n = 7$); Mohs number cancellation test ($n = 1$); recall tasks ($n = 3$); Rey 15-Item Memory Test ($n = 1$); Stroop Colour Word Interference Test ($n = 4$); token test ($n = 1$); trail making test ($n = 10$); and word recognition ($n = 1$).

Techniques for biological markers (71 trials measured at least one biological marker; nine different techniques)

Imaging: electroencephalography ($n = 3$); Doppler ultrasound ($n = 1$); MRI ($n = 30$); magnetic resonance spectroscopy ($n = 1$); positron emission tomography ($n = 20$); and single-photon emission computerised tomography ($n = 1$).

Fluid: blood tests ($n = 35$); cerebrospinal fluid analysis ($n = 48$); and urine analysis ($n = 1$).

BOX 1 Overview of findings of the systematic review (*continued*)

Neuropsychiatric outcomes (58 trials measured at least one neuropsychiatric outcome; 16 different outcomes)

Global: Alzheimer's Disease Assessment Scale – Non-Cognitive subscale ($n = 7$); Behavioural Pathology in Alzheimer's Disease Rating Scale ($n = 1$); Brief Psychiatric Rating Scale ($n = 3$); CERAD's Behavioural Scale ($n = 1$); Dysfunctional Behavior Rating Instrument ($n = 1$); Neuropsychiatric Inventory ($n = 38$); Nurses' Observation Scale for Geriatric Patients ($n = 2$); Plutchik Geriatric Rating Scale ($n = 1$); and Revised Memory and Behaviour Problems Checklist ($n = 1$).

Specific symptoms: Cohen-Mansfield Agitation Inventory ($n = 1$); Columbia Suicide Severity Rating Scale ($n = 3$); Cornell Scale for Depression in Dementia ($n = 3$); Geriatric Depression Scale ($n = 10$); Hamilton Depression Rating Scale ($n = 5$); Montgomery Depression Rating Scale ($n = 2$); and Zerssen Adjective Mood Scale ($n = 2$).

Quality-of-life outcomes (16 trials measured at least one quality-of-life outcome; three different measures)

Dementia quality-of-life measure ($n = 4$); EuroQol-5 Dimensions Scale ($n = 5$); and Quality of Life in Alzheimer's Disease Scale ($n = 8$).

Activities of daily living outcomes (68 trials measured at least one activities of daily living outcome; 12 different measures)

Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory ($n = 35$); Alzheimer's Disease Functional Assessment and Change Scale ($n = 2$); BADL ($n = 5$); Dependence scale ($n = 2$); Disability Assessment For Dementia ($n = 13$); Functional Activities Questionnaire ($n = 3$); Interview for Deterioration in Daily Living Activities in Dementia ($n = 2$); Katz Index of Activities of Daily Living Scale ($n = 4$); Lawton Instrumental Activities of Daily Living Scale ($n = 8$); Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living ($n = 3$); Physical Self-Maintenance Scale ($n = 3$); and Video Recorder Home Behavioural Assessment ($n = 1$).

Global outcomes (80 trials measured at least one global outcome; 10 different measures)

Impression of change: Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change ($n = 8$); Clinical Global Impression's Scale ($n = 15$); and Clinician's Interview-Based Impression of Change plus Caregiver Input ($n = 12$).

Multiple domains: Blessed Dementia Rating Scale ($n = 3$); Dementia Severity Rating Scale ($n = 3$); Gottfries–Bråne–Steen Rating Scale for Dementia ($n = 4$); Sandoz Clinical Assessment-Geriatric Scale ($n = 2$); and Short Cambridge Mental Disorders of the Elderly Examination ($n = 1$).

Staging of dementia: Clinical Dementia Rating Scale ($n = 48$); and Global Deterioration Scale ($n = 6$).

We contacted three authors to request extra information regarding outcomes; two of whom provided this.[9,24] There were 81 different outcomes used across the trials; 72 questionnaire- or interview-based measures and nine biological techniques used to measure biomarkers. We categorised outcomes by the domain they measured. The domains were:

- cognition
- quality of life
- ADLs
- neuropsychiatric symptoms

- global assessment
- biological markers.

To help understand the findings of the review, we first provide an overview of the outcome measures used and their frequency of use in individual studies before describing the characteristics of these studies. We have divided the studies into published studies, ongoing trials and protocols.

Box 1 shows the outcome measures found. When outcome measures were categorised by domains, cognition was the largest domain in terms of the variety of instruments used, with 31 outcome measures used across the trials. Furthermore, cognition was the most widely used domain, being measured through at least one outcome measure in 117 of the 125 included trials. The domain included measures that look at cognition globally ($n = 5$), individual neuropsychological tests focusing on specific elements of cognition ($n = 15$) and then batteries of individual cognitive tests ($n = 11$). Of the included batteries, two are solely computerised (Cogstate Alzheimer's Battery and Computerised Neuropsychological Test Battery).

The second most widely used outcomes were global measures, with 80 trials using at least one global outcome from a variety of 10 measures. The 10 measures included scales that look at clinical impressions of change ($n = 3$) that consider multiple domains ($n = 5$) and that stage dementia ($n = 2$). Seventy trials measured at least one biological marker, using one of nine biological techniques. The techniques can be further divided into imaging techniques [e.g. MRI ($n = 6$)] and fluid [e.g. blood tests ($n = 3$)]. Some of the biological markers measured via these techniques included the levels of amyloid-β peptide and microtubule-associated protein tau in blood and cerebrospinal fluid (CSF), changes in brain volume on MRI and changes in glucose metabolism and the density of amyloid-β peptide plaques on positron emission tomography (PET).

Activities of daily living were measured across 68 trials, with 12 different measures used. Neuropsychiatric symptoms were measured across 58 trials using 16 different measures. The neuropsychiatric outcomes included scales measuring symptoms globally ($n = 9$) and scales that focus on specific symptoms [e.g. depression or agitation ($n = 7$)]. Finally, quality-of-life outcomes were the least used across the trials; only 16 of the 124 trials measured this domain and they employed one of three measures.

Published trials

Characteristics of the included published trials are given in *Table 1*.

We included 95 trials published between 1990 and 2015. Most studies included all or some participants with AD ($n = 94$), and one study included only participants with vascular dementia. All were RCTs, except for one CCT. The trials included a total of 22,362 participants.

A total of 79 different outcomes were used. The majority of trials ($n = 94$) used at least one cognitive outcome,[25,27–29,31,33,37–41,43,45–47,49,51–55,57–59,61–64,66,68–71,73,75,77,78,81,85–90,92,93,96–99,101–116,118,119,121–146] of which there were 30 different measurement tools. The second most commonly measured domain was a global outcome, with nine different measures used across 64 trials.[25,27–29,31,33,37–39,41,45–47,49,52,54,55,57–59,62–64,66,68,73,75,78,81,86–90,92,97,104,106–108,110,112–114,118,119,121–128,131,133,134,137,139,142–146] Fifty trials included a neuropsychiatric outcome,[25,27,28,33,37,41,43,45–47,51,52,55,57,64,66,68,75,78,86–93,97,104,106,107,110,112,115,118,119,121,123,125,126,130,131,133,134,137–140,143,145,146] with a variety of 16 measures used. ADLs were measured in 55 trials, using 12 measures.[27,28,33,37,41,45,46,49,51,52,54,55,57,59,61,63,64,66,68,77,78,81,85–90,92,97,104,106–108,110–112,114,115,118,119,121–125,128,134,135,137,138,142–145] Biological markers were measured in 51 trials using a variety of nine biological techniques.[29,31,33,37,40,43,47,53–55,59,63,66,68–71,73,77,78,81,85,86,89,93,95,96,98,101,103–105,109–113,115,116,121,122,129–132,137,139–141,144,145] Eleven of the published trials measured quality of life, using one of three outcomes.[28,33,66,68,78,86,89,90,104,112,124]

Published protocols

The characteristics of the published protocols are described in *Table 2*.

TABLE 1 Published trials

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Aisen, 2000;[25] Aisen *et al.*, 2000[26]	USA	RCT	Mild to moderate AD	A MMSE score of 13–26	138	20 mg per day of prednisone (Deltasone, Pharmacia & Upjohn Inc., Kalamazoo, MI, USA) for 4 weeks, then 10 mg per day of prednisone for 1 year (69)	Placebo (69)	Prednisone, 49.3%; placebo, 50.7%	Prednisone, 73.4; placebo, 72.3	Primary: ADAS-Cog Secondary: CDR (SB), BDRS, HAM-D and BPRS
Aisen *et al.*, 2002[27]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA	40	200 mg per day of nimesulide (Mesulid, Helsinn Healthcare SA, Pazzallo, Switzerland) for 12 weeks (21)	Placebo (19)	Nimesulide, 38%; placebo, 47%	Nimesulide, 73; placebo, 74	ADAS-Cog, MMSE, CDR (SB), BPRS, HAM-D and BDRS (ADL section)
Aisen *et al.*, 2003[28]	USA	RCT	Mild to moderate AD	A MMSE score of 13–26	351	25 mg of rofecoxib (Vioxx, Merck Sharp & Dohme, Kenilworth, NJ, USA) per day (122) or 440 mg of naproxen per day (118) for 12 months	Placebo (111)	Placebo, 55.9%; naproxen, 48.3%; rofecoxib, 54.9%	Placebo, 73.8; naproxen, 74.1; rofecoxib, 73.7	Primary: ADAS-Cog Secondary: CDR (SB), NPI, QOL-AD and ADCS-ADL
Aisen *et al.*, 2006[29]	USA	RCT	Mild to moderate AD	DSM-4[30] and a MMSE score of 13–25	58	100 mg per day of 3-APS (15), 200 mg per day of 3-APS (16) or 300 mg per day of 3-APS (14) for 3 months	Placebo (13)	100 mg, 33%; 200 mg, 75%; 300 mg, 50%; placebo, 46%	75.1	CSF analysis (Aβ40, Aβ42, and T-tau), ADAS-Cog, MMSE and CDR (SB)
Aisen *et al.*, 2007[31]	USA	RCT	Mild to moderate AD	A MMSE score of 13–25	58	100 mg per day of tramiprosate (Alzhemed, BELLUS Health, Laval, QC, Canada), 200 mg per day of tramiprosate or 300 mg per day of tramiprosate for 3 months (*n* not specified)	Placebo (*n* not specified)	Not specified	Not specified	Primary: MMSE, ADAS-Cog and CDR (SB) Secondary: CSF analysis (biomarkers: only Aβ42 mentioned)

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Aisen *et al.*, 2008;[32] National Institute on Ageing, and the General Clinical Research Centre Programme, 2008;[33] Viswanathan, 2009[34]	USA	RCT	Mild to moderate AD	A MMSE score of 14–26	409	5 mg per day of folic acid, 1 mg per day of vitamin B_{12} and 25 mg per day of vitamin B_6 for 18 months (240)	Placebo (169)	56%	76.3 (50+)	Primary: ADAS-Cog Secondary: MMSE, CDR (SB), ADCS-ADL, NPI, QOL-AD and blood tests (homocysteine levels)
Aisen *et al.*, 2011;[35] Gauthier *et al.*, 2009;[36] Saumier *et al.*, 2009[37]	Canada and the USA	RCT	Mild to moderate AD	DSM-4,[30] NINCDS-ADRDA and a MMSE score of 16–26	1052	200 mg per day of tramiprosate (352) or 300 mg per day of tramiprosate (347) for 78 weeks	Placebo (353)	53%	73.9 (48–94)	ADAS-Cog, CDR (SB), MMSE, CIBIC+, NPI, DAD, blood tests (Aβ), CSF analysis (tau and Aβ) and urine analysis (Aβ) In substudy: MRI ($n = 312$; volumetric)
Akhondzadeh *et al.*, 2010[38]	Iran	RCT	Mild to moderate AD	DSM-4,[30] NINCDS-ADRDA and a MMSE score of 15–26	54	30 mg per day of saffron for 22 weeks (27)	Donepezil 10mg per day (27)	Saffron, 48%; donepezil, 44%	Saffron, 72.7; donepezil 73.85 (55+)	MMSE, ADAS-Cog and CDR (SB)
Akhondzadeh *et al.*, 2010[39]	Iran	RCT	Mild to moderate AD	DSM-4[30] and a MMSE score of 15–26	46	30 mg per day of saffron for 16 weeks (23)	Placebo (23)	Saffron, 43%; placebo, 48%	Saffron, 72.65; placebo, 73.13 (55+)	MMSE, ADAS-Cog and CDR (SB)
Alvarez *et al.*, 2000[40]	Spain	RCT	Mild to moderate AD or vascular dementia	NINCDS-ADRDA, DSM-4[30] and a MMSE score of 14–26	45	*Polypodium leucotomos* extract (Anapsos, A.S.A.C. Pharma, Alicante, Spain) 360 mg per day (15) or 720 mg per day (15) for 4 weeks	Placebo (15)	Not specified	73.8 (56–89)	Primary: ADAS-Cog Secondary: EEG and Doppler ultrasound (blood flow haemodynamics)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Alvarez *et al.*, 2006;[41] Alvarez *et al.*, 2011[42]	Spain	RCT	Mild to moderate AD	NINCDS-ADRDA, DSM-4[30] and a MMSE score of 14–25	279	10 ml per day of FPE 1070 (Cerebrolysin®, EVER Neuro Pharma GmBH, Unterach, Austria) (69), 30 ml per day of FPE 1070 (70), or 60 ml per day of FPE 1070 (71) 5 days per week for 4 weeks and on 2 days per week for next 8 weeks	Placebo (69)	10 ml, 71.7%; 30 ml, 75.4%; 60 ml, 70.6%; placebo, 65.5%	10 ml, 72.2; 30 ml, 73.4; 60 ml, 74.6; placebo, 73.9	Primary: ADAS-Cog and CIBIC+ Secondary: MMSE, NPI, trail making test and DAD
Asthana *et al.*, 1999[43]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA	12	0.05 mg per day of 17 β-oestradiol for 8 weeks (6)	Placebo (6)	100%	β-oestradiol, 79.5 (66–89); placebo, 77.6 (70–86)	Buschke Selective Reminding Test, Wechsler Memory Scale, Stroop Colour Word Interference Test, trail making test, fluency test, token test, MMSE, BDRS (cognitive section), BPRS and blood tests (IGF-1 and IGFBP-3)
Babiloni *et al.*, 2009;[44] Pasqualetti *et al.*, 2009[45]	Italy and the USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 16–25	132	800 mg per day of ibuprofen (and 20 mg per day of esomeprazole) for 12 months (66)	Placebo (66)	Placebo, 65%; ibuprofen, 61%	Placebo, 74.0; ibuprofen, 73.7	Primary: ADAS-Cog Secondary: MMSE, Geriatric DS, Katz ADL, Lawton IADL, NPI, CDR (SB and global) and CIBIC+
Bae *et al.*, 2000[46]	Korea	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 10–24	53	30 ml per day of Cerebrolysin for 4 weeks (34)	Placebo (19)	Cerebrolysin, 68%; placebo, 63%	Cerebrolysin, 73.1; placebo, 69.0	Primary: ADAS-Cog, CGI Secondary: MMSE, Geriatric DS, Katz ADL and Lawton IADL

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Ban *et al.*, 1990[47]	Italy	RCT	Mild to moderate primary degenerate dementia or vascular dementia	DSM-3[48]	178	90 mg per day of nimodipine (Periplum, ITALFARMACO S.p.A., Milan, Italy) for 12 weeks (89)	Placebo (89)	Nimodipine, 55%; placebo, 61%	75.4 (55–95)	CGI, HAM-D, MMSE, Global DS, SCAG, PGRS, Wechsler Memory Scale and blood tests [serum bilirubin, alkaline phosphatase, lactic dehydrogenase, electrolytes (Na, K, Cl), cholesterol, total CO_2, SGOT, SGPT and BUN determinations]
Bayer *et al.*, 2005;[49] Holmes *et al.*, 2008[50]	UK	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 14–26	80	Immunisation of AN-1792 (Aβ1–42 peptide, 50 µg or 225 µg) using QS-21 adjuvant (50 µg or 100 µg) for 24 weeks (16 in each group)	QS-21, 50 (8); QS-21, 100 (8)	QS-21 50 µg, 25%; QS-21 100 µg, 25%; AN-1792 50 µg + QS-21 50 µg, 37.5%; AN-1792 50 µg + QS-21 100 µg, 43.8%; AN-1792 225 µg + QS-21 50 µg, 43.8%; AN-1792 225 µg + QS-21 100 µg, 31.3%	QS-21 50 µg, 70.3; QS-21 100 µg, 72.5; AN-1792 50 µg + QS-21 50 µg, 74.3; AN-1792 50 µg + QS-21 100 µg, 74.1; AN-1792 225 µg + QS-21 50 µg, 72.3; AN-1792 225 µg + QS-21 100 µg, 71.7 (under 85)	Primary: ADAS-Cog, MMSE, ADCS-CGIC and DAD
Bentham *et al.*, 2008[51]	UK	RCT	Mild to moderate AD, with or without vascular dementia	DSM-4	310	75 mg per day of aspirin for 12 weeks (156)	Avoid aspirin (154)	Aspirin, 63%; non-aspirin, 62%	Aspirin, 51–90; non-aspirin, 46–90	Primary: MMSE and Bristol ADL Secondary: NPI
Bilikiewicz, 2004[52]	Poland	RCT	Mild to moderate AD	DSM-4,[30] NINCDS-ADRDA and a MMSE score of 10–24	105	Colostrinin (Colostrinin, Biotech, ReGen Therapeutics Plc, London, UK) was 100 µg on alternate days for 3 weeks followed by 2-week drug-free cycle repeated three times for 15 weeks (53)	Placebo (52)	Not specified	50+	Primary: ADAS-Cog and CGI Secondary: Lawton IADL, MMSE, Global DS, Geriatric DS and ADAS-Noncog

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Black *et al.*, 2010[53]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 14–26	30	0.5 mg/kg of i.v. bapineuzumab (Janssen Alzheimer Immunotherapy, San Francisco, CA, USA) (6), 1.0 mg/kg of i.v. bapineuzumab (6) or 5.0 mg/kg of i.v. bapineuzumab (10) every 10 weeks for 52 weeks	Placebo (8)	Placebo, 87.5%; 0.5 mg, 50%; 1.5 mg, 16.67%; 5 mg, 30%	Placebo, 69.88; 0.5 mg, 74.67; 1.5 mg, 72.33; 5 mg, 74.70 (50–85)	Primary: MMSE Secondary: blood tests (Aβ1 and Aβ40)
Blennow *et al.*, 2012;[54] Rinne *et al.*, 2010[55]	Finland and the UK	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 18–26	28	0.5 mg/kg of i.v. bapineuzumab (7), 1.0 mg/kg of i.v. bapineuzumab (7) or 2.0 mg/kg of i.v. bapineuzumab (6) every 13 weeks up to 78 weeks	Placebo (8)	Bapineuzumab groups, 42%; placebo, 57%	Bapineuzumab groups, 67.26; placebo, 70.00 (50–80)	Primary: ADAS-Cog, DAD, NTB, MMSE and PET (amyloid and glucose) Secondary: CDR (SB), NPI and MRI (volumetric) In substudy: CSF analysis (T-tau, P-tau and Aβ)
Blennow *et al.*, 2012;[54] Salloway *et al.*, 2009[56]	USA	RCT	Mild to moderate AD	A MMSE score of 16–26	229	Intravenous bapineuzumab in four ascending dose groups 0.15 mg/kg, 0.5 mg/kg, 1.0 mg/kg or 2.0 mg/kg every 13 weeks up to 78 weeks (124 between all 4 groups)	Placebo (110)	Bapineuzumab, 50.0%; placebo, 59.8%	69.1	Primary: ADAS-Cog and DAD Secondary: NTB, MMSE, CDR (SB) and MRI (volumetric) In substudy: CSF analysis ($n = 35$; T-tau, P-tau and Aβ42)
Bowen *et al.*, 2015[57]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 12–24	108	Leuprolide (Lupron, AbbVie, Maidenhead, UK) depot 11.25 mg (36) or 22.5 mg (36) every 12 weeks for 48 weeks	Placebo depot (36)	100%	11.25 mg, 78.75 (67–93); 22.5 mg, 78.25 (67–88); placebo, 76.97 (65–88)	Primary: ADAS-Cog and ADCS-CGIC Secondary: NPI, HAM-D and ADCS-ADL

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Claxton *et al.*, 2015[58]	USA	RCT	Amnestic MCI ($n = 39$) or mild to moderate AD ($n = 21$)	NINCDS-ADRDA and a MMSE score of > 15	60	20 IU per day insulin (20) or 40 IU per day insulin (20) for 21 days	Placebo (20)	Not specified	Not specified	Primary: recall tasks, Buschke Selective Reminding Test Secondary: DSRS, BVRT, dot counting *n*-back task, Stroop Colour Word Interference Test
Craft *et al.*, 2012[59]	USA	RCT	Amnestic MCI ($n = 64$) or mild to moderate AD ($n = 40$)	NINCDS-ADRDA and a MMSE score of > 15	104	20 IU per day insulin (36) or 40 IU per day insulin (38) for 4 months	Placebo (30)	Placebo, 43.3%; 20 IU, 38.9%; 40 IU, 47.4%	Placebo, 74.9; 20 IU, 72.8; 40 IU, 69.9	ADAS-Cog, ADCS-ADL and DSRS In substudy: PET ($n = 40$; metabolic rate of glucose) and CSF analysis ($n = 23$; Aβ42, Aβ40, tau protein and p181-tau)
Crapper McLachlan *et al.*, 1991;[60] Crapper McLachlan *et al.*, 1993[61]	Canada and the USA	RCT	AD (not specified if mild or moderate but all living at home)	NINCDS-ADRDA	48	250 mg of desferrioxamine intramuscularly daily, 5 days per week for 24 months (25)	Placebo (9) No treatment (14)	Desferrioxamine, 52%; placebo, 52%	63.1	Primary: Video Recorder Home Behavioural Assessment Secondary: Wechsler Adult Intelligence Scale – Revised, Wechsler Memory Scale and Western Aphasia Battery
Cucinotta *et al.*, 1998[62]	Italy	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 15–23	142	40 mg per day of dihydroergocryptine mesylate for 1 year (70)	Placebo (72)	70%	74.2 (63–83)	Primary: GBS Scale Secondary: Mental Deterioration Battery

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Dodel *et al.*, 2013[63]	Germany and the USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 16–26	55	0.2 g/kg of i.v. immunoglobulin (12), 0.5 g/kg of i.v. immunoglobulin (15) or 0.8 g/kg of i.v. immunoglobulin (14) every 4 weeks until 20 or 22 weeks	Placebo (14)	Immunoglobulin, 37%; placebo, 64%	Immunoglobulin, 69.4; placebo, 72.0	Primary: blood tests (Aβ1–40) Secondary: blood tests (Aβ1–42, and anti-Aβ autoantibodies), CSF analysis (Aβ1–40, Aβ1–42 and anti-Aβ autoantibodies, T-tau, and P-tau181), ADAS-Cog, CDR (SB), ADCS-ADL, MMSE, MRI (volumetric) and PET (glucose metabolism)
Doody *et al.*, 2008[64]	Russia	RCT	Mild to moderate AD	DSM-4,[30] NINCDS-ADRDA and a MMSE score of 10–24	183	40 mg per day of latrepirdine (Dimebon, Medivation, San Francisco, CA, USA) for 26 weeks (89)	Placebo (94)	Dimebon, 72%; placebo, 62%	Dimebon, 68.1; placebo, 68.4	Primary: ADAS-Cog Secondary: MMSE, NPI, ADCS-ADL, CIBIC+ and ADCS-CGIC
Doody *et al.*, 2013;[65] Doody *et al.*, 2015[66]	Argentina, Australia, Belgium, Canada, Chile, Denmark, Finland, France, Germany, India, Israel, Italy, Japan, Poland, South Africa, Spain, Sweden, the UK and the USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 16–26	1537	100 mg per day of semagacestat (Eli Lilly, Indianapolis, IN, USA) (507) or 140 mg per day of semagacestat (529) for 76 weeks	Placebo (501)	53%	73.2	Primary: ADAS-Cog and ADCS-ADL Secondary: CDR (SB), NPI, MMSE, EQ-5D and blood tests (Aβ) In substudy: CSF analysis ($n = 844$; Aβ and tau), MRI ($n = 208$; volumetric) and PET ($n = 108$; Aβ)

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Doody *et al.*, 2014;[67] Liu-Seifert *et al.*, 2015[68]	France, Japan and the USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 16–26	1659	400 mg of i.v. solanezumab (Eli Lilly, Indianapolis, IN, USA) every 4 weeks for 18 months (cohort 1, 506; cohort 2, 521)	Placebo (cohort 1, 506; cohort 2, 519)	Cohort 1: placebo, 56.7%; solanezumab, 59.1% Cohort 2: placebo, 65.7%; solanezumab, 50.6%	Cohort 1: placebo, 74.4; solanezumab, 75.0 Cohort 2: placebo, 72.5; solanezumab, 71.5	Primary: ADAS-Cog and ADCS-ADL Secondary: CDR (SB), NPI, MMSE, EQ-5D, blood tests (Aβ1–40 and Aβ1–42) and MRI (volumetric) In substudy: CSF analysis ($n = 121$; Aβ1–40, Aβ1–42 and tau) and PET ($n = 266$; amyloid)
Endres *et al.*, 2014[69]	Germany	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 14–27	22	30 mg per day of acitretin (11) for 4 weeks	Placebo (11)	Placebo, 55%; acitretin, 82%	Placebo, 73; acitretin, 67	CSF analysis (Aβ42, P-tau or t-tau), MMSE and NTB (CERAD)
Farlow *et al.*, 2012[70]	USA	RCT	Mild to moderate AD	A MMSE score of 15–26	52	100 mg of solanezumab every 4 weeks (10), 100 mg weekly (11), 400 mg every 4 weeks (10) or 400 mg weekly (11) for 12 weeks	Placebo (10)	53.8%	71.2 (53–89)	CSF analysis (Aβ1–40 and Aβ1–42), blood tests (Aβ1–40 and Aβ1–42) and ADAS-Cog In substudy: PET ($n = 24$; amyloid)
Faux *et al.*, 2010;[71] Lannfelt *et al.*, 2008[72]	Australia, Sweden, the UK and the USA	RCT	Mild to moderate AD	NINCDS-ADRDA, a MMSE score of 20–26 or an ADAS-Cog score of 10–25	78	50 mg of PBT2 per day (20) or 250 mg of PBT2 per day (29) for 12 weeks	Placebo (29)	Placebo, 52%; 50 mg, 45%; 250 mg, 52%	Placebo, 71.6 (60–83); 50 mg, 72.4 (58–83); 250 mg, 72.1 (58–83)	Blood tests (Aβ40, Aβ42, Zn^{2+}, and Cu^{2+}), CSF analysis (12 Aβ40, Aβ42, T-tau, P-tau, Zn^{2+} and Cu^{2+}), NTB, ADAS-Cog and MMSE

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Faxén-Irving *et al.*, 2013;[73] Freund-Levi *et al.*, 2006[74]	Sweden	RCT	Mild to moderate AD	DSM-4[30] and a MMSE score of 15–30	174	1.7 g per day of DHA and 0.6 g per day of EPA for 6 months (89)	Placebo (85)	Intervention, 57%; placebo, 46%	Intervention, 72.6; placebo, 72.9	Primary: MMSE and ADAS-Cog Secondary: CDR (SB and global) and blood tests (transthyretin) In substudy: CSF analysis ($n = 35$; transthyretin)
Ferrari *et al.*, 1998[75]	Italy	RCT	Mild to moderate AD	ICD-10[76] or DSM-4,[48] NINCDS-ADRDA and a MMSE score of 10–23	213	10 mg per day of posatirelin (Poli Industria Chimica S.p.A., Rozzano, Italy) for 3 months (107)	Placebo (106)	58%	78.8	Rey Memory test, GBS Scale, MMSE, HAM-D and Global DS
Fleisher *et al.*, 2008[77]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA	51	100 mg per day of LY-450139 (22) or 140 mg per day of LY-450139 (14) for 14 weeks	Placebo (15)	Placebo, 33%; 100 mg, 64%; 140 mg, 43%	Placebo, 68.7; 100 mg, 70.8; 140 mg, 68.1	Primary: blood tests (Aβ) and CSF analysis (Aβ) Secondary: ADAS-Cog and ADCS-ADL
Fleisher *et al.*, 2011[78]	USA	RCT	Mild to moderate AD	A MMSE score of 12–20	89	10–12 mg/kg daily of divalproex sodium (Depakote, Abbott Laboratories, Chicago, IL, USA) for 24 months (43)	Placebo (46)	Placebo, 67%; divalproex sodium, 33%	Placebo, 76; divalproex sodium, 73	Primary: MRI (volumetric) and NPI Secondary: ADAS-Cog, CDR (SB), MMSE, ADCS-ADL, ADCS-CGIC, CMAI and QOL-AD
Fox *et al.*, 2005;[79] Gilman *et al.*, 2005;[80] Hock *et al.*, 2003;[81] Koepsell *et al.*, 2007;[82] Orgogozo *et al.*, 2003;[83] Vellas *et al.*, 2009[84]	France and USA	RCT	Mild to moderate AD	A MMSE score of 15–26	131	Immunisation of 225 µg of AN-1792 plus 50 µg of adjuvant QS-21 at day 0 and months 1, 3, 6, 9 and 12 (59 responders)	Placebo (72)	Not specified	Intervention, 74.9; placebo, 73.7	Primary: blood tests (Aβ), DAD, CDR (global), MMSE, ADAS-Cog and MRI (volumetric) Secondary: NTB

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Galasko *et al.*, 2012[85]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of ≥ 16	79	500 mg per day of vitamin C and 800 IU per day of vitamin E and 900 mg per day of α-lipoic acid (E/C/ALA) (28) OR 1200 mg per day of coenzyme Q (25) for 16 weeks	Placebo (26)	E/C/ALA, 46%; coenzyme Q, 44%; placebo, 48%	E/C/ALA, 73.6; coenzyme Q, 71.4; placebo, 73.2	ADCS-ADL, MMSE and CSF analysis (tau, P-tau, Aβ42, F2-isoprostane)
Galasko *et al.*, 2014[86]	USA	RCT	Mild to moderate AD	A MMSE score of 14–26	399	5 mg per day of PF-04494700 (132) or 20 mg of PF-04494700 per day (135) for 18 months	Placebo (132)	5 mg, 53%; 20 mg, 61%; placebo, 57%	5 mg 73.6; 20 mg 73.0; placebo, 72.2	Primary: ADAS-Cog Secondary: CDR (SB), ADCS-ADL, NPI, MMSE, digit symbol substitution test, forward and backward digit span test, controlled oral word association test, Stroop Colour Word Interference Test, trail making test, DEMQOL and blood tests (Aβ1–40, Aβ1-x, Aβ1–42) In substudy: MRI (*n* = 186; volumetric) and CSF analysis (*n* = 52; Aβ1–40, Aβ1-x, Aβ1–42, tau and P-tau 181)
Gauthier *et al.*, 2015[87]	Canada and the USA	RCT	Moderate AD	NINCDS-ADRDA and a MMSE score of 10–20	403	10 mg per day of ST101 (50), 60 mg per day of ST101 (51) and 120 mg per day of ST101 (51) for 12 weeks	Placebo (51)	Placebo, 41.2%; 10 mg, 50%; 60 mg, 60.8%; 120 mg, 52.9%	Placebo, 78.3; 10 mg, 74.4; 60 mg, 77.8; 120 mg, 75.7	Primary: ADAS-Cog Secondary: ADCS-CGIC, ADCS-ADL, NPI and MMSE
Geldmacher *et al.*, 2011[88]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 12–26	29	45 mg per day of pioglitazone (14) for 18 months	Placebo (15)	Pioglitazone, 64%; placebo, 60%	Pioglitazone, 74.9; placebo, 67.0	Secondary: CDR (SB), ADAS-Cog, NPI, ADFACS, CIBIC+ and NOSGER

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Gold *et al.*, 2010[89]	Austria, Bulgaria, Chile, China, Croatia, Estonia, Germany, Greece, Hungary, Korea, Mexico, New Zealand, Pakistan, Peru, the Philippines, Puerto Rico, Russia, the UK and the USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 10–23	581	2 mg per day of extended-release rosiglitazone (166), 8 mg per day of extended-release rosiglitazone (165) for 24 weeks	Placebo (166) or 10 mg per day of donepezil (84)	2 mg, 64%; 8 mg, 65%; placebo, 60%; donepezil, 63%	2 mg, 71.7; 8 mg, 72.6; placebo, 72.5; donepezil, 72.9	Primary: ADAS-Cog and CIBIC+ Secondary: NPI, DAD, MMSE, blood tests (glycated haemoglobin) and EQ-5D
Green *et al.*, 2009;[90] Myrexis, Inc., 2010[91]	USA	RCT	Mild to moderate AD	A MMSE score of 15–26	1684	800 mg per day of tarenflurbil (Flurizan, Myrexis, Inc., Salt Lake City, UT, USA) (42) or 1600 mg per day (820) for 18 months	Placebo (822)	50.9%	74.6 (55+)	Primary: ADAS-Cog and ADCS-ADL Secondary: CDR (SB), MMSE, NPI and QOL-AD
Grimaldi *et al.*, 2014[92]	Italy	RCT	Mild to moderate AD	DSM-4[30] and a MMSE score of 20–26	42	66 µg per day of IFNβ1a for 28 weeks (23)	Placebo (19)	Placebo, 58%; IFNβ1a 65%	Placebo, 64.6; IFNβ1a, 63.0	ADAS-Cog, Global DS, CIBIC+, MMSE, ADAS-Noncog, Lawton IADL, PSMS and Geriatric DS
Hampel *et al.*, 2009[93]	Germany	RCT	Mild AD	DSM-4,[30] NINCDS-ADRDA and a MMSE score of 21–26	71	Lithium, various doses for 10 weeks (33)	Placebo (38)	52.1%	68.6 (50–84)	Primary: CSF analysis (P-tau) Secondary: CSF analysis (T-tau and Aβ42), blood tests (Aβ42), MMSE, NPI and ADAS-Cog
Hock *et al.*, 2003;[94] Hock *et al.*, 2000[95]	Germany and Switzerland	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 12–26	40	Talsaclidine (Boehringer Ingelheim, Rhein, Germany) various doses for 4 weeks (34)	Placebo (6)	Talsaclidine, 56%; placebo, 83%	Talsaclidine, 67.1; placebo, 69.7	CSF analysis (Aβ42 and Aβ40)

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Jhee *et al.*, 2004[96]	Korea and the USA	RCT	Mild to moderate AD	NINCDS- ADRDA and a MMSE score of 10–24	20	100 mg per day of celecoxib (5), 400 mg per day of celecoxib (5) or 800 mg per day of celecoxib (5) for 28 days	Placebo (5)	Placebo, 20%; 100 mg, 20%; 400 mg, 40%; 800 mg, 20%	Placebo, 77.2; 100 mg, 68.6; 400 mg, 75.2; 800 mg, 69.7	CSF analysis (PGE2, IL-6, Aβ1–42 and tau), blood tests (PGE2, IL-6, Aβ1–42 and tau), ADAS-Cog, MMSE and computerised NTB
de Jong *et al.*, 2008[97]	The Netherlands	RCT	Mild to moderate AD	NINCDS- ADRDA and a MMSE score of 10–26	51	100 mg per day of indomethacin for 12 months (26)	Placebo (25)	Placebo, 76%; indomethacin, 54%	Placebo, 72.2; indomethacin, 72.7	Primary: ADAS-Cog Secondary: MMSE, CIBIC+, ADAS-Noncog, NPI and IDDD
Kadir *et al.*, 2008[98]	Sweden	RCT	Mild AD	NINCDS- ADRDA and a MMSE score of ≥ 21	20	30 mg per day of phenserine (QR Pharma, Inc., Berwyn, PA, USA) for 3 months (10)	Placebo (10)	75%	68	PET (glucose and amyloid), CSF analysis (Aβ42, T-tau and P-tau, α- and β-secretase-cleaved amyloid precursor protein), blood tests (Aβ40 and Aβ42), MMSE, recall task, word recognition, digit symbol substitution test, trail making test and clock drawing task
Kessler *et al.*, 2008[99,100]	Germany	RCT	Mild AD	NINCDS ADRDA and a MMSE score of < 25	68	51.62 mg per day of *Cinnamomum verum* (verum) extract containing 8 mg per day of copper orotate for 12 months (35)	Placebo (33)	Placebo, 55%; verum, 40%	Placebo, 69.4; verum, 69.6	Primary: ADAS-Cog and MMSE

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Landen *et al.*, 2013[101]	Australia, Canada, Sweden and the UK	RCT	Mild to moderate AD	DSM-4,[30] NINCDS- ADRDA and a MMSE score of 16–26	37	Ponezumab (Pfizer, Inc., New York City, NY, USA) – one infusion of 0.1 mg/kg (4), 0.3 mg/kg (4), 1 mg/kg (4), 3 mg/kg (6) or 10 mg/kg (8)	Placebo (11)	Ponezumab (altogether), 42.3%; placebo, 27.3%	Ponezumab (altogether), 70.0 (50–84); placebo, 71.8 (61–85)	ADAS-Cog, MMSE, Cogstate Alzheimer's Battery and blood tests (Aβ1-x, Aβ1–40, and Aβ1–42) In substudy: CSF analysis (in 1- and 10-mg groups, *n* = 12; Aβ1-x, Aβ1–40, Aβ1–42, T-tau and P-tau)
Leszek *et al.*, 1999[102]	Poland	RCT	Mild to severe AD	NINCDS- ADRDA and DSM-3[48]	46	100 mg every second day of Colostrinin for 3 weeks followed by a 2-week hiatus – 10 cycles (15)	100 mg of selenium (15) or placebo (16)	Colostrinin, 80%; selenium, 80%; placebo, 62.5%	Colostrinin, 70.75 (45–83); selenium, 70.75 (50–82); placebo, 67.8 (59–76)	Primary: MMSE Secondary: additional psychosocial functioning of the AD patients provided by the patients' caregivers – no information as to what measures
Li *et al.*, 2015[103]	China	CCT	Moderate AD	A MMSE score of 10–20 and an ADAS-Cog score of 29–40	24	0.9 g per day of *Cistanches* herb extract for 48 weeks (10)	No treatment (6) or 5 mg per day of donepezil (8)	*Cistanches* herb, 60%; no treatment, 50%; donepezil, 62.5%	*Cistanches* herb, 70.3; no treatment, 71.3; donepezil, 73.5	MMSE, ADAS-Cog, MRI (volumetric), CSF analysis (protein, mRNA levels, T-tau, tumour necrosis factor alpha, and interleukin 1 beta)
Lovestone *et al.*, 2015[104]	Finland, France, Germany, Spain and the UK	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 14–26	307	500 mg per day (45) of tideglusib, 1000 mg per day of tideglusib (86) or 1000 mg of tideglusib every other day (91) for 26 weeks	Placebo (85)	Placebo, 55.3%; 500 mg, 64%; 1000 mg, 51.9%; 1000 mg every other day, 54.4%	Placebo, 70.8; 500 mg, 71.1; 1000 mg, 72.3; 1000 mg every other day 71.6	Primary: ADAS-Cog Secondary: MMSE, fluency test, ADCS-ADL, EQ-5D, NPI and CGI In substudy: MRI (*n* = 86; cerebral atrophy) and CSF analysis (*n* = 21; P-tau and Aβ1–42)

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Maher-Edwards *et al.*, 2015[105]	Bulgaria, Canada, Germany, Italy, Spain and Sweden	RCT	Mild AD	NINCDS-ADRDA and a MMSE score of 10–26	124	250 mg per day of rilapine (GlaxoSmithKline, London, UK) for 24 weeks (62)	Placebo (62)	Placebo, 54% rilapine, 47%	Placebo, 73.1; rilapine, 72.9	Primary: Cogstate Alzheimer's Battery and CSF analysis (Aβ1–42) Secondary: CSF analysis (Aβ1–40, T-tau, 181 P-tau, Lp-PLA2, neurofilament light chain and albumin quotient) and blood tests (Aβ1–40, Aβ1–42, and Lp-PLA2)
Marcusson *et al.*, 1997[106]	Belgium, Croatia, France, Germany, Sweden, the UK and Yugoslavia	RCT	Mild to moderate AD or vascular dementia	DSM-3[48] and a MMSE score of 15–25	261	300 mg of propentofylline (Hoechst Marion Roussel, Kansas City, MO, USA) three times daily for 12 months (130)	Placebo (131)	Not specified	Placebo, 72.9; propentofylline, 71.9	Primary: GBS scale, CGI and SKT Secondary: digit symbol substitution test, MMSE, NAI-ADL and AMS
Molloy *et al.*, 2013[107]	Canada	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 14–26	406	200 mg per day of doxycycline + 300 mg per day of rifampin (101), 200 mg per day of doxycycline (102) or 300 mg per day of rifampin (101) for 12 months	Placebo (102)	Doxycycline and, 50.5%; doxycycline, 50%; rifampin, 48%	Doxycycline and rifampin, 79.2; doxycycline, 78.7; rifampin, 78.6	Primary: ADAS-Cog and CDR Secondary: MMSE, Geriatric DS, CSDD, Lawton IADL and DBRI
Muresanu *et al.*, 2002[108]	Austria and Romania	RCT	Mild to moderate AD	NINCDS-ADRDA, DSM-4[30] and a MMSE score of 14–25	60	30 ml per day of Cerebrolysin for 5 days per week for 6 weeks (30)	Placebo (30)	Not specified	Not specified	DAD, ADAS-Cog and CGI
Muresanu *et al.*, 2008[109]	Romania and Spain	RCT	Mild to moderately severe vascular dementia	NINDS-AIREN and a MMSE score of 9–26	41	10 ml per day of Cerebrolysin (16) or 30 ml per day of Cerebrolysin (15) for 5 days per week for 4 weeks	Placebo (10)	51%	70.7 (51–88)	ADAS-Cog, MMSE and EEG

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Nygaard *et al.*, 2015[110]	USA	RCT	Mild to moderate AD	A MMSE score of 16–26	24	50 mg per day of saracatinib, 100 mg per day of saracatinib or 125 mg per day of saracatinib for 4 weeks. Six in each of the three treatment groups	Placebo (6)	61%	73	ADAS-Cog, ADCS-ADL, NPI, CDR (SB), MMSE, PET (glucose) and CSF analysis (Aβ40, Aβ42, Tau and P231-Tau)
Ostrowitzki *et al.*, 2012[111]	Denmark, Israel, the Netherlands, Sweden and the UK	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 16–26	18	60 mg of i.v. gantenerumab (F Hoffmann-La Roche AG, Basel Switzerland) (8) or 200 mg of i.v. gantenerumab (6) every 4 weeks for 3 months	Placebo (4)	Placebo, 75%; 60 mg, 25%; 200 mg, 50%	Placebo, 62.8; 60 mg, 70.9; 200 mg, 66.5	Primary: ADAS-Cog, MMSE, a modified NTB (not specified) and DAD Secondary and in substudy: PET (*n* = 16; amyloid)
Quinn *et al.*, 2010[112]	USA	RCT	Mild to moderate AD	A MMSE score of 14–26	402	2 g per day of docosahexaenoic acid for 18 months (238)	Placebo (164)	52.2%	76	Primary: ADAS-Cog and CDR (SB) Secondary: MMSE, ADCS-ADL, NPI and QOL-AD In substudy: MRI (*n* = 102; volumetric)
Regland *et al.*, 2001[113]	Sweden	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 10–24	20	20 mg per day of clioquinol (10) or 80 mg per day of clioquinol (10) for 21 days		65%	74.6 (61–83)	CSF analysis (Aβ42, tau and GAP43), MMSE, ADAS-Cog and GBS scale
Reines *et al.*, 2004[114]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 14–26	692	25 mg per day of rofecoxib (Vioxx, Merck Sharp & Dohme) for 12 months (346)	Placebo (346)	Placebo, 52%; rofecoxib, 54%	Placebo, 75; rofecoxib, 76	ADAS-Cog, CDR (global), MMSE, ADCS-ADL and CIBIC+

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Ringman *et al.*, 2012[115]	USA	RCT	Mild to moderate AD	NINCDS- ADRDA and a MMSE score of 17–29	36	2 g per day of curcumin C3 complex (12) or 4 g per day of curcumin C3 complex (12) for 24 weeks	Placebo (12)	63%	73.5	ADAS-Cog, NPI, ADCS-ADL, MMSE and blood tests (Aβ1–40 and Aβ1–42), CSF analysis (Aβ1–42, T-tau, P-tau181 and isoprostanes)
Ritchie *et al.*, 2003[116]	Australia	RCT	Moderately severe AD	ADAS-Cog score of 20–45 and a MMSE score of 10–24	36	Ascending doses of clioquinol up to 750 mg per day (18)	Placebo (18)	Clioquinol, 50.0%; placebo, 43.7%	72.5	ADAS-Cog and blood tests (Aβ, Zn and Cu)
Rüther *et al.*, 2000;[117] Rüther *et al.*, 1994[118]	Austria and Germany	RCT	Mild to moderate AD	DSM-3[48]	120	30 ml per day of Cerebrolysin (for 5 days a week) for 4 weeks (60)	Placebo (60)	66%	(55–85)	CGI, NAI-ADL, SCAG, trail making test and AMS
Ruether *et al.*, 2001;[119] Ruether *et al.*, 2002[120]	Austria and Germany	RCT	Mild to moderate AD	NINCDS-ADRDA, ICD-10[76] and a MMSE score of 14–24	149	30 ml per day of Cerebrolysin for 5 days a week for 4 weeks (76)	Placebo (73)	Cerebrolysin, 64.9%; placebo, 51.4%	Cerebrolysin, 72.5; placebo, 73.5	Primary: ADAS-Cog and CGI Secondary: SKT, MADR-S, NAI-ADL and ADAS-Noncog
Salloway *et al.*, 2011[121]	Canada and the USA	RCT	Moderate AD	A MMSE score of 16–26	353	500 mg per day of scyllo-inositol (89), 2000 mg per day of scyllo-inositol (89) or 4000 mg per day of scyllo-inositol (91) twice daily for 78 weeks	Placebo (84)	Placebo, 56.5%; 500 mg, 58.0%; 2000 mg, 53.9%; 4000 mg, 56.0%	Placebo, 73.4; 500 mg, 73.4; 2000 mg, 73.4; 4000 mg, 72.2	Primary: NTB and ADCS-ADL Secondary: ADAS-Cog, CDR (SB), NPI and MRI (volumetric) In substudy: MRS (*n* not specified) and CSF analysis ($n = 20$; Aβx-40, Aβx-42, T-tau, P-tau)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Salloway *et al.*, 2014[122]	Austria, Canada, Germany and the USA	RCT	Mild to moderate AD	A MMSE score of 16–26	2451	APOE ε4 carriers: 0.5 mg/kg of bapineuzumab every 13 weeks up to 78 weeks (673) Non-carriers: 0.5 mg/kg (337), 1.0 mg/kg (329) or 2.0 mg/kg (141 but discontinued and received 1.0 mg/kg) of bapineuzumab every 13 weeks up to 78 weeks	Placebo (carriers, 448; non-carriers, 524)	Carriers: placebo, 56.0%; 0.5 mg/kg, 54.4% Non-carriers: placebo, 50.3%; 0.5 mg/kg, 52.5%; 1.0 mg/kg, 57.0%	Carriers: placebo, 72.3; 0.5 mg/kg, 72.0 Non-carriers: placebo, 71.9; 0.5 mg/kg, 73.1; 1.0 mg/kg, 73.5	Primary: ADAS-Cog and DAD Secondary: NTB, CDR (SB), MMSE and Dependence Scale In substudy: PET (*n* = 154; amyloid) and CSF analysis (*n* = 390; P-tau181), MRI (*n* = 1149; volumetric)
Sano *et al.*, 1996[123]	USA	RCT	Moderate AD	NINDCS-ADRDA	486	Selegiline (4 mg per day) and atoc (1000 IU per day), placebo and atoc, selegiline and placebo for 2 years (*n* not specified)	Placebo (*n* not specified)	64.9%	73.3	Primary: Bristol ADL and CDR (global) Secondary: ADAS-Cog, MMSE, Dependence Scale and CERAD's Behavioural Rating Scale
Sano *et al.*, 2011[124]	USA	RCT	Mild to moderate AD	A MMSE score of 12–26	406	Increasing dose of simvastatin up to 40 mg for 18 months (204)	Placebo (202)	Placebo, 59.9%; simvastatin, 58.8%	Placebo, 75.1; simvastatin, 74.0	Primary: ADAS-Cog Secondary: ADCS-CGIC, MMSE, Dependence Scale, ADCS-ADL, NPI and QOL-AD
Scharf *et al.*, 1999[125]	Australia	RCT	Mild to moderate AD	DSM-4[30] and a MMSE score of 11–25	41	100 mg per day of diclofenac and 400 µg per day of misoprostol for 25 weeks (24)	Placebo (17)	Diclofenac/ misoprostol group, 67%; placebo, 47%	Diclofenac/misoprostol group, 71.8; placebo, 73.9	Primary: ADAS-Cog, Global DS and CGI Secondary: MMSE, ADAS-Noncog, Lawton IADL and PSMS

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Schwam *et al.*, 2014[126]	Canada, Chile, Czech Republic and the USA	RCT	Mild to moderate AD	A MMSE score of 14–26	191	50 mg per day of PF-04447943 for 12 weeks (91)	Placebo (100)	PF-04447943, 64%; placebo, 64%	PF-0444794, 73.6; placebo, 73.5	ADAS-Cog, NPI and CGI
del Ser *et al.*, 2013[127]	Germany	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 16–26	30	Up to 1000 mg per day of tideglusib (Noscira SA, Madrid, Spain) (20) for 20 weeks	Placebo (10)	Tideglusib, 65%; placebo, 70%	Tideglusib, 73.1; placebo, 72.6	Secondary: MMSE, ADAS-Cog, fluency test and CGI
Sevigny *et al.*, 2008[128]	USA	RCT	Mild to moderate AD	A MMSE score of 14–26	563	25 mg per day of ibutamoren for 12 months (282)	Placebo (281)	Ibutamoren, 56%; placebo, 59.8%	Ibutamoren, 75.9; placebo, 76.1	Primary: CIBIC+ Secondary: ADAS-Cog, CDR (SB) and ADCS-ADL
Siemers *et al.*, 2010[129]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 14–26	19	0.5 mg/kg of solanezumab (Eli Lilly) (4), 1.5 mg/kg of solanezumab (4), 4.0 mg/kg of solanezumab (4) or 10.0 mg/kg of solanezumab (4) single dose	Placebo (3)	Placebo, 100%; 0.5 mg/kg, 25%; 1.5 mg/kg, 25%; 4 mg/kg, 50%; 10 mg/kg, 25%	Placebo, 70.3; 0.5 mg/kg, 61.0; 1.5 mg/kg, 71.5; 4 mg/kg, 67.5; 10 mg/kg, 75.3	Blood tests (Aβ1–40 and Aβ1–42), CSF analysis (Aβ1–40 and Aβ1–42) and ADAS-Cog
Silverberg *et al.*, 2002[130]	USA	RCT	Mild to moderate AD	A MMSE score of 15–24	29	Surgical shunt for low-flow CSF drainage (15)	No shunt (14)	48%	72.4	Primary: MDRS and MMSE Secondary: CSF analysis (MAP-tau and Aβ1–42)
Silverberg *et al.*, 2008[131]	USA	RCT	Mild to moderate AD	A MMSE score of 15–24	164	Low-flow ventriculoperitoneal shunt (COGNIshunt, Intergra LifeSciences, Plainsboro, NJ, USA) (110)	Sham (occluded) shunt (120)	Occluded, 56%; COGNIshunt, 61%	Occluded, 74.0; COGNIshunt, 74.5	Primary: MDRS, Global DS Secondary: CSF analysis (Aβ1–42 and MAP-tau)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Simons *et al.*, 2002[132]	Germany	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 12–26	44	80 mg per day of simvastatin for 26 weeks (24)	Placebo (20)	Placebo, 47%; simvastatin, 63%	Placebo, 68.5; simvastatin, 68.0	CSF analysis (AβA40, AβA42, lathosterol, cholesterol, and 24S-hydroxycholesterol), ADAS-Cog and MMSE
Soininen *et al.*, 2007[133]	Australia, Belgium, Finland, France, Germany, the Netherlands and the UK	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 12–26	425	400 mg per day of celecoxib for 52 weeks (285)	Placebo (140)	Placebo, 59%; celecoxib, 53%	Placebo, 73.3; celecoxib, 73.7	Primary: ADAS-Cog and CIBIC+ Secondary: BEHAVE-AD, NOSGER and MMSE
Sparks *et al.*, 2005[134]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 12–28	63	80 mg per day of atorvastatin calcium for 12 months (32)	Placebo (31)	Placebo, 35.5%; atorvastatin calcium, 37.5%	Placebo, 78.9; atorvastatin calcium, 78.15	Primary: ADAS-Cog and CGI Secondary: MMSE, Geriatric DS and ADCS-ADL
Sweetlove, 2012[135]	New Zealand	RCT	Mild to moderate AD	A MMSE score of 12–24	1003	15 mg per day of latrepirdine or 60 mg per day of latrepirdine (*n* not specified)	Placebo (*n* not specified)	Males and females (*n* not specified)	(50+)	ADAS-Cog and ADCS-ADL
Tan and Pu, 2003[136]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA	10	200 mg every 2 weeks of intramuscular testosterone enanthate (Delatestryl®, Endo Pharmaceuticals, Malvern, PA, USA) for 12 months (5)	Placebo (5)	0% (all male)	72.4 (68–80)	Primary: ADAS-Cog and MMSE Secondary: clock drawing test

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Turner *et al.*, 2015[137]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 14–26	119	Resveratrol (Aptuit Laurus, Inc., Hyderabad, India) escalating doses up to 2000 mg per day (64)	Placebo (55)	Resveratrol, 62.5%; placebo, 51%	Resveratrol, 69.8; placebo, 73	Primary: blood tests (Aβ40 and Aβ42, and insulin and glucose) and CSF analysis (Aβ40, Aβ42, tau, and P-tau181), MRI (volumetric) Secondary: MMSE, ADAS-Cog, ADCS-ADL, CDR (SB) and NPI
Van Gool *et al.*, 2001[138]	The Netherlands	RCT	Mild AD	Minimal or mild severity scores according to the CAMDEX	168	A single dose of hydroxychloroquine (83; 400 mg in patients weighing ≥ 65 kg or 200 mg in those weighing < 65 kg)	Placebo (85)	Hydroxychloroquine, 54%; placebo, 60%	Hydroxychloroquine, 70.4; placebo, 70.7	Primary: IDDD Secondary: ADAS-Cog and RMBCP
Vellas *et al.*, 2011[139]	France	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 12–24	159	40 mg per day of EHT 0202 (51) or 80 mg per day of EHT 0202 (55) for 3 months	Placebo (53)	56%	40 mg per day, 76.4; 80 mg per day, 76.7; placebo, 75.8	Primary: ADAS-Cog, NTB, CDR (SB), NPI, ADCS-ADL, MMSE and CGI Secondary: blood tests (sAPPα)
Wang *et al.*, 2013[140]	China	RCT	Moderate to severe AD	NINCDS-ADRDA, DSM-4[30] and a MMSE score of 4–20	26	10 mg per day of memantine for 24 weeks (13)	Placebo (13)	Placebo, 54%; memantine, 54%	Placebo, 64.7; memantine, 65.7 (50–90)	Primary: Severe Impairment Battery, PET (glucose) and CSF analysis (T-tau, P-tau181, Aβ40 and Aβ42) Secondary: ADAS-Cog, MMSE and NPI

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Watson *et al.*, 2005[141]	USA	RCT	Amnestic MCI ($n = 9$) or mild AD ($n = 21$)	NINCDS-ADRDA and a MMSE score of > 15	36	4 mg per day of rosiglitazone (Avandia, GlaxoSmithKline) for 6 months (24)	Placebo (12)	30%	Rosiglitazone, 72.8; placebo, 73.3	Blood tests (insulin and Aβ), Buschke Selective Reminding Test, recall task, Stroop Colour Word Interference Test, trail making test and fluency test
Wilcock *et al.*, 2008[142]	Canada and the UK	RCT	Mild to moderate AD	A MMSE score of 15–26	210	400 mg per day of tarenflurbil (69) or 800 mg per day of tarenflurbil (70) for 12 months	Placebo (71)	Placebo, 48%; 400 mg per day, 52%; 800 mg per day, 48%	Placebo, 74.4; 400 mg per day, 73.4; 800 mg per day, 75.8	ADAS-Cog, ADCS-ADL and CDR (SB)
Winblad *et al.*, 2001[143]	Belgium, Germany, Italy, Sweden and the UK	RCT	Mild to moderate AD	MMSE score of 12–24	346	60 mg per day of nicergoline (Sermion, Pharmacia & Upjohn, Kalamazoo, MI, USA) for 6 months (177)	Placebo (169)	Nicergoline, 61%; placebo, 63.9%	73.7	Primary: ADAS-Cog, CGI and ADAS-Noncog Secondary: Lawton IADL and PSMS
Winblad *et al.*, 2012[144]	Sweden	RCT	Mild to moderate AD	DSM-4[30] and a MMSE score of 16–26	58	Cohort 1: a 50-mg CAD106 injection at 0, 6 and 18 weeks (24) Cohort 2: a 150-mg CAD106 injection at 0, 2 and 6 weeks (22)	Placebo (cohort 1, $n = 7$; cohort 2, $n = 5$)	Cohort 1: CAD106, 33%; placebo, 57% Cohort 2: CAD106, 59%; placebo, 60%	Cohort 1: CAD106, 68.9; placebo, 70.6 Cohort 2: CAD106, 68.2; placebo, 67.0	Primary: CSF analysis (serum Aβ-antibody) Secondary: CSF analysis (amyloid biomarkers), blood tests (amyloid biomarkers), NTB (CERAD), MMSE, CDR (global), ADCS-ADL and MRI (volumetric)

continued

TABLE 1 Published trials (*continued*)

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Total number of participants	Description of		Participants		Outcomes related to disease modification
						Intervention (*n*)	Control/ comparator group (*n*)	Sex (% of females)	Mean age (years) (range)	
Wischik, 2015[145]	Singapore and the UK	RCT	Mild to moderate AD	DSM-4,[30] NINCDS-ADRDA and a MMSE score of 10–26	321	69 mg per day of methylthioninium chloride (LMTX, TauRx Therapeutics Ltd, Singapore) (59), 138 mg per day of methylthioninium chloride (80) or 228 mg per day of methylthioninium chloride (90) for 24 weeks	Placebo (92)	54%	73.8	Primary: ADAS-Cog Secondary: ADCS-CGIC, MMSE, CDR (SB), Bristol ADL, ADFACS, NPI and dementia 'caseness' short CAMDEX In substudy: SPECT ($n = 135$; for regional cerebral blood flow)
Wolkowitz *et al.*, 2003[146]	USA	RCT	Mild to severe AD	A MMSE score of > 8	58	100 mg per day of dehydroepiandrosterone (Neuroscience Pharma Inc., Montreal, QC, Canada) for 6 months (28)	Placebo (30)	49%	Dehydroepiandrosterone, 75.5; placebo, 77.2	ADAS-Cog, CIBIC+, MMSE, ADAS-Noncog and CSDD

3-APS, 3-amino-1-propanesulfonic acid; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; ADAS-Noncog, Alzheimer's Disease Assessment Scale – Non-Cognitive subscale; ADCS-ADL, Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory; ADCS-CGIC, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; ADFACS, Alzheimer's Disease Functional Assessment and Change Scale; AMS, Adjective Mood Scale; APOE, apolipoprotein E; atoc, α-tocopherol; BDRS, Blessed Dementia Rating Scale; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BPRS, Brief Psychiatric Rating Scale; BUN, blood urea nitrogen; BVRT, Benton Visual Retention Test; CAMDEX, Cambridge Mental Disorders of the Elderly Examination; CDR, Clinical Dementia Rating scale; CERAD Consortium to Establish a Registry for Alzheimer's Disease; CGI, Clinical Global Impression; CIBIC+, Clinician's Interview-Based Impression of Change plus carers input; Cl, chlorine; CMAI, Cohen-Mansfield Agitation Inventory; CSDD, Cornell Scale for Depression in Dementia; Cu, copper; DAD, Disability Assessment for Dementia; DBRI, The Dysfunctional Behaviour Rating Instrument; DEMQOL, Dementia Quality of Life measure; DHA, docosahexaenoic acid; DHEA, dehydroepiandrosterone; DSM-3, *Diagnostic and Statistical Manual of Mental Disorders*-Third edition; DSM-4, *Diagnostic and Statistical Manual of Mental Disorders*-Fourth edition; DSRS, Dementia Severity Rating Scale; EEG, electroencephalography; EPA, eicosapentaenoic acid; EQ-5D, EuroQol-5 Dimensions; GBS scale, Gottfries–Bråne–Steen Scale; Geriatric DS, Geriatric Depression Scale; Global DS, Global Deterioration Scale; HAM-D, Hamilton Rating Scale for Depression; IADL, Instrumental Activities of Daily Living; ICD-10, *International Classification of Diseases*-10th edition; IDDD, Interview for Deterioration of Daily Living in Dementia; IFβA1, interferon beta 1A; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; IU, international unit; i.v, intravenous; K, potassium; Lp-PLA2, lipoprotein-associated phospholipase A2; MADR-S, Montgomery–Åsberg Depression Rating Scale; MDRS, Mattis Dementia Rating Scale; mRNA, messenger ribonucleic acid; MRS, magnetic resonance spectroscopy; Na, sodium; NAI-ADL, Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association; NOSGER, Nurses' Observation Scale for Geriatric Patients; NPI, Neuropsychiatric Inventory; NTB, Neuropsychological Test Battery; PBT2, phenanthrene-based tylophorine-2; P-tau, phosphorylated tau; P-tau181, phosphorylated tau 181; PGRS, Plutchik Geriatric Rating Scale; PSMS, Personal Self-Maintenance Scale; QOL-AD, Quality of Life in Alzheimer's Disease; RMBCP, Revised Memory and Behavioural Problems Checklist; SB, sum of boxes; SCAG, Sandoz Clinical Assessment-Geriatric Scale; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate pyruvate transaminase; SPECT, single-photon emission computerised tomography; SKT, Syndrom Kurz Test; T-tau, total tau; Zn, zinc.

TABLE 2 Published protocols

Author and year	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Participants		Description of		Outcomes related to disease modification
					Sex	Age range (years)	Intervention	Control/ comparator group	
Annweiler *et al.*, 2011[147]	France	RCT	Moderate AD	NINCDS-ADRDA, DSM-4[30] and a MMSE score of 10–20	Males and females	≥ 60	20 mg per day of memantine plus 3571 IU per day of vitamin D for 24 weeks	20 mg per day of memantine plus placebo	Primary: ADAS-Cog Secondary: MMSE, Frontal Assessment Battery, trail making test, Katz ADL and Lawton IADL
Egefjord *et al.*, 2012[148]	Denmark	RCT	Mild to moderate AD	A MMSE score of 18–21	Not specified	50–80	1.8 mg per day of liraglutide for 6 months	Placebo	Primary: PET (glucose uptake and Aβ deposits) Secondary: MRI (perfusion) and Wechsler Memory Scale (Brief Cognitive Examination)
Lawlor *et al.*, 2014[149]	France, Germany, Greece, Holland, Hungary, Ireland, Italy, Sweden and the UK	RCT	Mild to moderate AD	NINCDS-ADRDA and a MMSE score of 12–27	Males and females	≥ 50	8 mg per day of nilvadipine for 78 weeks	Placebo	ADAS-Cog, CDR (SB) and DAD

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR, Clinical Dementia Rating scale; DAD, Disability Assessment for Dementia; DSM, *Diagnostic and Statistical Manual of Mental Disorders;* IADL, Instrumental Activities of Daily Living; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association.

We included three protocols, published between 2011 and 2015. None of the results of the three trials have, as yet, been published. All three are randomised placebo-controlled trials, with participants with AD. All three are being conducted in Europe: one in Denmark,[148] one in France[147] and one multicountry study in France, Germany, Greece, the Netherlands, Hungary, Ireland, Italy, Sweden and the UK.[149]

All three trials used at least one cognitive outcome; there were five different cognitive outcomes. ADLs were measured across two trials using a variety of three measures. One trial measured biological markers, via two biological techniques. Only one trial used a global outcome. None of the published protocols measured neuropsychiatric or quality-of-life outcomes.

Ongoing trials

The characteristics of the ongoing trials are available in *Table 3*.

We included 27 ongoing trials registered on clinical trial databases as ongoing at the time of the search.[9,10,24,150–173] All are RCTs, including participants with vascular dementia ($n = 1$),[150] only AD ($n = 21$),[9,10,24,151,152,154–158,161,162,164–168,170–173] and AD or MCI ($n = 5$).[153,159,160,163,169] There was a total of 32 outcome measures used across the trials. Twenty of the trials measured cognition, using 1 of 12 outcome measures.[9,10,24,150,152–155,157–160,163,165,167–169,171–173] Similarly, 19 of the trials measured biological markers, using a variety of five biological techniques.[9,150–159,161–164,166,169,172,173] Thirteen trials measured the domain of neuropsychiatric symptoms, using four measures.[9,150,152,155–159,161,163,169,171,173] Quality of life was measured in five trials using three measures.[9,150,152,158,173] ADLs were measured across 11 trials, using four measures.[9,10,150,152,155,157–159,169,171,173] Fifteen trials measured a global outcome, using a variety of four measures.[24,150–154,157–160,167–172]

Validation data

The validation data for the outcomes in each domain are available in *Tables 4–9.*

We searched separately for validation information for each outcome measure, and also recorded how long each measure takes on average to complete and who completes it. Both the results of the review and the validation data were used at the consensus conference, which is discussed in *Chapter 6*.

Cognitive outcomes

As a result of the large number of cognitive outcomes, we shortlisted five cognitive outcomes for which we would search for validation data. These were the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog), MMSE, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)'s Neuropsychological Battery, the Neuropsychological Battery and the Cogstate Alzheimer's Battery.

We excluded the other cognitive outcomes for a number of reasons. They had only been used in one trial:

- Mattis Dementia Rating Scale[416] (one published trial; 149 participants)
- Modified Telephone Interview for Cognitive Status[417] (one ongoing trial)
- Vascular Dementia Assessment Scale Cognitive Subscale[418] (one ongoing trial)
- Computerised Neuropsychological Test Battery[419] (one published trial; 20 participants)
- Frontal Assessment Battery[420] (one protocol)
- Mental Deterioration Battery[421] (one published trial; 142 participants)
- Wechsler Adult Intelligence Scale[422] (one published trial; 48 participants).

They measure cognition in severe dementia:

- Severe Impairment Battery[423] (one published trial; 26 participants).

TABLE 3 Ongoing trials

Trial register number	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Participants		Description of		Outcomes related to disease modification
					Sex	Age range (years)	Intervention	Control/ comparator group	
ISRCTN16105064[10]	UK	RCT	Early AD	NIA-AA criteria and a MMSE score of > 23	Males and females	45–100	400 mg per day of minocycline or 200 mg per day of minocycline for 2 years	Placebo	MMSE and Bristol ADL
ISRCTN31208535[150]	UK	RCT	Mild to moderate subcortical ischaemic vascular dementia	DSM-4[30] and a MMSE score of 15–26	Males and females	≥ 50	5 mg per day of amlodipine for 2 weeks then 10 mg per day of amlodipine for 50 weeks	Placebo	Primary: VADAS-Cog Secondary: MMSE, trail making test, TICS-M, CGI, MRI (quantitation of lacunar lesions and diffuse white matter lesions), EQ-5D, DEMQOL, DAD and NPI
ISRCTN89711766[151]	UK	RCT	Early AD	Dubois criteria for early AD or NINCDS-ADRDA/ NIA-AA, and a MMSE score of ≥ 22	Males and females	50–85	1.8 mg per day of i.v. liraglutide for 12 months	Placebo	PET (change in glucose metabolism)
ISRCTN93682878[9]	UK	RCT	Mild to moderate AD	A MMSE score of 15–28 or a MoCA score of 12–24	Males and females	≥ 55	Losartan escalating doses to 100 mg per day for 12 months	Placebo	Primary: MRI (whole-brain atrophy) Secondary: MRI (white matter hyperintensity volume and cerebral blood flow), ADAS-Cog, DEMQOL, NPI and Bristol ADL
NCT01409915[24]	USA	RCT	Mild to moderate AD	A MMSE score of 10–26	Males and females	55–85	250 μg/m^2 of s.c. sargramostim (Leukine, Sanofi Genzyme, Cambridge, MA, USA) for 5 days per week for 3 weeks	Placebo	Secondary: MMSE, ADAS-Cog, CDR (global), trail making test and Mohs Number Cancellation Test

continued

TABLE 3 Ongoing trials (*continued*)

Trial register number	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Participants		Description of		Outcomes related to disease modification
					Sex	Age range (years)	Intervention	Control/ comparator group	
NCT01561053[152]	Spain	RCT	Mild to moderate AD	A MMSE score of 18–26	Males and females	55–85	Low-dose albumin and immunoglobulin, high-dose albumin and immunoglobulin, or low-dose albumin with no immunoglobulin	No intervention	Primary: ADAS-Cog and ADCS-ADL Secondary: MMSE, NTB (not specified), NPI, CDR (SB), ADCS-CGIC, CSDD, C-SSRS, QOL-AD, PET (glucose metabolism), CSF analysis (Aβ1–40 and Aβ1–42, T-tau and P-tau) and blood tests (Aβ1–40 and Aβ1–42)
NCT01767311[153]	USA and Japan	RCT	MCI or mild AD	NIA-AA and a MMSE score of ≥ 22	Males and females	50–90	BAN2401 2.5 mg/kg, 5 mg/kg or 10 mg/kg every 2 weeks; or 5 mg/kg or 10 mg/kg every 4 weeks, with placebo every 2 weeks		Primary: AD composite score [ADAS-Cog, MMSE, CDR (SB)] Secondary: MRI (volumetric) and PET (amyloid)
NCT01965756[154]	USA	RCT	Early AD	A MMSE score of > 21	Males and females	55–80	Metformin escalating doses to 4000 mg per day – then crossover with placebo	Placebo	Primary: ADAS-Cog Secondary: Cogstate Alzheimer's Battery, DSRS and MRI (pCASL, MPRAGE and Flair) and CSF analysis
NCT01966666[155]	USA	RCT	Mild to moderate AD	NIA-AA and a MMSE score of 14–26	Males and females	50–82	2 mg/m^2 of TPI-287, 6.3 mg/m^2 TPI-287 or 20 mg/m^2 TPI-287 by i.v. infusion once every 3 weeks for 9 weeks	Placebo	Secondary: CSF analysis (biomarkers for AD, but not specified), MRI (changes in brain network functional and structural connectivity and perfusion), ADAS-Cog, MMSE, ADCS-ADL and Geriatric DS

Trial register number	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Participants		Description of		Outcomes related to disease modification
					Sex	Age range (years)	Intervention	Control/ comparator group	
NCT02036645[156]	USA	RCT	Mild to moderate AD	Not specified	Males and females	55–85	Either i.v. or s.c. injection (single or multiple doses, 25–1800 mg) of MEDI1814	Placebo	Primary: C-SSRS Secondary: blood tests (Aβ1–42), CSF analysis (Aβ1–42 and Aβ1–40)
NCT02051608[157]	Argentina, Australia, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, Guatemala, Hungary, Italy, Japan, Korea, the Netherlands, Portugal, Russia, Spain, Sweden, Switzerland, Turkey, the UK and USA	RCT	Mild AD	NINCDS-ADRDA	Males and females	50–90	Gantenerumab (F Hoffmann-La Roche AG) (dose not specified) s.c. every 4 weeks for 100 weeks	Placebo	Primary: ADAS-Cog and ADCS-ADL Secondary: CSF analysis (T-tau, P-tau and Aβ1–42), NPI, CDR (SB and global), MMSE and MRI (volumetric) In subsample: PET (for amyloid)
NCT02080364[158]	USA	RCT	Mild AD	A MMSE score of 21–26	Males and females	50+	5 mg per day of Azeliragon (vTv Therapeutics Inc., High Point, NC, USA) for 18 months	Placebo	Primary: ADAS-Cog and CDR (SB) Secondary: MRI (volumetric), PET (glucose), NPI, MMSE, ADCS-ADL, controlled oral word association test, fluency test, DEMQOL and blood tests (Aβ)

continued

TABLE 3 Ongoing trials (*continued*)

Trial register number	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Participants		Description of		Outcomes related to disease modification
					Sex	Age range (years)	Intervention	Control/ comparator group	
NCT02245737[159]	Argentina, Australia, Belgium, Canada, France, Germany, Hungary, Italy, Japan, Poland, Romania, Spain, South Korea, Sweden, the UK and USA	RCT	MCI or mild AD	NIA-AA and a MMSE score of 20–30	Males and females	55–85	20 mg per day of LY3314814 or 50 mg per day of LY3314814 for 104 weeks	Placebo	Primary: CDR (global) Secondary: ADAS-Cog, FAQ, ADCS-ADL and NPI In substudy: CSF analysis (Aβ1–42, Aβ1–40, T-tau and phosphorylated tau), PET (amyloid and glucose) and MRI (volumetric)
NCT02322021[160]	USA	RCT	MCI or mild to moderate AD	NIA-AA	Males and females	50–85	Low, middle or high doses (not specified) of E2609 for 18 months	Placebo	Secondary: AD Composite Score [ADAS-Cog, MMSE and CDR (SB)]
NCT02353598[161]	USA	RCT	Mild to moderate AD	NINCDS-ADRDA or DSM-5, and a MMSE score of 18–28	Males and females	50–90	Dose level 1, 2 or 3 (not specified) of i.v. crenezumab (Genentech, South San Francisco, CA, USA) every 4 weeks until week 13	Placebo	Primary: C-SSRS and MRI (amyloid)
NCT02386306[162]	USA	RCT	Mild to moderate AD	NIA-AA and a MMSE score of 12–26	Males and females	55–85	One of three different doses (not specified) of GC 021109 for 28 days	Placebo	Secondary: blood tests (IL-12, Aβ and tau) and CSF analysis (IL-12, Aβ and tau)
NCT02389413[163]	Belgium, France, Germany, Finland, the Netherlands and Sweden	RCT	MCI or mild AD	A MMSE score of 21–30	Males and females	50–89	PQ912 twice daily for 12 weeks	Placebo	Secondary: MMSE, fluency tests, Geriatric DS, Cogstate Alzheimer's Battery, CSF analysis (QC activity, T-tau, P-tau, Aβ pattern and pro-inflammatory panel), MRI (brain functional connectivity) and EEG

Trial register number	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Participants		Description of		Outcomes related to disease modification
					Sex	Age range (years)	Intervention	Control/ comparator group	
NCT02406027[164]	Belgium, France, Germany, the Netherlands, Spain and Sweden	RCT	Early AD	Not specified	Males and females	50–85	10 mg per day of JNJ-54861911 or 25 mg per day of JNJ-54861911 for 52 weeks	Placebo	Secondary: CSF analysis [(Aβ1–37, Aβ1–38, Aβ1–40 and Aβ1–42), sAPP fragments (sAPP-alpha and sAPP-beta) and total] and blood tests [Aβ1–40 levels and sAPP fragments (sAPP-alpha and sAPP-beta)]
NCT02431468[165]	USA	RCT	Moderately severe to severe AD	A MMSE score of 4–15	Males and females	55–85	10 µg of bryostatin 1 (Blanchette Rockefeller Neurosciences Institute, Rockville, MD, USA), 20 µg of bryostatin 1 or 40 µg of bryostatin 1 via i.v. for 45 minutes every other week	Placebo	Severe Impairment Battery
NCT02434718[166]	Japan	RCT	Mild to moderate AD	Not specified	Males and females	55–85	Aducanumab (BIIB037) i.v. infusion in cohorts assigned to doses (single or multiple) up to 10 mg/kg	Placebo	MRI (for amyloid)
NCT02477800[167]	Australia, Austria, Canada, Denmark, France, Germany, Hungary, Italy, Japan, Korea, Portugal, Spain, Taiwan, the UK and USA	RCT	Early AD	A MMSE score of 24–30	Males and females	55–85	Aducanumab (BIIB037) (Biogen Idec Ltd, Maidenhead, UK) low or high dose via monthly i.v. infusion for 18 months	Placebo	Primary: CDR (SB) Secondary: MMSE and ADAS-Cog

continued

TABLE 3 Ongoing trials (*continued*)

Trial register number	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Participants		Description of		Outcomes related to disease modification
					Sex	Age range (years)	Intervention	Control/ comparator group	
NCT02484547[168]	Belgium, Canada, France, Germany, Italy, Japan, the Netherlands, Poland, Spain, Sweden, Switzerland and the USA	RCT	Early AD	A MMSE score of 24–30	Males and females	50–85	Aducanumab (BIIB037) low or high dose via monthly i.v. infusion for 18 months	Placebo	Primary: CDR (SB) Secondary: MMSE and ADAS-Cog
NCT02503501[169]	USA	RCT	Amnestic MCI or mild AD	NINCDS-ARDRA and a MoCA score of 18–27	Males and females	50–90	40 IU per day of insulin glulisine for 6 months	Placebo	Primary: ADAS-Cog, FAQ, CDR (SB and global), CSF analysis (Aβ42, tau and P-tau) and PET (glucose) Secondary: digit span, trail making test, fluency test, Wechsler Memory Scale and Geriatric DS
NCT02547818[170]	USA	RCT	Early AD	Score below the education-adjusted cut-off point on delayed paragraph recall (from the Wechsler Memory Scale)	Males and females	55–79	ALZT OP1a (cromoglicic acid) and ALZT OP1b (ibuprofen) together, or cromoglicic acid and placebo, or ibuprofen and placebo	Placebo	Primary: CDR (SB)
NCT02551809[171]	Taiwan	RCT	Mild AD	A MMSE score of 20–26	Males and females	60+	UB-311 either seven doses or five doses (with two placebo doses)	Placebo	Secondary: ADAS-Cog ADCS-ADL MMSE, CDR (SB) and NPI
NCT02579252[172]	Austria	RCT	Mild AD	NIA-AA and a MMSE score of 20–26	Males and females	50–85	AADvac1 (40 µg of axon peptide 108) for eight doses – six every 4 weeks, then two booster doses every 6 months	Placebo	Cogstate Alzheimer's Battery, CDR (SB), PET (for glucose metabolism), MRI (volumetric) and CSF analysis (biomarkers not specified)

Trial register number	Trial location	Trial type	Dementia type and severity	Criteria for dementia diagnosis	Participants		Description of		Outcomes related to disease modification
					Sex	Age range (years)	Intervention	Control/ comparator group	
NCT02600130[173]	USA	RCT	Mild to moderate AD	DSM-4, NINCDS-ADRDA, and a MMSE score of 18–24	Males and females	55–75	Target dose of 20 million or 100 million longeveron mesenchymal stem cells via i.v. infusion	Placebo	ADAS-Cog, Cogstate Alzheimer's Battery, MMSE, NPI, Geriatric DS, ADCS-ADL, QOL-AD, CSF analysis (inflammatory biomarkers, and tau, P-tau and Aβ), MRI (volumetric) and blood tests (IL-1, IL-6, TGF-β1, TNF-α, CRP, D-dimer, fibrinogen and ApoE)

ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL, Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory; ADCS-CGIC, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; ApoE, apolipoprotein E; CDR, Clinical Dementia Rating scale; CGI, Clinical Global Impression; CRP, C-reactive protein; CSDD, Cornell Scale for Depression in Dementia; C-SSRS, Columbia Suicide Severity Rating Scale; DAD, Disability Assessment for Dementia; DEMQOL, Dementia Quality of Life measure; DSM, *Diagnostic and Statistical Manual of Mental Disorders;* DSRS, Dementia Severity Rating Scale; EEG, electroencephalography; EQ-5D, EuroQol-5 Dimensions; FAQ, Functional Activities Questionnaire; Geriatric DS, Geriatric Depression Scale; IL, interleukin; i.v., intravenous; MoCA, Montreal Cognitive Assessment; MPRAGE, magnetisation-prepared rapid gradient-echo; NIA-AA, National Institute on Ageing/Alzheimer's Association; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association; NPI, Neuropsychiatric Inventory; NTB, Neuropsychological Test Battery; P-tau, phosphorylated tau; pCASL, pseudo-continuous arterial spin labelling; QC, glutaminyl cyclase; QOL-AD, Quality of Life in Alzheimer's Disease; sAPP, soluble amyloid precursor protein; SB, sum of boxes; s.c., subcutaneous; TGF-β1, transforming growth factor β1; TICS-M, Modified Telephone Interview for Cognitive Status; T-tau, total tau; TNF-α, tumour necrosis factor alpha; VADAS-Cog, Vascular Dementia Assessment Scale cognitive subscale.

TABLE 4 Validation of cognitive outcomes

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Global											
Alzheimer's Disease Assessment Scale – Cognitive subscale[174]	92 (75 published, two protocols and 15 ongoing)	20,419	20–25	Administered to PWD	Validated for mild to moderate dementia[175] Validated in Chinese, Indian, Turkish, Brazilian, and Spanish[176,177]	MCID of 3 points may be relevant for early AD[178] and was 4 points for the VISTA trial[175]	No floor or ceiling effects reported across 20 studies[176] Ceiling effects in mild dementia[179]	Sensitivity to change across 21 dementia treatment studies,[176] but can have poor sensitivity to detect change in mild to moderate AD[180,181]	No information found	Good across four studies[174,182–184]	Good across seven studies,[174,177,179,183–186] but low on some items[179]
MMSE[187]	83 (68 published, one protocol and 14 ongoing)	17,736	5–10	Administered to PWD	Translated into 50 languages and validated in many, including Slovenian, Persian, Urdu, Greek and Spanish[188–193]	MCID of 1.4 points in the DOMINO trial[194]	Moderate ceiling effects and small floor effects[195]	Sensitive to change in AD.[196] May not be sensitive to change in early dementia and dementia with Lewy bodies/ frontotemporal dementia[197]	Described as acceptable to patients[187]	Good[187,198]	Good[199–201]
Batteries											
CERAD's Neuropsychological Test Battery[202]	Two (two published)	80	30	Interviewer administered with PWD	Validated for various types of dementia including AD and fronto-temporal[203,204] Validated in French, Korean, Russian, and Cantonese[205–208]	No information found	No floor or ceiling effects[209]	Sensitive to progression of AD[202,210]	No information found	Good inter-rater reliability in PWD living in community[211]	Good[204]

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Cogstate Alzheimer's Battery[212]	Six (two published and four ongoing)	161	15–20	Computer administered with PWD	Validated for use in dementia[213]	No information found	No floor or ceiling effects[214,215]	Sensitive to cognitive changes in dementia across three studies[214–216]	No information found	No information found	Good in Alzheimer's[214,217]
Neuropsychological Test Battery[218]	Seven (seven published)	3429	70 for all components	Interviewer administered with PWD	Validated for mild to moderate dementia[219] Validated for use in China, Taiwan, Singapore, Hong Kong and South Korea[199]	No information found	No floor or ceiling effects in total score, but floor effects on RAVLT delayed recall test in moderate dementia[179]	Good ability to detect change in mild to moderate dementia[179,199,219]	No information found	Good[199]	Good in mild to moderate dementia[179,218,219]

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DOMINO, donepezil and memantine for moderate to severe Alzheimer's disease; MCID, minimal clinically important difference; PWD, person with dementia; RAVLT, Rey Auditory Verbal Learning Test; VISTA, Video Imaging Synthesis of Treating Alzheimer's Disease.

TABLE 5 Validation of neuropsychiatric outcomes

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Alzheimer's Disease Assessment Scale – Non Cognitive Scale[174]	Seven (all published)	792	20–25	Interview with PWD and caregiver	Validated for mild to moderate dementia[220]	No information found	No floor or ceiling effects[221]	Sensitivity to change in mild to moderate dementia[185,222]	No information found	Good across three studies[182,185,223]	Good[185]
Behavioural Pathology in Alzheimer's Disease[224]	One (published)	425	20	Informant interview by clinician	Validated in French, Swedish, German, Dutch, Spanish, Chinese and Korean[176]	No information found	No floor or ceiling effects[225,226]	Sensitive to change in moderate to severe dementia[227]	No information found	Good[225,226,228]	No information found
Brief Psychiatric Rating Scale[229]	Three (all published)	190	20	Rated by an observer	May be validated for AD[230]	No information found	No information found	No information found	No information found	Good[230]	No information found
CERAD's Behavioural Scale[231]	One (published)	486	20–30	Semistructured informant interview	Validated in French, Spanish, Arabic, Chinese and Japanese[176,232]	No information found	No information found	Some evidence of sensitivity[233]	No information found	Good[231]	Good[233]
Dysfunctional Behaviour Rating Instrument[234]	One (published)	406	20	Informant rated	Validated for PWD living in the community[234]	No information found	No information found	No information found	No information found	Good[234]	Good[235]
Neuropsychiatric Inventory[236]	38 (30 published and eight ongoing)	11,756	10–20	Informant interview	Validated across dementia severity[236] Validated in Italian, Greek, Japanese, Korean, Mexican, Polish, Spanish and Dutch[176,237]	MCID of 8 points in the DOMINO trial[194]	No floor or ceiling effects[238]	Sensitive to change across dementia severities and types[238–241]	No information found	Good[236,237]	Good across three studies[236,237,242]

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Nurses' Observation Scale for Geriatric Patients[243]	Two (both published)	454	3–5	Nurses on wards normally rate with a caregiver	Validated for people with dementia in hospitals[244]	No information found	No information found	Good sensitivity to change in two studies including PWD[243,245]	83% acceptability in mild to moderate dementia[244]	Good[244]	Good[244]
Plutchik Geriatric Rating Scale[246]	One (published)	178	5–10	Rated by an observer	Does not appear to be validated for use with people with dementia	No information found	No information found	No information found	No information found	No information found	No information found
Revised Memory and Behaviour Problems Checklist[247]	One (published)	168	10	Informant questionnaire	Validated in Taiwanese and Spanish[248,249]	No information found	No information found	May not be sensitive to detect progression of dementia in one study,[250] but appears sensitive to changes in another study[251]	No information found	No information found	Good[248]

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MCID, minimal clinically important difference; PWD, person with dementia.

TABLE 6 Validation of quality-of-life outcomes

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
DEMQOL[252]	Four (one published and three ongoing)	399	10–20	PWD and/or informant	Valid for mild to moderate dementia living in the community or residential care[252] Validated in Spanish, German and Russian[253–255]	No information found	No floor or ceiling effects[252]	Sensitive to change in mild to moderate dementia[256–258]	Good[252]	Good inter-rater reliability of PWD and proxy versions for mild/moderate,[252] thought PWD rate higher than proxy in one study[259] and proxy rate higher than PWD in another study[258]	Good across studies including PWD[252,260]
EuroQol-5 Dimensions[261]	Five (four published and one ongoing)	4084	4–15 for PWD and 2 for proxy	PWD and/or informant	Validated for mild to moderate dementia living in the community or residential homes[262] Available in 100 languages.[263] Validated in French[264]	No information found	No floor or ceiling effects observed in one study.[264] Substantial ceiling effect for patient ratings, but not proxy, in two studies[265,266]	Not sufficiently sensitive to detect changes in the progression of dementia[263]	High completion rate, but acceptability decreases with dementia severity[263,264]	PWD provides significantly higher rating than proxy across four studies,[263] but in one study PWD and proxy ratings are similar for mild to moderate dementia[262]	Patients' test–retest ratings unreliable for mild to moderate dementia and less reliable than carers ratings,[263] but two studies[264,265] report good test–retest reliability

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Quality of Life in Alzheimer's Disease[267]	Eight (six published and two ongoing)	3341	5 for informant version and 10–15 for PWD	PWD and/or informant	Validated for people living in the community or residential care[268] Validated for use in MMSE scores of > 10[269] Validated in English, French, Portuguese, Spanish, Japanese, Cantonese, Mandarin, Korean, Danish, Swedish, German and Greek[176,269]	One standard deviation[270]	No floor or ceiling effects observed.[271] Minimal floor-and-ceiling effects across eight studies[28,272–278]	Sensitive to change in studies of mild to moderate dementia[268]	Good[271]	Mixed inter-rater reliability of PWD and informant responses across eight studies[267,268,279–285]	Good[267,268]

DEMQOL, Dementia Quality of Life measure; MCID, minimal clinically important difference; PWD, person with dementia.

TABLE 7 Validation of ADL outcomes

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory[286]	34 (28 published and six ongoing)	11,500	15–20	Informant rated	Validated for person with mild to moderate dementia living in the community[287] Validated for use in Spain, Sweden, Latvia, and Bosnia and Herzegovina[176]	No information found	No information found	Sensitive to change in mild to moderate dementia in three studies,[288–290] but not in one[291]	No information found	No information found	Good across four studies[286,289,292,293]
Alzheimer's Disease Functional Assessment and Change Scale[286]	Two (two published)	350	15–20	Informant rated	Validated in Spanish[294]	No information found	No information found	No information found	No information found	No information found	No information found
BADL[295]	Five (three published and two ongoing)	1117	15	Informant rated	Validated for PWD living in community[296]	MCID of 3.5 points in the DOMINO trial[194]	No information found	Sensitive to change in dementia[245,296]	Carers report it is easy to complete[295]	Mixed across studies[297]	Good[295,297]
Dependence scale[298]	Three (all published)	3343	15–20	Informant rated	Valid for use with PWD living in the community[298]	No information found	Floor effect on cognition subscale[299]	Sensitive to dementia progression,[298] but may not pick up small changes in clinical trials[300]	No information found	Good[57]	Good[298]
Disability Assessment For Dementia[301]	13 (11 published, one protocol and one ongoing)	2914	15	Informant rated	Validated across dementia severities living in the community.[302] Validated in Korean, Chinese, Italian, Spanish, Persian, Portuguese and Turkish[302–308]	No information found	No floor or ceiling effects[301,309]	Good sensitivity to change in six studies,[310–315] but one study[316] found it was not sensitive to change in comparison to other measures	No information found	Good[301]	Good[301]
Functional Activities Questionnaire[317]	Two (ongoing trials only)	N/A	10	Informant interview	Validated for mild dementia[318]	No information found	No information found	No information found	No information found	Good[317]	No information found
Interview for Deterioration in Daily Living Activities in Dementia[319]	Two (published trials only)	219	15	Informant rated	Validated for mild dementia living at home[320] Validated in Spanish and Dutch[97,138,321]	No information found	No floor or ceiling effects[322]	Thought to be responsive to change[299]	No information found	Good[320]	Good[299]

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Katz Index of Activities of Daily Living Scale[323]	Three (two published one protocol)	185	10	Informant rated	Validated as more of a clinical assessment than a measure of treatment effectiveness[324]	No information found	No information found	Sensitive to dementia progression,[325,326] but may not be sensitive to small changes[327]	No information found	Good[327,328]	Good[327]
Lawton Instrumental Activities of Daily Living Scale[329]	Eight (seven published and one protocol)	1125	10	Clinician/ researcher rated	Validated in Asian older adults living in the community (some with dementia)[330]	No information found	Ceiling effect reported[331]	Sensitive to treatment effects in moderate to severe dementia[332]	No information found	Good[333]	Good[333]
Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living[334]	Three (all published)	530	Not specified	Self-complete or informant questionnaire	Does not appear to be validated for use with people with dementia	No information found	No information found	May not be sensitive to change over time[335]	No information found	Family carers rate more deficits than paid carers[335]	No information found
Physical self-maintenance scale[329]	Three (all published)	429	5	Self-complete or observer rated	Validated for PWD living in the community[328]	No information found	Ceiling effect likely in PWD living in community[299]	Sensitive to treatment effects in moderate to severe dementia[332]	No information found	Good[333]	Good[333]
Video Recorder Home Behavioural Assessment[60]	One (published)	48	Not specified	Researcher rated	Does not appear to be validated for use with people with dementia	No information found	No information found	May be sensitive to change[60]	No information found	Good[60]	Good[60]

MCID, minimal clinically important difference; N/A, not applicable; PWD, person with dementia.

TABLE 8 Validation of global outcomes

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Impression of change scales											
Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change[336]	Eight (seven published and one ongoing)	1590	20	PWD and informant	Validated for use in clinical and home settings[337]	No information found	No information found	Sensitive to detect changes in mild to moderate dementia over 12 months[336]	No information found	Good[336]	Good[336]
Clinical Global Impression's Scale[338]	15 (14 published and one ongoing)	2063	5	Clinician rated by interview with PWD/informant	Does not appear to be validated for use with people with dementia	No information found	No information found	No information found	No information found	No information found	No information found
Clinician's Interview-Based Impression of Change plus Caregiver Input[339]	12 (12 published)	4087	10–40	Clinician semistructured interview with PWD and informant	Validated in Japanese[340]	No information found	No information found	Sensitive to change in dementia treatment studies[336,341]	Good acceptability[341]	Good[342]	Good[341]
Multiple domain scales											
Short CAMDEX[343]	One (published)	321	30	Clinician	Used to screen for and diagnose dementia[343]	No information found	No information found	No information found	No information found	No information found	No information found
Blessed Dementia Rating Scale[344]	Three (all published)	190	15	Informant rated	Validated in Taiwanese, Chinese, Korean and Czech[345–348]	No information found	Floor-and-ceiling effects in two studies[344,349]	Sensitive to progression of dementia[350]	No information found	Good in two studies[298,351]	Good in three studies[350,352,353]
Dementia Severity Rating Scale[354]	Three (two published and one ongoing)	164	5	Carer questionnaire	Validated for mild to severe dementia[355]	No information found	No floor or ceiling effects[354]	Sensitive to change across mild to severe dementia[354–356]	No information found	Good inter-rater reliability of caregiver responses compared with clinician information[354]	Good[354,357]

Measure	Number of		Time taken (minutes)	Who completes	Relevant populations validated with	MCID	Floor-and-ceiling effects	Sensitivity to change	Acceptability	Reliability	
	Trials	Participants								Inter-rater	Test–retest
Gottfries–Bråne–Steen rating Scale for Dementia[358]	Four (all published)	636	20–30	Clinician interview with PWD and informant interview	Validated across dementia severities[359] Translated into Czech, Danish, Italian, Japanese, Norwegian, Spanish and Swedish[359]	No information found	Can have a ceiling effect in mild dementia[360]	Sensitive to change across dementia severities[359]	No information found	Good across nine studies[359]	No information found
Sandoz Clinical Assessment-Geriatric Scale[361]	Two (two published)	298	15–30	Clinician observation	Validated in French and German[176]	No information found	No information found	Sensitive to change across three studies[361–363]	No information found	Good in two studies[361,362]	Low across three studies[352,362,364]
Staging of dementia scales											
Clinical Dementia Rating scale[365]	48 (34 published, one protocol, and 13 ongoing)	14,596	40	PWD and carer	Valid for mild to severe dementia[366] Valid in community and residential care settings[176] Available in Chinese, Czech, Dutch, English, Finnish, French, German, Hebrew, Polish, Spanish, Swedish and Portuguese[176,367,368]	No information found	Minimal floor-and-ceiling effects across 11 studies[369–379] Floor-and-ceiling effects in one study[380]	Sensitive to treatment effects across 12 studies[369–379,381,382]	No information found	Good to very good across 12 studies[365,380,383–392]	Good[388]
Global Deterioration Scale	Six (six published)	809	2	Informant rated	Validated in community or residential care[393] English version has been translated and validated in German and Korean[176,394]	No information found	No information found	Good sensitivity to change in two studies,[395,396] but not in another study[397]	No information found	Good across four studies[230,398–400]	Good[398]

CAMDEX, Cambridge Mental Disorders of the Elderly Examination; MCID, minimal clinically important difference; PWD, person with dementia.

TABLE 9 Validation of biological markers outcomes

Type of biological technique	Number of		Type of biological marker in trials	Accuracy	Sensitivity to change	Risks
	Trials	Participants				
MRI	30 (16 published, one protocol, and 13 ongoing)	4788	Mostly serial structural MRI for volume (22 trials; 4788 participants) The other eight trials used MRI for: • perfusion (one trial) • amyloid (two trials) • changes in brain network functional and structural connectivity and perfusion (one trial) • brain functional connectivity (one trial) • quantitation of lacunar lesions and diffuse white matter lesions (one trial) • whole-brain atrophy, white matter hyperintensity volume and cerebral blood flow (one trial) • unknown (one trial)	Serial structural MRI: gives accurate measurements of hippocampal volume and correlates with neuronal numbers[401]	Serial structural MRI: • hippocampal atrophy correlates with AD pathology,[402] including with Braak staging of dementia, tau, amyloid beta burden in people with AD[403] • there is consistent replication of hippocampal atrophy in assessing neurodegeneration caused by AD across disease severity, including evidence from 11 different research groups[403] • atrophy in the entorhinal cortex, ventricle and particularly the hippocampus and whole brain, accelerates with increasing cognitive decline across dementia[402,404–408] • structural MRI more sensitive to change across AD severities than amyloid markers measured via PET imaging or CSF[409–411]	• Strong magnetic field so not appropriate for anyone who has metallic implants inside their body (e.g. pacemaker)[412] • Can be noisy so need appropriate hearing protection[412] • Short-term exposure causes no harmful biological effects[413] • Can have psychological risks (e.g. anxiety and claustrophobia)[414,415]

They are not available in the English language:

- Syndrome Short Test[424] (two published trials; 410 participants).

They refer to only one domain:

- Wechsler Memory Scale[425] (five trials; three published, one protocol and one ongoing; 238 participants)
- Western Aphasia Battery[426] (one published trial; 48 participants).

We also did not search for validation of the individual cognitive tests, as they are neuropsychological tests rather than cognitive scales, with the validation process of these tasks different as they are designed to do different things.[427] Furthermore, the individual tests focus on specific domains of cognition, and as dementia is an impairment of more than one cognitive domain a global scale is more appropriate. Most of the individual tests have only been used in a small number of trials and often in combination. These include:

- Buschke Selective Reminding Test[428] (three published trials; 108 participants)
- Benton Visual Retention Test[429] (one published trial; 60 participants)
- clock drawing task[430] (two published trials; 30 participants)
- controlled oral word association test[431] (two trials; one published and one ongoing; 399 participants)
- digit span test[432] (two trials; one published and one ongoing; 399 participants)
- digit symbol substitution test[422] (three published trials; 680 participants)
- dot counting *n*-back task[58] (one published trial; 60 participants)
- fluency tests (seven trials; four published and three ongoing; 385 participants)
- Mohs Number Cancellation Test[433] (one ongoing trial)
- recall tasks (three published trials; 116 participants)
- Rey Memory Test[434] (one published trial; 213 participants)
- Stroop Colour Word Interference Test[435] (four published trials; 507 participants)
- token test[436] (one published trial; 12 participants)
- trail making test[437] (10 trials; six published, one protocol and three ongoing; 866 participants)
- word recognition (one published trial; 20 participants).

Neuropsychiatric outcomes

Similarly, for the neuropsychiatric outcomes we decided that we would not recommend measures of specific neuropsychiatric symptoms, such as agitation or depression; therefore, we did not search for validation data for the seven specific symptom measures included. These were:

1. Cohen-Mansfield Agitation Inventory[438] (one trial, 89 participants)
2. Columbia Suicide Severity Rating Scale[439] (three trials, all ongoing)
3. Cornell Scale for Depression in Dementia[440] (three trials, 464 participants)
4. Geriatric Depression Scale[441] (10 trials, 803 participants)
5. Hamilton Depression Rating Scale[442] (five trials, 677 participants)
6. Montgomery Depression Rating Scale[443] (two trials, 269 participants)
7. Zerssen Adjective Mood Scale[444] (two trials, 381 participants).

Biological outcomes

For the validation of the biological outcomes, the two champions first used their expertise and own searches for validation information to make their recommendations. Afterwards we added to this with regard to serial structural MRI, as this is the only biological outcome we are recommending; therefore, MRI is the only biological outcome we have recorded validation information for in *Table 9*.

Chapter 5 Methods of patient and public involvement consultation

Purpose

The purpose of PPI within this project was to present people both directly and indirectly affected by dementia, including those with experience of research participation, with some of the findings from our systematic review to seek their views on which of the domains they considered core and their assessment of the acceptability of individual and packages of measures. We also wanted to know their thoughts about general matters around completing outcome measures, including the length of testing that was acceptable, who they thought should complete outcomes, opinions about invasive tests and travel distances to a research site.

Procedure

We planned to consult through face-to-face focus groups followed by e-mail consultation, with people recruited from AS's Research Network volunteers. After meeting with the groups we sent a summary by e-mail to those who attended to check that the recommendations we intended to present at the consensus conference reflected what they thought had been said across the groups. We also asked participants if they had anything else to add.

After the consensus conference we conducted a second e-mail consultation with people from the AS Research Network, excluding those who had already attended the focus groups, to gain further feedback about the conclusions of the consensus conference.

Focus groups

We held three consultations, one in each of Cambridge, London and Sheffield, in February and March 2016. All were led by Lucy Webster and Anna Grinbergs-Saull from the AS. Champions within the group agreed to co-facilitate the focus groups. The AS had found that in previous focus groups including a clinician who uses these measures, and is therefore able to explain them, aids discussion, allowing participants to ask specific questions. The clinicians in each group were Gail Mountain in Sheffield, Gill Livingston in London and John O'Brien in Cambridge. Participants were e-mailed an information sheet and asked at the groups if they all consented to the session being recorded, with only Lucy Webster or the AS able to listen to the recording before it was destroyed (see *Appendix 4*). Participants who lived within travelling distance of each focus group were invited from the research network. For the Cambridge focus group, following recommendations made by a co-applicant, we also invited additional people from a local dementia and ageing research PPI group. Focus groups lasted 1–2 hours.

We focused on a different set of domains in each group, although there was an overlap between domains discussed at focus groups (*Table 10*). Discussions were audio-recorded and, to allow the participants to generate conclusions as easily as possible throughout the discussion, we summarised the conversations on

TABLE 10 Consultation topics

Sheffield	London	Cambridge
ADLs, cognition	Quality of life, global, outcome sets	Biomarkers, neuropsychiatric, outcome sets

flipchart paper. This allowed volunteers to see the notes that we were recording and refer to them when they felt it was necessary.

First e-mail consultation

To gain a wider range of views, we ran an e-mail consultation with focus group participants on a summary report of the focus group discussions. This was to allow the volunteers to comment on measures that they had not discussed in their focus group and respond to the conclusions we drew (see *Appendix 5*).

Second e-mail consultation

We then ran a second e-mail consultation on a report including recommendations made at the consensus conference (see *Appendix 6*). This was sent to research network volunteers who had not participated in a focus group. This consultation included volunteers who had expressed an interest in focus groups but were unable to attend, and those living in different areas, including Wales, Northern Ireland and the Midlands.

Chapter 6 Results of patient and public involvement consultation

Demographic details of participants

Table 11 includes an overview of the experiences and geographical locations of all 18 participants who were involved in the PPI consultations.

Focus groups

The face-to-face focus groups involved 12 people overall: three people living with dementia, two current family carers, six former family carers and one PPI group member. Some had participated in research or supported a family member through participation; others had no trial experience. There was an even split between men and women. Participants gave their ages in bands as 45–54 years ($n = 1$), 55–64 years ($n = 2$), 65–74 years ($n = 5$) or ≥ 75 years ($n = 4$). Ten of the participants were white British and two were

TABLE 11 Volunteer background information

Background information	Number of participants
Care experience	
Person living with dementia	4
Current carer	6
Former carer	7
Ageing and research PPI	1
Dementia experience	
AD	14
Vascular	2
FTD	1
PCA	1
Research experience	
Participant	6
Carer of participant	1
Steering group	7
None	7
Geographical region	
London	1
East Anglia	7
North England	8
Northern Ireland	1
Wales	1

FTD, frontotemporal dementia; PCA, posterior cortical atrophy.

white other (one white South American and one not specified). Most participants were married or living with their partner ($n = 7$), four were widowed and one divorced. Participants had a range of occupational backgrounds with current or last employment given as architect, care assistant, civil servant, footwear manufacturer, ecotoxicologist, civil servant, information technology manager, marketing communications director, NHS team leader, NHS therapy manager, senior staff nurse and retiree.

First e-mail consultation

The first e-mail consultation was sent to the 12 people who participated in the focus groups, of which five responded.

Second e-mail consultation

The second consultation was sent to the wider AS research network, excluding focus group participants. We received six responses from people with experience of AD, including one person with dementia and five carers (three current carers and two former carers).

This report gives a summary of the views of those consulted on different outcome measures, their use and the design of a core outcome package. Where possible we have included direct quotes from volunteers, identifying only whether they were a person with dementia (PWD) or a carer. We have separated the recommendations by the most common themes that were suggested by participants during the focus groups.

What should be measured?

At the start of each focus group session people were asked 'what should be measured?'. Responses were varied but gave broad support to each of the six domains covered. Suggestions not directly covered by the domains were:

- side effects of pharmacological interventions
- frequency of falls
- sleep disturbance – thought to be a significant indicator of progression
- carer outcomes – described by carers as a potential indicator of progression and likely to affect patient outcomes.

General recommendations

Throughout our discussions participants suggested potential improvements to the way in which outcome measures are delivered or packaged. Volunteers suggested several factors affecting the acceptability of outcome measures. We also received feedback on these suggestions during the e-mail consultation.

Questioning and terms used

Too many questions and fast delivery can cause anxiety in people with dementia, and intensive questioning can be perceived as 'getting at you' (carer).

The way in which questions were asked and the types of questions asked were also discussed. People with dementia stated that the questioning should be clear, as they may give completely different answers dependent on certain words. For example, the questions 'On a good day? or 'On a bad day?' (PWD) would elicit different responses.

Across the questionnaires shown to people living with dementia, two people had a preference for positive questions that did not 'focus on the negative stuff as much' and rather the 'things we can do'. However, another person living with dementia also noted 'it's more relevant what they cannot do than they can do, because there's an awful lot more we can't do than we can do'.

Several volunteers also strongly disagreed with the word 'carer', suggesting that this discounted those who did not identify as caring/cared for by a family member and those who lived alone. To conform to conventions within the literature, the word 'carer' is used here. However, we felt it was important to note the dislike for the term.

Time and travel requirements

The groups all thought that both time and travel could be a barrier to participation. Measures were deemed less appropriate if they required participants to travel to a specific centre each time. Long, single meetings were described as too tiring for people with dementia (most preferred a full day with several breaks). One and a half hours was described as the absolute maximum time for a single meeting or test without a break; however, volunteers suggested that researchers should be encouraged to aim for shorter periods. People with dementia particularly discussed reaching a stage where they cannot concentrate during longer sessions, but suggested that they may not be immediately aware that they had reached this point. Shorter testing would prevent this from happening:

> *Where it's got to the stage that you're not aware that you're not giving the right answer, or what you would have given at the beginning.*
>
> *PWD*

Volunteers also stressed the importance of clearly explaining the time required, including any breaks and waiting periods. Carers suggested that waiting for a meeting can seem aimless and can therefore be particularly difficult to explain to the person they support.

Having to travel far is a barrier, as people with dementia are 'going to have comorbidities . . . They're going to have all the other things going on . . . so it makes it much more difficult' (carer). Carers noted that being able to participate in research locally, rather than having to travel far, would encourage and help with participation.

Role of the 'carer' in completing outcomes

Discussing carer-assessed measures, volunteers highlighted the likely disparity between the answers given by people with dementia and carers. Although some thought that this was a problem, two volunteers also pointed out that a difference in responses might provide an additional source of data. The participants said that many people with dementia live alone. Although measures do not require co-residence, volunteers also pointed out that not all people with dementia will have a defined carer, family member or friend who could give an accurate assessment. However, all agreed the 'importance of the carer in the decision-making' around participating in research, as their time and availability play a part in the trial:

> *You can't expect them to take days off work to come with you to an assessment . . . it's difficult because then you're relying on what I'm saying.*
>
> *PWD*

Engagement: communication and relevance

Many participants thought that clear communication about the reasons why particular measures were chosen would aid continued engagement in the trial. Participation requires commitment and time, and they felt that participants need to know what they are contributing and why. Although volunteers understood the need for standardisation to improve the usefulness of data, some people with dementia and carers did not like standardised questionnaires. It was suggested that standard sets of questions might not be relevant to different types of dementia. For example, a carer with frontotemporal dementia experience suggested that receiving questions about memory made the research seem 'a waste of time'. Furthermore, some volunteers felt that standardised questions lack contextual detail about an individual's background, and that results would be relative to each person's experience of dementia and its symptoms.

Standardised interviews

Cognition

Overall, volunteers agreed that cognition should be core. However, volunteers felt that it should not be used in isolation as the only core measure and suggested that cognitive scores needed contextual, qualitative information. Carers, in particular, suggested that more weight should be placed on the interaction between cognition and ability rather than cognition alone:

> *It is more important to understand how a person's cognitive impairments affect their activities of daily living and quality of life . . . than it is to rate their underlying cognitive skills.*
>
> *Carer*

Although they acknowledged its use as a standard cognitive measure, performed in a range of research and clinical contexts, several people did not like the MMSE. People with dementia suggested that it seemed irrelevant, as it gives a restricted account of dementia and carers described how they thought it would be difficult to have a cognitive measure that seemed relevant to all people with dementia:

> *It doesn't seem useful.*
>
> *PWD*

> *It doesn't have anything to do with what we have.*
>
> *PWD*

> *Cognitive testing, because we are so different and the way it progresses in the different forms of dementia makes it so complicated to try and produce some kind of standardised measure.*
>
> *Carer*

Volunteers, including both people with dementia and carers, felt that memory tests can be demoralising; carers particularly felt that it is distressing 'watching someone fail a test'. People with dementia described the distress of seeing their score and performance worsen, and a tendency to try to prepare for tests to prevent this from happening. Some people preferred the ADAS-Cog to the MMSE, as it is more detailed in terms of the answers you can give.

Activities of daily living

Volunteers disagreed over the use of ADLs. Some focus group discussions concluded that it was not core; however, other people with dementia considered ADLs an accurate, practical measure of dementia. Volunteers consulted electronically also expressed some support for ADLs as a useful measure. Overall, volunteers preferred instrumental ADLs, rather than basic ADLs, as the activities seemed more relevant to daily life in mild to moderate dementia:

> *A lot of what's down there now doesn't apply to me.*
>
> *PWD on the items of the Katz ADL scale that refers to basic ADLs*

Some people with dementia also suggested that discussing reduced ability to perform tasks was less distressing than cognition:

> *Your body thinks it can do it, but your brain doesn't allow it.*
>
> *PWD*

> *Some days you can do them and you are brilliant . . . other days you cannot do them.*
>
> *PWD*

The Katz instrument was not liked by some people with dementia because yes/no questions did not allow for gradations in ability. Volunteers suggested that questions should ask why someone cannot perform a task or what they do differently to complete it. For example, volunteers pointed out that they may still be able to do activities but in a different way to how they may have performed them before dementia, such as by wearing clothes that are easier to put on or cooking simpler meals:

> *Some task you can still do, just differently, just adapted.*
>
> *PWD*

People with dementia felt that this should be considered when questioning them about ADLs:

> *Say can you do them but differently than what you used to?*
>
> *PWD*

Additionally, people living with dementia suggested that they might avoid tasks because of a lack of confidence rather than an inability to complete them:

> *I can use the telephone, but I don't have the confidence, I don't like using the telephone.*
>
> *PWD*

Therefore, several volunteers felt that ADL measures lacked the nuance necessary to understand how, and if, an individual's ability to perform daily tasks had been impaired.

Carers also raised the interesting point that some ADL questionnaires that they have had to complete were very similar to disability benefits assessments. The similarity was strong enough that they felt it could cause alarm and suspicion as to the use of trial data, and may affect the answers that participants give:

> *The link across into disability benefits . . . it's suspicious.*
>
> *Carer*

Neuropsychiatric symptoms

Some participants said that behaviour is core because it is a significant aspect of dementia and seems more sensitive to illness than ADLs. However, some volunteers felt that behaviour should not be used in isolation, as it may be less applicable in mild to moderate stages and does not consider the reasons behind behaviour changes. Volunteers suggested that behavioural measures should be analysed alongside contextual information about the individual and their personality to give a more accurate insight into the behavioural changes caused by dementia:

> *It's teasing out the brain damage from actual personality traits.*
>
> *Carer*

> *It's about behavioural change over time.*
>
> *Carer*

In particular, some felt that behaviour should be measured alongside cognition and understanding, which could affect agitation and aggression. Volunteers suggested that, if behaviour were measured, it should, as it usually does, include sleep, agitation, walking ('wandering'), violence/temperament, compulsive/repetitive behaviours and changes in diet and taste (i.e. preferences for certain foods). Some participants thought that measures should include an ability to hold a conversation or follow a television programme, which are usually not considered as behavioural.

Quality of life

Volunteers disagreed over the inclusion of quality-of-life measures as core. One volunteer considered these to be core, as they can give a summary of an individual's experience of dementia. However, throughout the discussions and consultation there was some debate as to the sensitivity of quality-of-life measures. Some carers suggested that it would be difficult to assess another person's quality of life and that these measures rely on accurate interpretation of an individual's responses. Others thought that carer assessment would be necessary, as they may have a clearer insight into changes. It was suggested that comparing carer and patient responses would give the most accurate account of quality of life.

When one volunteer was shown all three of the measures, they described both the EuroQol-5 Dimensions (EQ-5D) and Quality of Life in Alzheimer's Disease (QOL-AD) as lacking in detail. In particular, in reference to the EQ-5D, they said, 'I don't know how much you'd get out of it' (carer). However, the Dementia Quality of Life measure (DEMQOL) was decided to be 'reasonably easy to do and it's going to give a lot of information' (carer).

In particular, some felt that quality-of-life measures lack detail regarding the individual's personality; for example, they may always have disliked social events. Therefore, in general, quality of life was considered important but not a core measure for all trials.

Global measures

Volunteers had differing opinions about global rating scales. Some approved of the breadth of the measure:

> *I like the global one . . . it's all encompassing.*
>
> *Carer*

However, others suggested that global measures were superficial, depending too much on the individual's experience on the day, and not meaningful:

> *You might be feeling particularly bad that day.*
>
> *Carer*

> *Is that really valuable . . . . Am I giving my time for something that's meaningful? I'm not really convinced.*
>
> *Carer*

Those who did not like global scores suggested that a larger package of specific measures would give the holistic view of an individual with more detail.

Biological measures

Volunteers generally agreed that biomarkers should be core, viewing them as being the most reliable, objective measure and, therefore, least affected by environmental factors and day-to-day symptom variation. However, although these were thought to be more tangible and objective measures, there was also some uncertainty about their value and what type of data they actually provide.

For example, biomarkers were described as the more tangible measures:

> *Biological measures you've got something that everyone can agree on . . . you can compare like with like.*
>
> *Carer*

That said, there was some disagreement as to the use of certain measures, and volunteers also suggested that, although reliable, biomarkers should not be used in isolation and should be combined with measures such as cognition and behaviour.

Carers had a number of general questions about the type and quality of data biological measures could actually provide, including:

> *Do you get more information from a lumbar puncture than a scan?*
>
> *Carer*

> *Would you be looking for a reduction in amyloid or tau, or would you be looking for an arrest in the size of brain shrinkage?*
>
> *Carer*

> *How many people would you need for it to be significant?*
>
> *Carer*

Cerebrospinal fluid measures

Some volunteers particularly liked CSF measures, even though they were aware of possible side effects and general misconceptions about what the procedure involves (e.g. very large needles) that might discourage some from taking part. However, the volunteers felt that having to give CSF would not discourage most people from participating and that, although uncomfortable, it would be bearable. One volunteer described the person they care for as happy to undergo annual CSF as part of an ongoing trial:

> *A couple of hours and its done . . . it doesn't put him off going the following year . . . he knows exactly what he's let himself in for and he does it.*

Indeed, for most, the main criticism was the need to take CSF measurements in a specific location. Those with experience of the measure suggested that travelling to and from the specified site was the greatest drawback. Some suggested that, if it were possible to take CSF in convenient locations, they would consent to two or three samples a year:

> *I think the practicalities of it would be the bit that concerns me . . . practicalities should be made easier for the patient.*
>
> *Carer*

That being said, the support was not unanimous, and one volunteer suggested that the two people she had cared for would not be able to cope with the procedure, and that 'it might put people off taking part' (carer).

Blood tests

The usefulness of blood tests in terms of showing disease modification was questioned by carers:

> *Do they produce something meaningful?*
>
> *Carer*

One volunteer who spoke against CSF measurements suggested that taking blood had been difficult for her family members (this was the reason that she doubted their tolerance for CSF procedures). However, overall, volunteers agreed that blood tests were unproblematic and that it would not be difficult to commit to frequent tests. The main barrier discussed was travel, with one group suggesting that, subject to location, 'weekly blood tests would be very happily tolerated' (carer).

Imaging

Most volunteers agreed that imaging could be core. However, their discussion focused on hopes and expectations that this would provide 'sophisticated', 'sensitive', 'objective' and 'useful' data:

> *Making sure the scans themselves are sophisticated enough to be able to give you what you're looking for . . . are they sensitive enough to give the objective results you're looking for?*
>
> *Carer*

Volunteers also suggested that many would consent to scans, as giving biological data can make the person with dementia feel that they are contributing useful information:

> *In going through that he is doing absolutely everything he can to further the research.*
>
> *Carer*

> *It's a positive action.*
>
> *Carer*

> *It's something physical happening . . . now logically you know it isn't going to alter your dementia or do anything to it, but somehow it would make me feel better, that somebody somehow was actually doing something . . . although it has drawbacks obviously.*
>
> *Carer*

Practical issues around travel and the need for concentration were raised but, in general, 3- to 6-monthly scans were considered bearable. However, volunteers agreed that, although MRI is straightforward, it could be difficult for some people with dementia. Four people caring for someone with either vascular dementia or AD felt strongly that the person they cared for would be unable to lie still for 10 minutes and that doing so for 45–60 minutes would be impossible:

> *Vascular and Alzheimer's when it gets to the middle . . . you can't keep people still . . . they don't understand what's happening.*
>
> *Carer*

> *It bothers me about the scan . . . incredible noise being lashed down. I knew what was going on . . . but for people with dementia it could ruin them.*
>
> *Carer*

> *I've been in one and I can imagine her staying in there still . . . not for an hour.*
>
> *Carer*

> *I can't imagine they'd tolerate an hour.*
>
> *Carer*

Participants did also note that 'different people react in different ways' (carer). Some had more positive experiences: one carer said that the person they care for 'quite enjoys these'. Having music or a screen to watch was said to improve the experience, giving the individual something to focus on, and that could be done for most participants 'If there is some flexibility' (carer) around the MRI environment.

Carers agreed that PET scanners were less restrictive than MRI scanners, although the issue of having to keep still remains.

Overall, volunteers agreed with the suggestion made at the consensus conference regarding the use of MRI in a select number of participants who had consented to the procedure, rather than including MRI as a core component for every individual in the study design. Volunteers agreed that this could improve

recruitment and retention, as the prospect of MRI can discourage participation. Allowing those who are anxious about MRI to opt out of that part of the study would enable them to join trials they would otherwise not consider.

Summary

During the focus groups, some volunteers thought that an outcome set should include biological tests, cognition and possibly behaviour. One volunteer suggested that a package could potentially include global measures. Most participants favoured biological measures as they perceived these to provide a more objective outcome. The volunteers who reviewed our report of the focus group discussions broadly supported this recommendation and the recommendations made in the consensus conference. Volunteers also suggested additional considerations for the design of a core package:

- Burden of time: 1–1.5 hours maximum without a break.
- Include both people with dementia and carers: carer assessments rely on positive relationships and an accurate understanding of an individual's dementia. Consider how to involve those without a defined carer.
- Prioritise explaining the reason for the test; clear idea of purpose may improve retention.
- Efficiency: several tests within 1 day cuts further visits, weekend visits would remove the need for working carers to take time off.
- Different types of dementia may need different core measures: some of those consulted felt that this was illustrated by the variation in volunteer opinions.

Volunteers suggested that the current research would present the opportunity to encourage dementia-friendly trial designs, with fewer individual measures and a lower burden on the person with dementia and their carer. This was despite consistently advocating for individualised and longer measures. One carer, when discussing a trial protocol involving a large number of exploratory measures, said:

> *There is a need to ensure that does not happen in dementia trials as the extra burden on patients cannot be justified.*

The practicalities of research and carer and patient burden were in many ways a greater concern for those consulted here than the individual measures:

> *When you're trying to recruit people, take as many of the barriers out of the way as possible.*
>
> *Carer*

The recommendations made by people with dementia and carers focus on the importance of reducing the personal impact of research participation, ensuring that the research methods chosen are relevant and acceptable to people affected by dementia, and the importance of trials enhancing a sense of achievement from participation:

> *That's where I think research can come into its own on enhancing our situation by making us feel good that we're taking part in something.*
>
> *PWD*

> *The experience of dementia is extremely isolating . . . being part of a dementia study certainly made me feel as though someone was remotely interested in what was going on, which was actually terribly important.*
>
> *Carer*

Chapter 7 Consensus conference

Purpose

The purpose of the consensus conference was to bring together the NIHR dementia research community to discuss which outcome domains should be core, any specific recommendations of outcomes within each domain and other issues that should be considered for potential participants completing the core set.

Preparations

We chose a central London venue for the conference; this was felt to be the easiest location for group members to travel to from around the UK and many of the participants were based in London.

We chose champions for each domain from within the group based on expertise. We split the biological marker domain into imaging markers and fluid-based markers with a champion for each, meaning that there were seven champions overall. The champions were:

1. ADLs: Gail Mountain
2. biological markers: fluid – Robert Perneczky
3. biological markers: imaging – John O'Brien
4. cognition: Rob Howard
5. global: Bob Woods
6. neuropsychiatric symptoms: Gill Livingston
7. quality of life: Sube Banerjee.

Each champion was sent the data from the systematic review about their domain, along with some validation information, and was asked to use both of these alongside their professional expertise and knowledge to evaluate if the domain was core and which measures they would recommend. Each champion was asked to prepare a short presentation (10–15 minutes) for the consensus conference around their recommendations and to write up their presentation in up to 1000 words.

Participants

The list of people who attended the conference is in *Appendix 7*.

We invited all participants who agreed to collaborate on the project within the protocol, and also additional people who had become involved during the project: a Master of Science student who had volunteered to work on the project (DG), the AS Research Engagement Officer who had led the day-to-day work on the PPI (AGS) and a representative from Alzheimer's Research UK. A member of the original collaboration left academia (Mary Bond) and so put forward a colleague in her place (JTC).

Participants who attended had a range of academic and clinical expertise within dementia research, including:

- AS research lead – James Pickett
- applied psychosocial dementia research/occupational therapy – Gail Mountain (co-applicant)
- dementia care – Frances Bunn and Claire Goodman
- health service research – Sasha Shepperd

- health outcome measurement – Sallie Lamb and Charlotte Roberts (co-applicant)
- old age medicine – Roy Jones
- old age psychiatry – Sube Banerjee, Chris Fox, Rob Howard (co-applicant), Gill Livingston (principal investigator), John T O'Brien and Robert Perneczky
- psychology and dementia – Georgina Charlesworth, Esme Moniz-Cook and Bob Woods
- public health and ageing – Louise Lafortune (co-applicant)
- social care and social policy – David Challis, Katie Featherstone, Justine Schneider and Claire Surr
- systematic reviews – Jo Thompson-Coon.

Conference proceedings

The conference began with a summary of the project, including the background, aims and workstreams of the project. Gill Livingston, who was chief investigator of the project, gave an overview of the purpose and workstreams of the project. Lucy Webster presented an overview of the systematic review, including the methods, numbers screened and searched, and the main findings from this in terms of outcomes. The main feedback from the focus groups was also presented by Anna Grinbergs-Saull. Gill Livingston and Rob Howard chaired the meeting and Gill Livingston and Lucy Webster took notes of the discussion.

Cognition

Champion: Rob Howard, Professor of Old Age Psychiatry, University College London

With the central feature of dementia being cognitive impairment, it is essential that a cognitive outcome would be a core measure in disease-modifying trials. By definition, at least two cognitive domains are disrupted in dementia and different dementias are characterised by disruption to different cognitive domains. Therefore, no single neuropsychological test will be sufficient as an outcome tool, hence the need to recommend a global cognitive scale or battery of tests that can be used across all dementia trials. We therefore did not consider cognitive scales that focused on only one cognitive domain. We shortlisted the five most commonly used scales and searched for validation data for these scales: ADAS-Cog, MMSE, CERAD's Neuropsychological Battery, the Neuropsychological Battery and the Cogstate Alzheimer's Battery.

For cognition, there are really only two serious contenders. The ADAS-Cog and the MMSE have overwhelmingly been the most widely used cognitive measures in disease-modifying trials. The ADAS-Cog has been used in 92 trials involving 20,419 participants, the MMSE in 83 trials involving 17,736 participants and both scales have been used in combination in 68 trials involving 15,949 participants. The MMSE has mostly been used with the ADAS-Cog or other cognitive tests; it has been the sole cognitive measure in only six of the included trials. ADAS-Cog, on the other hand, has solely been used in 20 of the trials.

Both scales are validated and demonstrated good sensitivity to change in the earlier cholinesterase inhibitor trials. The ADAS-Cog is scored out of 70 points, whereas the MMSE is scored out of 30 points. Minimum clinically important difference figures of 3.0 points for the ADAS-Cog and 1.4 points for the MMSE have been used. If trials can be designed to anticipate differences of this magnitude, either scale could be used.

Both scales are pencil and paper tests. The ADAS-Cog can only be administered by a trained tester and takes 45 minutes to complete. The MMSE can be administered by clinical staff with minimal extra training and takes 10 minutes to complete.

The MMSE has been criticised for being affected by age and education, for lacking sensitivity in differentiating between very early AD or MCI and normal ageing, for not including items sensitive to executive functioning and for being insensitive to disease progression in severe AD. However, in mild to moderate AD it has reasonable psychometric properties and performed well in the detection of small treatment effects in trials of cholinesterase inhibitors and memantine.

The ADAS-Cog was developed to detect incremental improvement or decline in cognitive functioning in clinical trials. It has been the gold standard cognitive assessment for use within AD trials conducted by the pharmaceutical industry. The larger number of items included certainly gives the impression of potential greater sensitivity to change than the MMSE, but superiority was not seen in the trials of symptomatic treatments. That is to say, in trials in which the ADAS-Cog showed a significant drug–placebo difference, the MMSE (if it was also used) would also detect this. Furthermore, because the ADAS-Cog is not used in clinical practice, clinicians do not have a 'feel' for what difference in score would constitute a meaningful change.

The ADAS-Cog has been criticised for not sufficiently assessing attention, planning, working memory and executive functioning, all of which are impaired at the earliest stages of AD. This has led to the addition of extra tests to the original ADAS-Cog, including delayed word recall, a maze and digit cancellation task, and a subjective assessment of concentration and distractibility.

Batteries of neuropsychological tests

In response to concerns that the ADAS-Cog and MMSE show low sensitivity to change in mild AD, with placebo-allocated patients typically showing a mean decline of as little as 1 ADAS-Cog point over 6 months in some trials, the Neuropsychological Test Battery (NTB) was developed to include measures of memory and executive function considered to be most affected at this stage of the disease. Through a combination of six validated neuropsychological tests, the NTB has been shown to have excellent psychometric properties across mild to moderate AD. The NTB has been used in seven trials involving 3429 participants. As a test of high sensitivity, but uncertain clinical significance, the NTB would seem most useful in early-phase trials in which detection of preliminary, proof of concept signal is sought. The battery can only be administered by trained raters.

Biological markers: imaging

Champion: John O'Brien, Professor of Old Age Psychiatry, University of Cambridge

Imaging biomarkers are used in clinical trials of disease-modifying therapies in AD for a number of reasons. First, they are used to clarify the clinical diagnosis through the application of research diagnostic criteria for AD. Second, they are used to stratify subjects for entry; for example, a trial using a therapy based on decreasing amyloid might stratify subjects by including only those who showed increased amyloid burden. This may be important, as previous failed studies of immunotherapy in AD have found that around one-third of subjects with supposed AD did not have any evidence of increased brain amyloid.[122] Third, imaging is used to ensure that inclusion criteria are met, for example the absence of multiple microbleeds on MRI for an immunotherapy trial. Fourth, MRI, in particular, is used as a safety outcome measure (examining for an increase in microbleeds and/or oedema). Fifth, imaging is used to demonstrate target engagement (e.g. showing that anti-amyloid therapy actually lowers brain amyloid). Finally, imaging markers are used as outcome measures in their own right, either because imaging changes are more directly related to pathology (e.g. amyloid or tau imaging) or because they have much greater reliability and sensitivity to change than clinical measures (e.g. serial structural MRI), therefore allowing studies to be done more quickly and with fewer subjects.

Imaging outcome measures used in 49 (30.4%) of the studies identified in the literature review included magnetic resonance spectroscopy (one study, 353 subjects), serial structural MRI (30 studies, 4788 subjects), PET (19 studies, 761 subjects), electroencephalography (EEG) (three studies, 96 subjects), perfusion single-photon emission computerised tomography (one study, 135 subjects) and Doppler ultrasound (one study, 45 subjects). PET can be divided into studies that used metabolic PET (13 studies) or amyloid PET (10 studies). Some studies have used multiple markers. Metabolic PET has been exclusively undertaken with fludeoxyglucose PET, while amyloid imaging most frequently uses Pittsburgh compound B (PiB) or florbetapir, although that may reflect the order in which amyloid imaging ligands became available, with PiB the best established, followed by florbetapir. There are two other amyloid imaging compounds that have been licensed for clinical use, flutemetamol and florbetaben. Tau imaging ligands are now available, with at

least three (AV1451, PBB3 and THK) being the subject of ongoing validation studies. One ongoing trial was identified using AV1451 PET, but several more are planned. Magnetic resonance spectroscopy and Doppler blood flow measurement were each included in only one clinical trial. There is a strong suggestion that the inclusion of imaging biomarkers is increasing over time, as they were present in 25% of published studies but are included in 53% of currently ongoing studies.

Serial structural MRI has, therefore, been the most widely used imaging outcome measure, with scans repeated over a period ranging from 24 weeks to 2 years. Most studies have used 1.5-T magnetic resonance, although some a mixture of 1.5 T and 3 T. The outcome measures analysed most commonly are whole-brain volume change and/or change in hippocampal volume. Structural MRI has proved sensitive to change over time, but changes between placebo and treatment have not always been as expected. For example, in some of the early immunotherapy studies serial brain volume loss was actually higher in the treated (amyloid-lowering) groups,[79] a finding explicable in terms of greater amyloid removal but not paralleling the accepted relationship between greater volumetric loss and worse disease progression.

Fludeoxyglucose PET has shown itself to be a sensitive marker of disease progression in studies over 6–18 months. In some studies, decreased glucose metabolism has been greater in placebo groups.[59,64,140] Amyloid imaging is becoming an almost essential requirement, both for target engagement and as an outcome measure, in clinical trials aimed at lowering brain amyloid. Its use was particularly important in the bapineuzumab studies,[122] as clear differences in brain PiB retention could be demonstrated between placebo and actively treated groups, demonstrating to some extent target engagement, despite no effect on clinical outcome measures. This study was particularly interesting because whole-brain volume change was similar between groups, so not sensitive to the effect of amyloid lowering (although paralleling the lack of change in clinical measures). Perfusion single-photon emission computerised tomography, although a well-validated marker, has been used in only one Phase II study and is unlikely to be a useful biomarker for the future given the much greater sensitivity, wider availability and similar cost of fludeoxyglucose PET.

Electrophysiological and functional imaging markers have not been well studied in AD trials, despite the fact that they have potential for greater sensitivity to change over shorter temporal periods than structural, metabolic or amyloid imaging. Only three studies (of which two have completed) have used EEG, although, interestingly, both showed a change in EEG in the treated group.[40,109] There are too few data to draw any conclusions, but both EEG (and magnetoencephalography) and functional MRI merit further investigation and validation in future studies, especially those undertaken over short treatment periods (4–26 weeks).

Cerebrospinal fluid biomarkers can also capture information on tau and amyloid, and show a relationship to changes on imaging. Advantages of CSF include the ability to capture both amyloid and tau in a single measure, and the fact that it is relatively cheap to collect compared with imaging. Disadvantages include still considerable and largely unexplained variability between sites in results, the loss of any spatial (regional brain) information about pathology, a relatively indirect relationship to brain changes, the need for an invasive lumbar puncture and the inability to capture information provided by some imaging modalities (e.g. structural MRI).

In conclusion, around one-third of disease modification studies have used imaging biomarkers as outcome measures, with an increasing proportion over time. Serial structural MRI remains the most widely used and best-validated biomarker, and robustly demonstrates disease progression in untreated AD subjects. For example, it can be measured in a study to show that improvement in cognition is related to disease modification via a reduction in atrophy, rather than just a symptomatic change, and it does not require all participants to undergo MRI.

Metabolic PET has also been widely used and demonstrates sensitivity to change in untreated patients, and may be of particular interest for compounds that are purported to influence glucose or energy metabolism. More specific ligands, including those for amyloid and tau, are now available and are becoming increasingly validated as outcome markers. Longitudinal changes in amyloid PET, and most likely in tau PET (although

this remains to be demonstrated), will be expected to be less sensitive to change over shorter periods than, for example, serial MRI. However, they will be essential to include in some studies of disease modification in AD, depending on the mechanism of action of the compound under study, to show target engagement.

Biological markers: cerebrospinal fluid

Cerebrospinal fluid and blood biomarkers

Champion: Robert Perneczky, Reader in Cognitive Impairment and Dementia, Imperial College London

Recently revised diagnostic guidelines for AD emphasise the use of biomarkers, heralding a paradigm shift towards a more biological definition of the disorder. Currently available biomarkers offer added diagnostic accuracy in certain situations, but their performance in terms of early diagnostic sensitivity and specificity does not fully live up to the desired standards. The hope for disease modification as well as technological advances in biomarker discovery fuel the search for biological indicators of the AD pathophysiological process, which can be used to identify neurodegeneration independently of its clinical manifestations. Ideally, such a biomarker, alone or in combination with other markers, would distinguish between individuals with and without AD pathology independently of the clinical symptomatology. Individuals with asymptomatic early AD would probably benefit most from interventions aiming to prevent further neural damage to maintain their independence, ability to work and fulfilment of social roles. Furthermore, pathophysiological markers may also offer the added benefit of directly assessing response to treatment options that target core processes of AD pathogenesis. The application of novel therapeutics with potentially significant side effects could thereby be restricted to patients with biological evidence of treatment response in line with the notion of personalised medicine. However, biomarker evidence of treatment efficacy should not replace clinical evidence of patient benefit.

Currently available AD biomarkers can generally be grouped into two categories. The first category comprises markers that indicate the type of pathology present, including CSF levels of amyloid-β (Aβ) 42, total tau (T-tau) and phosphorylated tau (P-tau)181 and PET tracers of fibrillar amyloid such as flutemetamol, florbetapir, florbetaben and PiB. The second category consists of markers that provide information on the topography of pathological changes, such as MRI and fludeoxyglucose PET. The diagnostic accuracy of the aforementioned biomarkers to distinguish between AD dementia and physiological ageing is high in selected patient cohorts, recruited at specialised centres and, therefore, enriched with relatively pure AD cases. However, the clinical usefulness of available biomarkers is limited when it comes to the identification of early or atypical AD cases, especially in unselected populations.

The sensitivity and specificity requirements set out in the consensus report of the Working Group on Molecular and Biochemical Markers of AD[445] are rarely met when fluid biomarkers are compared with autopsy results. Little is known about the ability of biomarkers to identify AD pathophysiology in asymptomatic individuals. Studies in carriers of pathogenic mutations have shown that biomarkers can become abnormal many years before the onset of clinical symptoms. In addition, longitudinal observations in cognitively healthy older people have demonstrated that an AD-typical CSF biomarker profile is associated with greater cognitive decline. However, it is unclear how accurately current biomarkers can predict future dementia and the time of onset in individuals who have no symptoms. Furthermore, Aβ immunisation trials show that markers of AD pathophysiology show changes even if no clinical benefit is present, which limits their usefulness as study end points or surrogate measures (even though they may be useful to show target engagement).

Our systematic review confirms that the three established markers Aβ42, T-tau and P-tau181 are also the most widely used markers in AD dementia clinical trials. CSF levels were measured in 51 out of 125 (41%) studies, whereas 35 out of 125 (28%) studies reported blood levels. Even though AD fluid markers are useful for diagnosis to ensure that studies have AD cases with true AD pathology, and to measure target

engagement, their usefulness as outcome measures is limited based on the available evidence. They are therefore not recommended as core outcomes for dementia clinical trials.

Neuropsychiatric symptoms

Champion: Gill Livingston, Professor of Psychiatry of Older People, University College London

Neuropsychiatric symptoms or behavioural and psychological symptoms of dementia are the symptoms of abnormal mood, disturbed behaviour, thinking or perception, which become more common as dementia progresses from mild to moderate so that each individual with dementia will almost inevitably develop neuropsychiatric symptoms at some point during the illness.[446]

Although neuropsychiatric symptoms are almost universal if individuals are considered throughout the course of the disease, individuals with mild to moderate dementia occasionally have no neuropsychiatric symptoms and frequently have no clinically significant symptoms. For example, 94% of participants with dementia in a study designed to be representative of people with AD had one or more neuropsychiatric symptoms, but only 74% had clinically significant symptoms.[447] Similarly, a study of newly diagnosed patients with AD found that 78% had neuropsychiatric symptoms and 59% had clinically significant symptoms.[448] As people with mild to moderate dementia may not have any or clinically significant neuropsychiatric symptoms and, therefore, have no potential for these to improve, if the underlying disease is modified, this floor effect means that effective treatments for disease modification would require hugely increased samples size to show a significant effect on neuropsychiatric symptoms.

Neuropsychiatric symptoms are common and contribute significantly to decreased quality of life for patients with dementia, caregiver burden and care home admission.[449] These are therefore very important symptoms and we would like to encourage their measurements to understand what a disease-modifying treatment is doing in important domains. It is also important to recognise that neuropsychiatric symptoms can sometimes be influenced by social factors (e.g. care and relationships around a person). Therefore, if neuropsychiatric symptoms are being measured, studies would need to account for whether social or relational factors external to the intervention might be influencing this, possibly through measurement in control and intervention groups.

We will use the opportunity afforded by our systematic review of the literature in this field, PPI and consensus conference to make recommendations for which instrument to use.

Desirable characteristics of measures

1. We prespecified that potential measures must have some form of validation and reliability in the population to be tested. This particularly includes content validity for neuropsychiatric symptoms (i.e. not only reliability and concurrent validity but that the measure covers neuropsychiatric and only neuropsychiatric items rather than include, for example, ADLs or memory). In addition, these items should be neuropsychiatric symptoms found in dementia rather than, for example, symptoms of schizophrenia.
2. We measured how often they had been (or are being) used. Ideally, they would have been used often, as this is a measure of how an instrument is valued, how practical it is and how much it is likely to be used in practice. The frequency of use in disease-modifying trials to date is summarised in *Table 12*.
3. Neuropsychiatric symptoms can be considered in terms of severity or frequency. Some scales cover only one of these. Knowing the frequency without the severity or vice versa means that the scale is less useful in measuring change. This is because the symptoms may improve either by being of reduced frequency or severity, or one of these dimensions may improve while the other deteriorates. Both dimensions are important characteristics and are often used in a summary score in an instrument, and this is desirable.

4. The time taken should not be too long as the instrument would be part of a package ideally, but not essentially. In addition, the minimal clinically important difference should have been calculated and it should be translated into different languages.

Our systematic review has identified nine measures that have been used to detail the range of neuropsychiatric symptoms in disease-modifying trials in dementia, detailed in *Table 12*. These are the Neuropsychiatric Inventory (NPI),[236] Brief Psychiatric Rating Scale (BPRS),[229] Alzheimer's Disease Assessment Scale-Non Cognitive scale (ADAS-Noncog),[174] CERAD's Behavioural Rating Scale for Dementia,[231] the Revised Memory and Behaviour Problems Checklist,[247] Dysfunctional Behaviour Rating Instrument,[234] Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD),[450] Nurses' Observation Scale for Geriatric Patients[243] and Plutchik Geriatric Rating Scale.[246]

Measure of individual neuropsychiatric symptoms

There are also some measures that have been used to consider individual neuropsychiatric symptoms (e.g. agitation[451] and depression) but these are too specialist to recommend for all trials of disease modification as no specific symptom is common enough to measure individually, unless the object of the study is to change it. The NPI was the most commonly used measure and is being used most often currently. It is valid and reliable, and measures both frequency and severity. It has good reliability statistics and sensitivity to change. It takes slightly less time than CERAD and, possibly, BEHAVE-AD (10–20 minutes). The minimal clinically important difference has been calculated as 8 points.[452] It has also been translated into Italian, Greek, Japanese, Korean, Mexican, Polish, Spanish and Dutch.[176,237]

The measures included that only assess the severity of symptoms are:

- BEHAVE-AD – sensitivity to change in moderate and severe dementia, but unclear in mild dementia. It takes 20 minutes to complete, and there are 26 items on a four-point scale. There was no floor or ceiling effects. The questions ask about severity not frequency. It has been translated into French, Swedish, German, Dutch, Spanish, Chinese and Korean.[176]

TABLE 12 Neuropsychiatric outcomes found

Name of measure	Number of				Time taken to complete measure (minutes)
	Studies	Studies published	Studies ongoing	Participants	
NPI	38	30	8	11,756	10–20
ADAS-Noncog	7	7	0	792	20–25
BPRS	3	3	0	190	20
Nurses' Observation Scale for Geriatric Patients	2	2	0	454	3–5
CERAD's Behavioural Rating Scale for Dementia	1	1	0	486	20–30
BEHAVE-AD	1	1	0	425	20
Dysfunctional Behaviour Rating Instrument	1	1	0	406	20
Plutchik Geriatric Rating Scale	1	1	0	178	5–10
Revised Memory and Behaviour Problems Checklist	1	1	0	168	10

ADAS-Noncog, Alzheimer's Disease Assessment Scale – Non-Cognitive scale; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BPRS, Brief Psychiatric Rating Scale; NPI, Neuropsychiatric Inventory.

- ADAS-Noncog – is commonly used (in terms of number of studies), but measures only the severity of symptoms. It is long, taking around 20–25 minutes to complete. It is sensitive to change in mild to moderate AD.

The measures included that only assess the frequency of symptoms are:

- Nurses' Observation Scale for Geriatric Patients – it only covers 3 days, which may be too short a period. It is commonly used (in terms of patient numbers), but measures only the frequency of symptoms. It is rapid to complete and has test–retest validity.
- CERAD's Behavioural Rating Scale for Dementia – is reliable and valid, and sensitive to change in mild to severe dementia. Takes 20–30 minutes to complete and is designed for mild to moderate dementia. It measures frequency but not severity, and has been translated into French and Spanish.[176]
- Dysfunctional Behaviour Rating Instrument – only measures frequency.

Content includes other domains:

- BPRS – only measures severity and is designed for general psychiatric patients (e.g. includes blunted effect and concerns about physical illness).
- Revised Memory and Behaviour Problems Checklist – incorporates memory problems in its total and, therefore, is not a pure test of behaviour. This may be why it is the least used.
- Plutchik Geriatric Rating Scale – is validated in geriatric inpatients who are not necessarily those with mild to moderate dementia. It incorporates sensory impairment, social isolation and activities, and is therefore not a good measure of behaviour.

In summary, neuropsychiatric symptoms should not be core measures in dementia modification studies but, as they are very important, many studies may wish to measure them. We recommend the NPI for the reasons outlined above.

Activities of daily living

Champion: Gail Mountain, Professor of Health Services Research, University of Sheffield

The main rationale for applying ADL measures in disease-modifying studies is to assess changes in participant abilities to undertake functional activities following an intervention, with scores providing an estimation of deterioration or improvement. Such measures can include basic ADLs such as washing, dressing and toileting and complex or instrumental ADLs (IADL) such as cooking, shopping and money management. Newer measures are also taking into account other daily activities such as engagement with social and leisure activities.

The systematic review identified 12 measures that have been applied in disease-modifying studies:

1. Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) (34 studies: 28 studies published, six ongoing; 11,500 participants)
2. Alzheimer's Disease Functional Activity and Change Scale (ADFACS) (two studies: two published; 350 participants)
3. BADL (five studies: three published, two ongoing; 1117 participants)
4. Dependence Scale (three studies: three published; 3343 participants)
5. Disability Assessment for Dementia (DAD) (12 studies: 10 published, one protocol and one ongoing; 2914 participants)
6. Functional Activities Questionnaire (two studies: two ongoing)
7. Interview for Deterioration in Daily Living Activities in Dementia (two studies: two published; 219 participants)
8. Katz ADL (four studies: three published and one protocol; 185 participants)

9. Lawton IADL (eight studies: seven published and one protocol; 1125 participants
10. Nuremberg ADL (three studies: three published; 530 participants)
11. Personal Self-Maintenance Scale (PSMS) (three studies: three published; 429 participants)
12. Video Recorder Home Behavioural Assessment (one published; 48 participants).

Initial considerations

1. The ADCS-ADL and ADFACS are both derived from the work of the Alzheimer's Disease Cooperative Group and have the same primary reference.[286] The author has now confirmed that the ADFACS is a version of the ADCS-ADL developed by one of the team (Rachelle Doody, Baylor College of Medicine Medical Center), who has since participated in studies led by Douglas Galasko (University of California San Diego Medical School) using the ADCS-ADL.
2. Lawton IADLs and the PSMS are derived from the same authors and are frequently used in combination, thereby spanning both ADLs and IADLs.
3. The Video Recorder Home Behavioural Assessment has only been applied in a single study and, therefore, has been discounted.

This leaves nine measures for consideration. The following four measures have been used most frequently:

1. ADCS-ADL
2. DAD
3. Lawton/PSMS
4. BADL.

The Dependence Scale has been used in only three studies, but with a large number of participants.

Alzheimer's Disease Cooperative Study Activities of Daily Living Scale

There is a 19-item scale for basic ADLs and a 23-item IADL scale, which includes reading, leisure activities and basic chores. The measure has good test–retest reliability (assessed in four studies),[286,289,292,293] is sensitive for use with people with mild to moderate dementia and sensitive to change in three out of four studies.[288–291] It has been translated and validated in several European languages.

Disability Assessment for Dementia

The 40-item measure was developed for use with people with different severities of AD living in the community. It can be applied in 15 minutes by a clinician interviewing the carer or by a trained observer rating performance. It determines whether or not the person with dementia needs help to initiate, organise, plan and perform in 10 ADL and IADL areas (including leisure activities). Content validity and reliability has been demonstrated independently[331] and by the measure developers,[301] and there are reportedly no floor or ceiling effects.[301,309]

Lawton Instrumental Activities for Daily Living/Personal Self-Maintenance Scale

These two measures were originally developed for use with non-cognitively impaired older people and can be used separately or in combination. The PSMS contains six domains of basic ADL functions (toileting, bathing, feeding, dressing, mobility and physical ambulation), rated from 0 to 1. The Lawton ADL has eight IADL domains (ability to use the telephone, shopping, food preparation, housekeeping, laundry, transport, managing medications and finance) rated on a scale from 1 to 5. Both can be completed in a short (5- to 10-minute) interview with the person with dementia, as well as through a proxy.[331] There are questions regarding the extent of sensitivity with dementia.[331,453] It has also been noted that this ADL measure has a ceiling effect.[331]

Bristol Activities of Daily Living scale

This 20-item questionnaire is used to measure abilities in both ADLs and IADLs by people in the early stages of dementia, using proxy report.[295] Face validity is determined by carer agreement regarding important items. BADL has good content and construct validity, but there are different views regarding test–retest reliability.[331,454]

Dependence Scale

The Dependence Scale comprises 13 items, completed with an informant. It was designed to identify the level of required care. Items range from need for reminders or advice to undertake IADL/recreational activities to needs for assistance with basic ADLs and need for supervision. The final four items in the measure are concerned with needs for interventions to maintain basic function (catheterisation/tube feeding). The developer of the measure was able to demonstrate good psychometric properties and sensitivity to dementia progression, but this has not been replicated.[298] In addition, given the wide range of items within the measure, dependency at different stages of dementia is estimated by very few items.

The following measures are less frequently applied.

Interview for Deterioration in Daily Living Activities in Dementia

This is designed to assess both basic ADLs and IADLs in community living people with dementia, with both initiative to perform tasks and performance being assessed. The 33 items are assessed on a seven-point scale.[319] It was initially designed for use in a 15-minute carer interview, but there is now a self-complete version for the carer.

Functional Activities Questionnaire

This 10-item measure solely comprises IADL items, including travel and recreation, each being assessed on a six-point scale by an informant. It is valid for use only with people with mild dementia and has been used to distinguish between MCI and dementia.

Katz Activities of Daily Living

This measures independence in basic activities of older adults and is not dementia specific. Included items are bathing, feeding, dressing, toileting, transferring, continence and bathing, with rating being independence or dependence. The results from application of the Katz are highly correlated with MMSE scores,[455] and it is sensitive to dementia progression.

Nuremberg Activities of Daily Living

The Nuremberg Activities of Daily Living is for use with people with severe dementia in a residential setting and, therefore, should not be considered for mild to moderate dementia.

Conclusions and recommendations

Only five of the most frequently applied instruments measure ADLs; the Dependence Scale includes items to measure dependency. All are for use with people with mild to moderate dementia apart from the PSMS and the Dependence Scale. All are dementia specific apart from the Lawton/PSMS measures.

The shortlist is:

1. DAD
2. Bristol ADL
3. Lawton ADL/PSMS
4. ADCS-ADL.

Although the ADL outcome is very important and is necessary for regulatory purposes and definitive trials, in some countries it is not core as it may change for other reasons than a change in dementia. However, we would encourage its inclusion and based on use and psychometrics the following measures are recommended:

1. DAD is the most often used for community living people and has an observation option
2. Lawton ADL/PSMS is the only measure that includes self-completion; however, this may not be reliable in terms of the answers given.

Quality of life

Champion: Sube Banerjee, Professor of Dementia, Brighton and Sussex Medical School

Health-related quality of life (HRQoL) is a multidimensional concept that reflects the individual's subjective perception of the impact of a health condition on everyday life.[456] The science of developing instruments that can measure HRQoL has grown during the past 30 years. Such measures are increasingly seen as a useful complementary source of evidence of the value of impact throughout health care. They provide one approach to the measurement of overall impact and, importantly, they generate an appraisal of the subjective view of the individual affected. It has become clear that people with dementia have things that positively and negatively influence the quality of their lives, and that they can report these.[457–459]

However, measuring HRQoL in people with dementia is difficult. In any type of dementia there are disorders of memory, attention, communication, insight, judgement and behaviour, all of which might impair the ability to complete measures of HRQoL. In addition, because of its progressive nature, what works at one stage of dementia may not work later on as the disease becomes more severe. All this means that instruments not developed for those with cognitive impairment will generally not work well in those with dementia. Thus, the generic instruments available to measure HRQoL across different disease states (e.g. the EQ-5D or Short Form Health Survey) do not work well in dementia.[252] For example, one study found that 48% of people with dementia self-reported being in full health using the EQ-5D questionnaire, with no problems on any dimension.[266] Disease-specific measures of HRQoL in dementia have therefore been developed.[267,460–462] The field is one that has developed rapidly, and there has been progressive improvement in methodology and measurement during the past 15 years.

There has been an underlying assumption in much of the literature until quite recently that HRQoL must necessarily decrease as dementia becomes more severe. From the outside, it might seem counterintuitive that HRQoL could do anything other than drop with increasing cognitive impairment and activity limitation. In this case there would be limited value in measuring multiple variables that all vary predictably together, rather than just measuring one (such as cognition). However, it now seems clear that activity limitation and cognition do not have a simple or linear relationship with HRQoL in dementia.[463–465] The data suggest that there is the possibility of good quality of life at all stages of dementia and that there are individuals with poor quality of life at all stages of the illness who may therefore benefit from interventions to improve quality of life in dementia. This does not mean that improving cognition would not cause an improvement in HRQoL. Woods *et al.*[272] looked in detail at data from a trial in which a psychological therapy had both a positive impact on HRQoL and a positive effect on cognition. In that study there were no cross-sectional associations between severity of dementia and HRQoL. This makes clear the limitations of using a profile approach, with HRQoL being more than the sum of the discrete measures used.

Depending on the specific questions being investigated, HRQoL can be a primary or secondary outcome in itself. The focus here is the evaluation of disease-modifying medication in mild to moderately severe AD, and it is unlikely that HRQoL would be used as a primary outcome measure in any Phase II or pivotal Phase III study. However, the measurement of HRQoL is an obligatory part of the economic evaluation of emerging health technologies or interventions. In cost–utility analyses, quality-adjusted life-years (QALYs) are used to measure the impact of an intervention on both quality and quantity of life. Quality of life is measured by using health-state values that are scored using preference information typically gained from a representative sample of the general population. Generic preference-based measures of health, such as the EQ-5D, discussed previously in this section, are widely used as a means of generating health-state values for use in the calculation of QALYs. Given the debate around the extent to which generic preference-based measures fully capture aspects of quality of life associated with some medical conditions, and that the validity of using generic preference-based measures in dementia is uncertain, there has been interest in developing preference-based measures from condition-specific measures to target medical conditions more effectively in terms of HRQoL. Recent developments of the DEMQOL system allow the use of a dementia-specific instrument to be used in cost-effectiveness analyses of interventions in dementia.[466–468]

The systematic review identifies one generic measure of HRQoL, the EQ-5D, and two measures of disease-specific HRQoL that have been and are being used in evaluations of potentially disease-modifying compounds in AD. The information on their use is summarised in *Table 13*.

An assessment of the relative merits of the two disease-specific systems in terms of their psychometrics is presented in *Table 14*. This enables a comparison of the two instruments with earlier instruments and shows that the current instruments are a significant advance on the earlier methodologies.

The main points from this analysis are as follows:

- the QOL-AD is older and has been used more widely, particularly in the USA
- the DEMQOL system development process was stronger in psychometric terms
- the quality of development and subsequent data on DEMQOL-Proxy is symmetrical with that of the self-report versions, unlike the QOL-AD
- there are questions about the validity of the framing of the questions in the proxy-rated QOL-AD, which are not present for DEMQOL-Proxy
- the QOL-AD is less time-consuming for patients by 5–10 minutes
- there are relatively few data on responsiveness published for either, although because of the DEMQOL's longer form, development process and framing, it confers theoretical advantages in sensitivity to change
- in economic evaluations DEMQOL has advantages because of the unique programme of work developing it as a preference-based measure with no additional burden to respondents or researchers.

In summary, there is a need for broad measures of overall impact of interventions in dementia but nonetheless, although important, it is not a core measure in disease modification. We are now at a stage in which HRQoL in dementia can be measured with instruments specifically designed to do so. It appears that cognition (or activity limitation) is not the same as HRQoL and is in fact a rather poor proxy for it. HRQoL should be measured as and for itself. It is complementary to the measurement of discrete specific outcomes, and a rational approach to measurement would ensure that both sorts of instrument were completed in evaluation of interventions in dementia. It is therefore not core but health decision-makers, such as the National Institute for Health and Care Excellence, place high value on such data when reimbursement decisions are being made. This is likely to include a generic quality-of-life measure, but a dementia-specific quality-of-life measure will be more likely to be valid. If one is used the current evidence suggests that it should be the DEMQOL.

Global

Champion: Bob Woods, Professor of Clinical Psychology of Older People, Bangor University

The development of global assessments of outcome in relation to disease-modifying treatments in the field of dementia may be seen as a rational response to the wide-ranging effects of the dementias.

TABLE 13 Use of measures of HRQoL in published and ongoing studies

	Instrument		
Studies measure is used across	EQ-5D	QOL-AD scale	DEMQOL
Number of studies	5	9	4
Studies published	4	7	1
Studies ongoing	1	2	3
Number of participants	4084	3341	399

TABLE 14 Summary of psychometric properties of HRQoL instruments by gold standard criteria

Psychometric properties	Instrument					
	Progressive Deterioration Scale	Pleasant Events Schedule – Alzheimer's Disease	QOL-AD		DEMQOL	
			Patient	Proxy	Patient	Proxy
Conceptual model	0	+	++	0	+++	+++
Acceptability	0	0	++	++	++	++
Reliability						
Internal consistency	0	0	+++	+++	+++	+++
Test–retest	+++	0	+++	++	+++	+++
Inter-rater reliability	0	0	NA	0	+	+
Validity						
Content	+	0	+++	+++	+++	+++
Criterion related	0	0	0	0	++	++
Construct						
Convergent validity	0	+	+++	+++	+++	+++
Discriminant validity	0	0	0	0	++	++
Known groups differences	+	0	+++	0	+++	+++
Experimental intervention	0	0	0	0	++	++
Factor analysis	0	0	+	+	+	+
Responsiveness	0	0	+	+	+	+
Respondent burden	0	++	+++	+++	++	+++
Cultural and language adaptations	0	0	++	++	++	++
Economic evaluations	0	0	0	0	+++	+++
Health state classification	0	0	0	0	+++	+++
Preference-based measures	0	0	0	0	+++	+++
Population values	0	0	0	0	+++	+++

0, no evidence or not tested; +, some limited evidence; ++, some good evidence, but some aspects do not meet criteria or some aspects not tested/reported; +++, good evidence; NA, not applicable.

Diagnostic criteria have highlighted the presence of difficulties in multiple domains, including memory and other cognitive impairments, changes in day-to-day function and changes in behaviour. An outcome measure that is able to encompass the range of domains affected and, accordingly the range of potential targets for change, may have advantages over multiple measures, each evaluating a single domain. Specifically, if a treatment is an effective disease-modifying agent, but different aspects of the condition are improved in different individuals, for example through differences in disease progression or symptom expression, a global measure may reflect this through its combination of multiple domains. Global measures also have the potential to combine multiple perspectives, with input from caregivers and the person with dementia informing a global rating, again reflecting the reality of a condition that has effects beyond those reported by the person with the diagnosed condition.

Our literature search identified 10 global outcome measures in the included studies. These could be grouped into three distinct types: global rating scales, dementia staging instruments and clinician impression of change interviews. One of the staging instruments, the Clinical Dementia Rating scale (CDR) had been used in 48 studies. The Clinician Impression of Change interviews had been used in 35 studies altogether, with each of the five global rating scales being used in four or fewer studies.

The five global rating scales identified each included a number of domains, typically without a clear rationale for how each domain might contribute to any total global outcome score. Among the earliest of these scales was the Blessed Dementia Rating Scale, comprising a total of 22 items. These cover three domains, rated in an interview with an informant: everyday activities (eight items), ADLs – eating, dressing, toilet (three items) and personality changes (11 items). The scale does not specifically include cognitive items, but is often used with the Blessed Dementia Information, Memory and Concentration Test, a brief cognitive test. Completion of the Sandoz Clinical Assessment Geriatric Scale is based on an interview with the person with dementia and on observation. The 19 domains (which fall into five factors) include aspects of cognition ('confusion' and mental alertness), self-care ability, mood (e.g. anxiety, fatigue) and behaviour (e.g. hostility, 'bothersome', irritability, unsociability). The Gottfries–Bråne–Steen Rating Scale for Dementia is similarly completed from a semistructured interview with the person with dementia and observation, and comprises subscales measuring intellectual (12 items), emotional (three items), ADLs (primarily items of self-care) (six items), and behavioural and psychological symptoms of dementia (six items). The most recent of these global rating scales, the Dementia Severity Rating Scale (DSRS),[354] is designed for completion by a carer, with 12 domains ranging from cognitive aspects such as memory, orientation, speech and language, and the ability to make decisions, through higher-level functional abilities such as social and community activity, home activities and responsibilities to basic functions (e.g. personal care and cleanliness, and control of urination and bowels). Rikkert *et al.*[469] comment from their systematic review of dementia staging scales that the reliability (inter-rater, intra-rater and internal consistency) of the DSRS and the Gottfries–Bråne–Steen scales are well established, but that evidence for their validity in staging severity of dementia has not been studied, although our review identified a report of sensitivity of change for each scale. The focus of the DSRS on ratings by a family carer, without external moderation, may introduce bias related to factors such as carer stress and depression.

Our review identified two staging scales for dementia severity that have been used as outcome measures: the CDR and the Global Deterioration Scale. The CDR is based on an interview with the person with dementia and caregivers, covering six domains: memory, orientation, judgement and problem-solving, community affairs, home and hobbies and personal care. An algorithm is used to combine the ratings of each domain into an overall stage categorisation, ranging from 'no dementia' to 'severe dementia', usually on a five-point scale (although extended versions are available). The algorithm does not weight different domains equally, although interestingly in many of the trials using the CDR, an unweighted 'sum-of-boxes' score is used, presumably to increase the range of scores. The Global Deterioration Scale has seven stages (three being 'pre-dementia') and is intended to be used with measures of cognition and functional ability. Rikkert *et al.*[469] comment on the strong support for the reliability of the CDR and for its discriminant validity (including with the sum-of-boxes scoring). Our review suggested that the CDR shows sensitivity to change, whereas the evidence for both reliability and sensitivity to change of the Global Deterioration Scale is more limited.

The third group of outcome measures has two additional features. First, they bring to bear the judgement of an experienced clinician in combining the different domains, balancing the significance and relevance of specific areas of strength and impairment in each case. There is no predetermined algorithm or a simple summation of scores across domain; the clinician simply rates their 'impression' of the person's situation, taking into account all available sources of information. Second, at follow-up assessments, the clinician's task is to rate how much change there has been since the baseline assessment, using detailed notes taken at that time to assist this judgement. The final outcome is then a score on a seven-point scale ranging from 'marked worsening' to 'very much improved'. This overcomes the potential weakness of the staging instruments in that they would not be sensitive to change within what may in practice be quite a broad

severity category, such as 'mild dementia', missing clinically significant change. The emphasis on change and being able to focus on changes of most importance to the individual are commendable features of these scales. It should be noted that they would only be suitable for studies that are double blind; in a trial of a non-pharmacological intervention where the participant is aware of the treatment being received, maintaining the blindness of the assessor would be impossible to guarantee.

Our review initially identified three scales of this type: the Clinical Global Impressions Scale, the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change and the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC+). However, for this purpose they may be viewed as a single entity. They are completed following a semistructured interview, with both the person with dementia and a caregiver. Four major categories are covered in the interview: (1) 'general' including relevant history (and at follow-up assessments changes since baseline), (2) cognitive function, (3) behaviour and (4) ADLs. Each category is divided into domains, with probe questions suggested for each domain. After completing the interview, the clinician is able to consult all available information, including cognitive tests such as the MMSE or ADAS-Cog carried out on that visit. Inter-rater reliability would be a key issue for these measures, which are so dependent on the clinician's judgement, but there appears to be little evidence to support this,[469] although there is better evidence of retest reliability. Sensitivity to change has been demonstrated in at least one study in our review.

Of the three types of approach to global assessment, both staging and impression of change outcome measures have merits, in combining different aspects through algorithms or clinical judgement, whereas the multiple domain rating scales do not offer advantages over carrying out a specific assessment of each of the included domains. The potential for the CIBIC+ to be sensitive to individual trajectories of change is attractive, in view of the diversity of profiles of function of people even with the same type of dementia. The CDR, which has been the most widely used staging scale, shows good reliability and has demonstrated sensitivity to change. Disease-modifying treatments should have a demonstrable influence on the rate of progress through the stages of dementia reflected by the CDR. However, it should be noted that, if the sum-of-boxes score is used, this places it in the same category as the multiple domain rating scales.

Discussion

Cognition

It was agreed that cognition is a core domain. Any recommended cognitive outcomes should show reliable detection of decline in cognition, which the ADAS-Cog and MMSE have both been shown to do. They are also the most commonly used and validated outcomes. The PPI consultation emphasised that patients dislike failing in tests of cognition and it was recommended that to improve the experience of cognitive tests in the future timed measures which estimate cognitive processing speed should be considered, although they would need validating, including looking for clinical significance and calculating the minimal clinically important difference. The ADAS-Cog is longer, but if more sensitive to change then it may need fewer participants than a trial powered on the MMSE. However, the ADAS-Cog has a problem when there are lots of missing data.

Recommendation

Overall, for cognition we recommend the MMSE or ADAS-Cog, as they are the best-available measures.

Imaging

Imaging is important; however, changes in imaging and cognition are not always highly correlated; between-group differences may show mechanism of change as well as disease modification.

Magnetic resonance imaging is the most sensitive imaging technique to change, and because of this may need fewer participants to still be fully powered, as well as to be able to see changes over 1 year. MRI changes, therefore, can be conducted in a subgroup of participants in disease modification trials.

This means that, for example, it would be unnecessary to exclude from a study all patients who do not tolerate MRI, are unable to travel or who have a pacemaker. However, volumetric MRI does not always show expected changes in terms of atrophy (e.g. if amyloid is removed, then the volume may go down in treated patients), but does show changes, which is important.

Recommendation

The recommendation of the consensus conference was that serial structural MRI was the core biological marker that has utility to monitor disease progression. There is rapid innovation of biomarkers and this recommendation may change in the future.

Fluid makers

The four types of biological markers were discussed, as was how fluid biomarkers for AD are more advanced than other illnesses. However, CSF examination is expensive as people may need to go to hospital as a day case. Importantly, they are not helpful biomarkers for disease modification – a meta-analysis showed that changes in putative biomarkers of Aβ42 are not related to change in the MMSE[470] – but they can be useful in aiding diagnosis.

Recommendation

It was agreed that currently CSF level does not have a role as an outcome measure for disease modification studies in dementia and, therefore, we do not recommend a fluid biomarker as part of the core set.

Neuropsychiatric symptoms

There was debate around whether or not neuropsychiatric symptoms should be a core domain. Not every individual with dementia, particularly in the early stages, will have neuropsychiatric symptoms, and if they do they may not be clinically significant, meaning that, if they are measured, no difference may be found. Problematic behavioural symptoms may also be measured in measures of global functioning or quality of life.

However, neuropsychiatric symptoms were considered to be core by many members of the group as symptoms increase with the progression of dementia severity. If a disease-modifying treatment was found, they would want behaviour to improve, or at least not decline. If cognition improved, but neuropsychiatric symptoms increased, potentially as a side effect of a pharmacological intervention, then this would be an important outcome to identify. The group judged this to be important but not core to every future study of disease modification as many people with mild dementia do not have any neuropsychiatric symptoms; if this was a core or primary measure it might lead to a false-negative finding.

Recommendation

We recommend that the NPI should be used to measure neuropsychiatric symptoms, as it includes frequency and severity of symptoms and has appropriate psychometric properties, but this is not a core outcome.

Activities of daily living

Function, in terms of ability to complete everyday activities, is often a driver of presentation. In the USA, ADLs is a possible measure in disease modification, whereas in Europe it has been mandatory. It should be measured by proxy, ideally as some people with dementia may underestimate any impairments, although not all will. Some scales try to differentiate between the performance and initiation of ADLs, and also may include that people with dementia may need prompting to complete ADLs.

Activity of daily living is being used less often in new disease modification trials as physical health confounds it and it may not demonstrate change over 1 year. Most of the included ADL scales have good psychometric properties, but sensitivity to change may be a problem and it may not measure what is

relevant to mild to moderate dementia, and people from a range of backgrounds. Overall, it was therefore decided that it is not core.

Recommendation
Overall, we recommend the DAD as it is the best-available dementia-specific measure of ADLs.

Quality of life
Quality of life is different from other domains, as people with severe dementia can have good life quality and, thus, it is not a sensible primary outcome to measure disease progression. Nonetheless, it is a useful measure, as it could record any negative or positive impact of pharmacological interventions.

As the EQ-5D is not dementia specific, it may not necessarily give an accurate reflection. In addition, as the self-reporting of quality of life becomes worse over time, it is sensible to get a proxy report too so that measures can be compared over the whole population in a trial.

It was also discussed how quality of life is important in Phase III trials where economics need to be measured for cost by a dementia QALY. The conference did not have the required expertise to discuss or make recommendations about QALYs.

Recommendation
We recommend the DEMQOL, which measures quality of life from both the person with dementia and proxy perspectives, and from which QALYs can be calculated.

Global functioning
The group considered that global functioning could be an important measure as it encompasses several domains and could replace ADLs. Either a staging or impression-of-change outcome measure should be used, rather than a multidomain scale, with a staging instrument most favourably regarded.

Recommendation
We therefore recommend the CDR, as it has good psychometric properties. However, as the sum-of-boxes score of the CDR is similar to a multidomain scale, we recommend the global functioning score, which may be more appropriate.

Main findings
Although all domains are potentially relevant and important, cognition and biological outcomes are the only two domains that were decided to be core by consensus within the group (i.e. they should be measured in every trial of disease-modifying treatment in dementia). Overall, the group consensus was to recommend either the MMSE or ADAS-Cog for cognition. For biomarkers, serial structural MRI currently should be included as a core, but optional, outcome for individuals and used in a subset of participants. If and when future biological markers become available, it would be necessary to have a clear ability to measure progression if they were to be included.

There was debate about all other domains being core. Overall it was agreed that, although each domain is important, ADLs, neuropsychiatric, quality of life and global are not core domains that should be selected dependent on the type of study, and we have recommended the DAD, NPI, DEMQOL and CDR, respectively.

We also discussed the issue of informant-rated scales, and how the informant needs to have seen the person regularly in the weeks prior to completing the scale, so, therefore, the availability of information for each participant is required in study design.

After the conference

With the core recommendations from the conference, we conducted a second electronic consultation with the AS Research Network, the methods and results of which are detailed in *Chapters 5* and *6*. This additional consultation confirmed the main recommendations from the conference.

Chapter 8 Discussion

Findings

The main conclusions from the synthesis of the information at the consensus conference were that both cognition and biological outcome measures should be included in the core set of outcomes, although all domains are thought to be important. Most of the trials identified in the systematic review included only participants with AD, so our recommendations are mainly for AD.

Cognition is included as a core domain because it is the fundamental symptom of dementia, and there would be no purpose in modifying the underlying disease if this did not lead to cognition in an intervention group being better than in a control group over time. The biological outcome measures are core as they are the only way of being sure that the disease is being modified rather than the treatment being purely symptomatic.

The PPI conclusions are that the most important consideration for people with dementia and their carers are not what measures are used, but the overall burden of the study in terms of time, travel and inconvenience.

Recommendations of outcomes

Core domains

Within the cognitive domain, we recommend the use of either the ADAS-Cog or MMSE, as both have the best psychometrics of the included measures. Cognitive measures were described as often distressing, by both people with dementia and their families within the PPI consultation, as people are often aware that they are deteriorating, although as cognition is a core symptom of dementia it not possible to avoid measuring it. As one of the purposes of defining core measures is to make individual studies comparable and meta-analysable, it would be helpful for a future study to formulate an algorithm to be able to compare scores on both the ADAS-Cog and the MMSE and to consider developing algorithms specifically for individual subtypes of dementia. This has recently been accomplished for the ACE-3 (Addenbrooke's Cognitive Examination – third edition)[471] and the MMSE (Professor Gill Livingston, University College London, 4 April 2016, personal communication). This should be possible as a recently published study of the longitudinal cognitive decline of mild to moderate AD participants in placebo arms of 20 trials found the trajectories of the ADAS-Cog and MMSE to be similar.[472] We have longitudinal data from an earlier study in which 224 participants completed the ADAS-Cog and the MMSE and for whom, therefore, data are available.[473]

For biological outcomes it was agreed that serial structural MRI currently offers the best indication in a biological outcome of disease progression, although it is not a perfect biomarker. As it would not require as large a number as a cognitive outcome for satisfactory power, we recommend MRI as a core outcome, but only as an optional part of the study. Therefore, people who want to be in the study but could not or would not undergo MRI could be included. Some people are unable to undergo MRI because they have a pacemaker or a fear of enclosed spaces or because it is too far for them to travel to the MRI scanner. Thus, not wanting to undergo MRI should not put people off participating.

To power a full-scale trial on MRI, an early paper recommends 200 participants per trial arm,[474] and a more recent paper reduced this to 81 participants per trial arm.[475] Despite needing a reduced number to power a trial on MRI, the potential costs of both baseline and follow-up scans in a group of 162 participants are expensive. The commercial cost of MRI in research starts from £365.76, although the NHS tariff is around £110.

Non-core domains

The assumption of a recommendation of a core set of outcomes is that measures can be added to it, but none can be taken away. Although we do not judge the domains of ADLs, global, neuropsychiatric symptoms and quality of life to be core, they are still important outcomes and their need to be included as a chosen outcome depends on the specific focus of individual trials. We have made recommendations about which measures we would recommend within each of these domains. In addition, a decline in social engagement can be one of the most important outcomes in mild to moderate dementia. There are no current measures for this in the literature in dementia, but one has been developed (Gill Livingston, University College London, 10 May 2016, personal communication; Sommerlad *et al.*[476]).

We judge ADLs to be an important domain, as functional impairment increases as dementia progresses, it is often one of the first areas where symptoms are noticed and many problems within families arise as people with dementia become more dependent but do not want to accept help.[477] We recommend that the measure used is a proxy measure as people with dementia can sometimes underestimate their functional impairment, although sometimes they can be more accurate than a proxy (Linda Clare, University of Exeter, 25 May 2016, personal communication; Martyr and Clare[478]). As described in *Chapter 6*, *Standardised interviews*, *Activities of daily living*, in view of the time taken, the acceptability and the psychometric properties, we recommend that the DAD, a dementia-specific proxy ADL measure, is the best instrument to use.

Global outcomes are also important as they encompass and summarise the range of functions affected by dementia, with a staging instrument thought to be better for disease modification trials than a multidomain or clinician impression scale. For global outcomes we recommend the CDR, a staging instrument specific to dementia, as it has the most satisfactory psychometric properties. In particular, we recommend the use of the global CDR score over the sum of boxes, as using the sum of boxes makes the CDR more of a multidomain scale rather than a staging one.

Neuropsychiatric symptoms are also an important domain, as most people with dementia will experience at least one symptom over the course of their dementia. However, although important, they do not change in line with disease progression; many neuropsychiatric symptoms are no worse or may improve as dementia progresses from moderate to severe and, thus, the use of these symptoms to measure disease progression might be misleading. They are distressing for people with dementia, their family and those around them, and often lead to care home admission. Within this category we are therefore recommending that triallists use the NPI, as this has acceptable psychometric properties in this domain and is the only measure included in ongoing disease modification trials.

The domain of quality of life is important, as if, for example, a pharmacological intervention has a positive impact on cognition, it is also possible that it would have a negative impact on quality of life, and then it would be important to record this. From the conference we recommend using a dementia-specific measure, the DEMQOL, as it has adequate psychometric properties and coverage of the domain. In addition, it can be collected from both the person with dementia and a proxy.

It was suggested that we should have different outcomes recommended for different types of dementia, particularly with cognitive tests, which are the most sensitive to the change within the specific cognitive domain that is key to a particular type of dementia. However, because the majority of studies include only participants with AD, it is not possible to make recommendations for the specific types of dementia. This is something to be considered in future trials of disease-modifying drugs.

It was also suggested that we should have different core outcomes for different phases of trials (e.g. we could recommend different measures within the domain for different phases of trials). However, the three phases of trials do not always translate to non-pharmacological intervention trials.

We did not include outcomes that related solely to economics, carers or drug levels. Although all three may be important outcomes in a disease modification trial, they are not necessarily core. Health economics

is particularly relevant in Phase III trials, requiring data on costs and QALYs. We also did not include measures of side effects, which were mentioned across all three focus groups. These will always be measured as they are as relevant as measuring how effective a pharmacological intervention is.

Recommendations around completing outcomes

To ensure that side effects are measured accurately, an informant may also need to participate in the study. Having an informant for each participant would also be useful to ensure that, if the intervention is pharmacological, it is taken in adherence with the protocol, as medication management can be difficult for people with dementia, and often caregivers provide support.[479,480]

Informants are also often involved in the completion of outcomes on behalf of the person with dementia they care for. There was discussion around who completes outcomes at both the PPI consultation and consensus conference and, although it is important that people with dementia should be enabled to complete measures, informal carers also need to be involved. This is due to the nature of dementia, including deterioration. Although this can mean that people with dementia who wish to participate in research are excluded because they do not have a defined carer, it is by definition the case that most people living with mild to moderate dementia have someone helping to care for them in some capacity, although not necessarily living with them.

As we are recommending some measures that are informant based, either partly or fully, there also needs to be a way to standardise who the informant is that is completing outcomes. It is important to consider how pragmatic researchers can and should be in their identification of an informant (e.g. does this have to be a carer/can this be a neighbour/friend/health professional). An informant should also be the most reliable person available, in terms of both the information they give and their ability to commit to the full duration of the trial,[481] as when an informant is changed between study visits, the answers on outcomes show greater variability than when the informant is the same.[482] Future research should also consider how to establish robust methods of using informant-supplied information for the completion of questionnaires, and also how to supplement responses from participants, as this could be very useful in terms of ensuring full data collection of all items and has the potential to expand the range of participants who can contribute to this research area.

As part of the project, we also considered the practicalities of participants completing the core set of outcomes, and how we can minimise any problems. We recommend that an outcome package at the very maximum should take no longer than 90 minutes without a break for a person with dementia, which was accepted by the people consulted within the PPI group. Researchers should aim for shorter time periods, particularly dependent on the person's comorbid health conditions and how they are on the day. The people consulted at the focus groups also accepted that long assessments could take place over 1 day but be split into several time periods, with breaks and refreshments, if necessary.

They also want researchers to be clear about why assessments are being done as this would allow them to feel that their time is being well used. Despite giving informed or consultee consent at the beginning of the trial, people are required to be reminded of participation and what it involves at the time the assessments are happening. This is in line with process consent,[483] which is the idea that consent runs throughout the whole research process, not just at the start of the trial when informant consent is taken, and is of particular importance in dementia research as a participant may lose capacity over the course of the trial period.

Patient and public involvement

A small but growing literature[484–486] suggests that using qualitative methods to examine participant perspectives can provide triallists with important insights that can inform the design and implementation of clinical trials. A proactive approach to consider the design and development of clinical trials is needed at this early stage in the development of potentially disease course-modifying treatments that respond to the

wider challenges in the design and implementation of clinical trials, and also to understand the needs, hopes and expectations of this patient population and their families.

The experiences and beliefs of our PPI group broadly reflect the wider literature. Reasons for refusals to participate appear to vary according to the type of trial and the severity of treatment,[487] with key factors including inconvenience, difficulties with transport, too many clinic visits and time taken, as well as a distrust of medicine or the hospital and worries about side effects.[488,489] Much of the literature examining trial participation has identified altruism, trust in recruiting clinicians and an expectation of personal benefit as the main motivations for participation in trials.[490,491]

However, altruism may be overstated as a motivation for participants, and a small but increasing number of studies using qualitative methods to examine the perspectives of clinical trial participants[484–486] have concluded that patients participate in a clinical trial because they believe that they are receiving personalised care. One study[486] found that, even when participants recalled the involvement of chance, most also held other coexisting (and sometimes contradictory) views about how and why they had been allocated to the treatment or intervention and believed that they would receive the best treatment for them. Similarly, a number of studies have identified that personal benefits, hope, access to the most effective treatment,[492] and the enthusiasm and hopes of family and friends were often the driving force behind and key motivations for participation.[490] Such beliefs highlight the vulnerability of some groups and the risks that they are willing to take if there is a chance of survival,[493] and this may be an important factor for trials involving potentially disease course-modifying treatments.

Future of biomarkers

Although outcomes, such as cognition, give an indication of clinical benefit, they do not necessarily demonstrate if an intervention has disease-modifying properties, whereas a biomarker could.[494] Change in current biomarkers of AD, in particular, does not always translate to changes in disease, and the improvement of current and development of new biomarkers are the key challenges in working towards a disease-modifying treatment, even more so with the development of adaptive trial designs.[19] Sensitive biomarkers could enable trials of potential disease-modifying interventions to be shorter, as they would be able to detect changes in disease progression; however, the development and validation of biomarkers takes time.[495] The development of biomarkers for dementia, particularly AD, is a hugely innovative field, meaning that it may be important to consider other biomarkers as core outcomes in the future if they are objective and reliable enough to show a potential disease-modifying effect. Ultimately, the choice of a biological marker depends, in a pharmacological study, on the compound being tested, and also the resources available.

When biomarkers are to be used in disease modification trials, it is also important to consider the impact this will have on participants' willingness to take part in the research. From the PPI consultation, participants were generally enthusiastic about potentially invasive biological tests, but did also highlight how they may put off potential participants because of side effects, misconceptions and anxiety. They supported our recommendation that MRI should be optional rather than compulsory, and indicated that this would make them more willing to take part in a trial. As biomarkers develop, consideration will need to be given to reducing the side effects of the biological techniques, particularly CSF examination, as 30% of people in memory clinics report side effects, although very rarely are these serious or long-lasting problems.[496]

Previous outcome recommendations

There have been previous recommendations related to the outcomes that should be used in disease modification trials. The current US Food and Drug Administration guidelines for all types of clinical trials for AD are that treatments must show efficacy on both a cognitive and a functional or global outcome

measure.[497] For disease modification trials, in particular, the US Food and Drug Administration draft guidelines recommend that, as well as a benefit on clinical outcomes, a disease-modifying effect could be shown via a reliable biomarker, or by an adaptive trial design, such as a randomised start design, that can determine a long-lasting effect on disease course. Furthermore, the European Medicines Agency has recently published draft guidelines around medical trials of treatments for dementia.[498] These state that disease modification should be demonstrated by a slowing decline of clinical symptoms and also be linked to a change in validated biomarkers that reflect underlying disease pathology. These recommendations are in line with, but not as detailed as, our recommendations. Around a decade ago, a European task force reached consensus around a number of topics in dementia trials, including recommendations for the end points of disease modification trials.[499,500] They recommended measuring cognition, ADLs and global functioning as core, and within the domains, respectively, recommended the measures of the ADAS-Cog, ADCS-ADL and CDR sum of boxes.

Strengths and limitations

As part of the project, we have incorporated other research from members of our group around the development of core outcome sets for dementia from perspectives other than disease modification. The first is the recently published standard set of outcomes of what matters the most to people living with dementia, developed by ICHOM.[501] The second is funded by the JPND, and was a project to develop a set of core outcomes to be used in psychosocial intervention trials of dementia.[502,503] We also used references gathered for a project about non-pharmacological interventions for dementia. We conducted additional searches on top of those specified in the protocol, including for ongoing trials on two clinical trial registries.

We conducted both e-mail and face-to-face consultations with people living with dementia and carers, and gained a wide variety of views around completing outcomes from the 18 participants. Although the feedback from the PPI group was very useful, we conducted focus groups only in three locations, and the overall number of people consulted was small, even including the second e-mail consultation. In addition, all participants were part of the AS Research Network and/or a dementia PPI group, and were knowledgeable about dementia. Although this meant that they were able to give informed views, they did not cover the possible range of opinions, and only one-third of the participants had experience of participating in research. Furthermore, context makes a huge difference, and advocacy group members often have different ideas from the patient and carers attending memory clinics. The background of participants can also influence ideas, with the majority of those who participate in PPI being from middle-class backgrounds and of white ethnicity and thus not necessarily reflective of wider society,[504] which is a potential limitation within our PPI sample. In addition, we did not conduct detailed, in-depth, open-ended interviews and, therefore, the information we gained was limited. Although there were three research team members present in each location, with differing backgrounds (so views were not filtered through a single researcher's perspective), we did not do formal and independent thematic analyses. With more time and funding we would like to have further widened the consultation to include, for example, the clinical research nurses who often run dementia trials.

Many of the opinions arising from this consultation were contradictory. Thus, people suggested that they wanted more importance on interpreting scores within the context of an individual's experiences and individualised instruments with more detail, but also wanted testing to be of shorter duration with fewer questions. Overall, it appeared that people were saying that they wanted to be recognised as a full person with an illness rather than to be summed up by declining scores on questionnaires. This is an important message for researchers, although most will think they do this already, as well as being the only acceptable way for health professionals to practise. Contextual information is of great importance in clinical practice and, although it should be considered in trials, it is of less relevance if participants have been randomised as those in each group have been matched for individual differences.

We included outcomes that are informant rated, which will limit people living with dementia taking part if they do not have an informant available. We also included only outcomes that have been or are currently being used in trials. Outcomes are not perfect and there may be better measures in the future. It has been suggested that one problem for disease modification trials is that outcomes need to be very sensitive in the early stages of dementia, when subtle and slow changes occur.[495] However, most people with dementia do deteriorate cognitively over the period of trials, and drugs which modify the disease need to be able to show a clinically important difference in cognitive deterioration, which would be seen in current measures. This may not be true of MCI, but this was not part of the study presented here.

This project was delivered in 6 months with a very limited budget, so we included only, as specified in the brief, mild to moderate dementia. We cannot make recommendations for disease modification trials involving other stages of dementia, such as severe, prodromal or mild cognitive impairment. Work has been completed around more appropriate measures to be used in other stages, such as those with dementia living in long-term care.[505] Similarly, we are unable to make recommendations for separate types of dementia, such as vascular or frontotemporal dementia, as most of the trials included only participants with AD. This is potentially a limitation of the outcome set for use in disease modification trials not focusing on participants with AD; although as AD is the most common type of dementia, the outcome set would reflect those most affected. If, and when, a disease modification treatment for AD is found, this could significantly decrease the burden of dementia on public health by up to 50%, although more work is needed to address the disease modification of the less prevalent types of dementia and reduce the burden of these.[506]

We have also not had time or resources to consult with regulators and pharmaceutical industries; however, we have plans to do this in the future, possibly through collaboration with Alzheimer's Research UK. Similarly, we did not consider economic measures as outcomes and did not include health economists on our team. This was because of the limitation in time and resources and the commissioning brief. Our recommendations did not consider the financial cost in detail although it was mentioned in the discussion. We did not attempt a cost analysis but are aware that MRI is expensive. If there are better biological measures in the future this recommendation will be superseded.

We included the highest standard of trials, RCTs and then CCTs, that compared the intervention with a control or another intervention. This means that we will have missed early-stage disease modification trials, in which the dosage and safety are the main focuses, rather than the efficacy from the comparison of interventions with each other or control groups. Despite including both ongoing and published trials, we may also have missed a number of trials that have been completed but not yet published in an academic journal article, whether a protocol or the study results. We did, however, conduct a large-scale systematic review, screening 22,918 references, in the hope of picking up the majority of relevant trials. Most of the trials included were conducted in English-speaking countries, with a large proportion conducted solely or partly in the USA. We included many trials from countries where the native language was not English as long as the trial was reported in English, and have reported whether or not validation of the measures has been carried out in other languages, but are unable to make definitive recommendations about measures in other languages. We excluded 30 full-text articles because they were not available in English.

Chapter 9 Conclusions

At present there are 81 different outcome measures used across disease modification trials, if we include published and ongoing trials. These include 72 questionnaire- or interview-based outcomes and nine techniques for measuring biological markers. This illustrates the importance and difficulty of the development of a consensus about a core set of the best available measures in allowing the comparison and combination of disease modification trials.

The main conclusions from the synthesis of all the information at the consensus conference were that cognition and biological markers are the only core outcome domains. For cognition we recommend the ADAS-Cog or MMSE, and for a biological marker we recommend using MRI as an outcome, which is optional for participants. This means that those who are unable or do not wish to undergo MRI can still participate. Other biological outcome markers would be appropriate depending on the proposed mechanism of action of the therapy, and selecting a universal set of biomarker outcome measures for all studies was not possible. We have also made outcome recommendations for the important, but non-core, domains of ADLs, global functioning, neuropsychiatric and quality of life, respectively, recommending the DAD, CDR, NPI and DEMQOL.

We have reached our conclusions and recommendations through discussion at the consensus conference based on the psychometric properties and suitability of the outcomes found within the systematic review, in discussion with expert researchers and clinicians, and informed by the voluntary sector and patients and families. We also considered the practicalities of the completion of the core outcome set, including timing, breaks, travel and if the person with dementia and/or an informant completes the measures.

As the recommended measures are currently the best available, we expect that additional or alternative outcome measures may supersede the current core set, particularly for biological markers where there is considerable current research. The principles on which we have made our choices are laid out here and they will not change.

Recommendations for future research

The recommendations throughout this report are in the most part for AD; therefore, there is a need to extend the development of core outcome sets for other dementias. As we are recommending the use of either the ADAS-Cog or MMSE, which are the most commonly used cognitive outcomes in the included disease modification trials, and we wish to be able to directly compare scores on each item, it would be useful to develop an algorithm to directly compare scores on both. Patients also feel that they are failing in tests of cognition as they notice their deterioration over time. It was suggested that timed measures, which estimate cognitive processing speed, should be further developed and validated against other measures, so that they can be considered in terms of clinical significance and minimal clinically important difference. These would mean that patients would be able to complete cognitive scales where they would not feel like they were failing.

We are also recommending measures that are partly or fully rated by informants, so it would also be useful to consider ways of making informant data more robust, including thinking about who the most appropriate informant is. We did not make any economic recommendations; however, future research could consider both QALYs and cost data.

Through PPI we gathered a wide variety of feedback about outcomes and trial participation; however, this was not a full qualitative study and only a small number of people participated, which highlights the need for further qualitative research. This could also include consultations with trial staff, such as clinical research nurses, and to see how those that administer outcomes can influence participants' attitudes towards them.

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Patient and public involvement

We consulted 18 people, either those living with dementia or family caregivers, to inform the recommendations of the core outcome set.

Contributions of authors

Lucy Webster, **Anna Grinbergs-Saull** and **Gill Livingston** drafted the report.

Lucy Webster, **Derek Groskreutz** and **Anna Grinbergs-Saull** screened papers, located references and extracted data.

Rob Howard, **John T O'Brien**, **Gail Mountain**, **Sube Banerjee**, **Bob Woods**, **Robert Perneczky** and **Gill Livingston** acted as champions for each of the domains in the review of outcomes.

Lucy Webster, **Anna Grinbergs-Saull**, **John T O'Brien**, **Gail Mountain** and **Gill Livingston** facilitated the PPI focus groups.

Gill Livingston is guarantor.

Derek Groskreutz, **Rob Howard**, **John T O'Brien**, **Gail Mountain**, **Sube Banerjee**, **Bob Woods**, **Robert Perneczky**, **Louise Lafortune**, **Charlotte Roberts**, **Jenny McCleery**, **James Pickett**, **Frances Bunn**, **David Challis**, **Georgina Charlesworth**, **Katie Featherstone**, **Chris Fox**, **Claire Goodman**, **Roy Jones**, **Sallie Lamb**, **Esme Moniz-Cook**, **Justine Schneider**, **Sasha Shepperd**, **Claire Surr**, **Jo Thompson-Coon**, **Clive Ballard**, **Carol Brayne**, **Orlaith Burke**, **Alistair Burns**, **Linda Clare**, **Peter Garrard**, **Patrick Kehoe**, **Peter Passmore**, **Clive Holmes**, **Ian Maidment**, **Fliss Murtagh** and **Louise Robinson** revised the paper critically for important intellectual content.

Data sharing statement

All data from the project are included in the report. Any further information can be obtained from the corresponding author.

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Appendix 1 MEDLINE (via OvidSP) search strategy

Search strategy

1. exp Alzheimer Disease/
2. exp Dementia, Vascular/
3. exp 'Pick Disease of the Brain'/
4. exp Dementia, Multi-Infarct/
5. exp Cognition Disorders/ or exp Dementia/
6. dement*.mp.
7. alzheimer*.mp.
8. (lewy* and dement*).af.
9. multiple infarcts.mp.
10. exp Supranuclear Palsy, Progressive/
11. (pick adj5 disease).mp.
12. 'Frontotemporal Dementia'.mp. or exp Frontotemporal Dementia/
13. (park* and dement*).af.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp 'Outcome Assessment (Health Care)'/
16. 'outcome'.mp.
17. 'instrument'.mp.
18. 'measure'.mp.
19. outcome*.mp.
20. instrument*.mp.
21. measure*.mp.
22. 16 or 17 or 18 or 19 or 20 or 21
23. intervention.mp.
24. therap*.mp.
25. trial*.mp.
26. 23 or 24 or 25
27. control*.mp.
28. 22 or 26 or 27
29. limit 28 to english language

Appendix 2 Disagreements on exclusion of full texts

The raters disagreed on the inclusion of four full texts.

For the first paper,[33] across the three raters there were two exclusions and one inclusion, with disagreement about the trial's aim being symptomatic or disease modification. After looking at a second paper (within the database) that was referring to the same trial,[32] it was much clearer that the aim of the trial was disease modification, so we agreed by consensus to include the first paper.

For the second paper, there was disagreement between raters – two raters excluded and one included – and we agreed to exclude, as it was a conference abstract.[507]

The third and fourth paper referred to the same trial,[25,26] and across the three raters there was one include, one undecided and one exclude. The raters could not reach a consensus, so we consulted with Gill Livingston who decided it should be included as the intervention was aiming to change neuronal dysfunction in AD.

Appendix 3 List of excluded studies and reasons for exclusion

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$)

Reference	Reason for exclusion
Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, *et al.* Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol* 2009;**8**:613–18	Not a disease modification trial
AbbVie. *NCT02573740 Safety, Tolerability and the Effects on Cerebrospinal Fluid Spectrin Breakdown Product-145 Levels of ABT-957 in Subjects With Mild Alzheimer's Disease and Mild Cognitive Impairment*. URL: https://clinicaltrials.gov/ct2/show/NCT02573740 (accessed 29 January 2016)	No quantitative outcome relating to disease modification
Adair JC, Knoefel JE, Morgan N. Controlled trial of N-acetylcysteine for patients with probable Alzheimer's disease. *Neurology* 2001;**57**:1515–17	Not a disease modification trial
Adami M, Scarpini E, Bruno G, Zappala G, Richarz U, Gaudig M, *et al.* Cessation versus continuation of 12 months galantamine therapy in patients with Alzheimer's disease: a randomised, double blind, placebo controlled withdrawal trial. *Alzheimers Dement* 2011;**1**:S794	Not published in a peer-reviewed journal article or is an ongoing trial
Adamus WS, Leonard JP, Tröger W. Phase I clinical trials with WAL 2014, a new muscarinic agonist for the treatment of Alzheimer's disease. *Life Sci* 1995;**56**:883–90	No participants with mild or moderate dementia
Agid Y, Dubois B, Anand R, Gharabawi G. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. *Curr Ther Res Clin Exp* 1998;**59**:837–45	Not a disease modification trial
Aguglia E, Onor ML, Saina M, Maso E. An open-label, comparative study of rivastigmine, donepezil and galantamine in a real-world setting. *Curr Med Res Opin* 2004;**20**:1747–52	Not a disease modification trial
Aguiar P, Monteiro L, Feres A, Gomes I, Melo A. Rivastigmine transdermal patch and physical exercises for Alzheimer's disease: a randomised clinical trial. *Curr Alzheimer Res* 2014;**11**:532–7	Not a disease modification trial
Aguirre E, Spector A, Hoe J, Russell IT, Knapp M, Woods RT, *et al.* Maintenance Cognitive Stimulation Therapy (CST) for dementia: a single-blind, multi-centre, randomised controlled trial of Maintenance CST vs. CST for dementia. *Trials* 2010;**11**:46	Not a disease modification trial
Ahlin A, Nyback H, Junthe T, Ohman G, Nordgren I. Tetrahydroaminoacridine in Alzheimer's dementia: clinical and biochemical results of a double–blind crossover trial. *Hum Psychopharmacol* 1991;**6**:109–18	Not a disease modification trial
Ahmed MA, Darwish ES, Khedr EM, El Serogy YM, Ali AM. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. *J Neurol* 2012;**259**:83–92	Not a disease modification trial
Akanuma K, Meguro K, Meguro M, Sasaki E, Chiba K, Ishii H, *et al.* Improved social interaction and increased anterior cingulate metabolism after group reminiscence with reality orientation approach for vascular dementia. *Psychiatry Res* 2011;**192**:183–7	Not a disease modification trial
Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. *J Neurol Neurosurg Psychiatry* 2003;**74**:863–6	Not a disease modification trial
Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised and placebo-controlled trial. *J Clin Pharm Ther* 2003;**28**:53–9	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Alva G, Grossberg GT, Schmitt FA, Meng X, Olin JT. Efficacy of rivastigmine transdermal patch on activities of daily living: item responder analyses. *Int J Geriatr Psychiatry* 2011;**26**:356–63	Not a disease modification trial
Alva G, Isaacson R, Sadowsky C, Grossberg G, Meng X, Somogyi M. Efficacy of higher-dose 13.3 mg/24 h (15 cm^2) rivastigmine patch on the Alzheimer's Disease Assessment Scale-cognitive subscale: Domain and individual item analysis. *Int J Geriatr Psychiatry* 2014;**29**:920–7	Not a disease modification trial
Alvarez XA, Cacabelos R, Sampedro C, Couceiro V, Aleixandre M, Vargas M, *et al.* Combination treatment in Alzheimer's disease: results of a randomised, controlled trial with cerebrolysin and donepezil. *Curr Alzheimer Res* 2011;**8**:583–91	Not a disease modification trial
Alvarez A, Iglesias O, Aleixandre M, Linares C, Figueroa J, Muresanu D, *et al.* Cerebrolysin and combination therapy enhance serum BDNF in AD patients. *Alzheimer's Dement* 2014;**10**:774	Not published in a peer-reviewed journal article or is an ongoing trial
Amenta F, Carotenuto A, Fasanaro AM, Rea R, Traini E. The ASCOMALVA trial: association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alphoscerate in Alzheimer's disease with cerebrovascular injury: interim results. *J Neurol Sci* 2012;**322**:96–101	Not a disease modification trial
Amici S, Lanari A, Romani R, Antognelli C, Gallai V, Parnetti L. Cerebrospinal fluid acetylcholinesterase activity after long-term treatment with donepezil and rivastigmine. *Mech Ageing Dev* 2001;**122**:2057–62	Not a disease modification trial
Amieva H, Dartigues JF. ETNA3, a clinical randomised study assessing three cognitive-oriented therapies in dementia: rationale and general design. *Rev Neurol* 2013;**169**:752–6	Not a disease modification trial
Andersen F, Viitanen M, Halvorsen DS, Straume B, Wilsgaard T, Engstad TA. The effect of stimulation therapy and donepezil on cognitive function in Alzheimer's disease. A community based RCT with a two-by-two factorial design. *BMC Neurol* 2012;**12**:59	Not a disease modification trial
Andrade LP, Gobbi LT, Coelho FG, Christofoletti G, Costa JL, Stella F. Benefits of multimodal exercise intervention for postural control and frontal cognitive functions in individuals with Alzheimer's disease: a controlled trial. *J Am Geriatr Soc* 2013;**61**:1919–26	Not a disease modification trial
Annweiler C, Herrmann FR, Fantino B, Brugg B, Beauchet O. Effectiveness of the combination of memantine plus vitamin D on cognition in patients with Alzheimer disease: a pre–post pilot study. *Cogn Behav Neurol* 2012;**25**:121–7	Not a RCT/CCT
Antonanzas F, Rive B, Badenas JM, Gomez-Lus S, Guilhaume C. Cost-effectiveness of memantine in community-based Alzheimer's disease patients: an adaptation in Spain. *Eur J Health Econ* 2006;**7**:137–44	Not a disease modification trial
Araki T, Wake R, Miyaoka T, Kawakami K, Nagahama M, Furuya M, *et al.* The effects of combine treatment of memantine and donepezil on Alzheimer's disease patients and its relationship with cerebral blood flow in the prefrontal area. *Int J Geriatr Psychiatry* 2014;**29**:881–9	Not a disease modification trial
Arcoverde C, Deslandes A, Moraes H, Almeida C, Araujo NB, Vasques PE, *et al.* Treadmill training as an augmentation treatment for Alzheimer's disease: a pilot randomised controlled study. *Arq Neuropsiquiatr* 2014;**72**:190–6	Not a disease modification trial
Arlt S, Muller-Thomsen T, Beisiegel U, Kontush A. Effect of one-year vitamin C- and E-supplementation on cerebrospinal fluid oxidation parameters and clinical course in Alzheimer's disease. *Neurochem Res* 2012;**37**:2706–14	Not a disease modification trial
Aronson S, Van Baelen B, Kavanagh S, Schwalen S. Optimal dosing of galantamine in patients with mild or moderate Alzheimer's disease: post hoc analysis of a randomised, double-blind, placebo-controlled trial. *Drugs Ageing* 2009;**26**:231–9	Not a disease modification trial
Arrigo A, Moglia A, Borsotti L. A double-blind, placebo-controlled, crossover trial with nicergoline in patients with senile dementia. *Int J Clin Pharmacol Res* 1982;**2**(Suppl. 1):33–41	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Ash E, Bregman N, Moore O, Korczyn A, Zangen A. Transcranial magnetic stimulation of deep brain regions in Alzheimer's disease. *Alzheimer's Dement* 2014;**10**:P450	Not published in a peer-reviewed journal article or is an ongoing trial
Ash EL, Vakhapova V, Bova I, Simon E, Korem M, Eldad M, *et al.* Transcranial magnetic stimulation of deep brain regions in Alzheimer's disease: a pilot study. *Ann Neurol* 2012;**72**:S126	Not published in a peer-reviewed journal article or is an ongoing trial
Ashford JW, Adamson M, Beale T, La D, Hernandez B, Noda A, *et al.* MR spectroscopy for assessment of memantine treatment in mild to moderate Alzheimer dementia. *J Alzheimers Dis* 2011;**26**(Suppl. 3):331–6	Not a disease modification trial
Asp E, Cloutier F, Fay S, Cook C, Robertson ML, Fisk J, *et al.* Verbal repetition in patients with Alzheimer's disease who receive donepezil. *Int J Geriatr Psychiatry* 2006;**21**:426–31	Not a disease modification trial
Asthana S, Baker LD, Craft S, Stanczyk FZ, Veith RC, Raskind MA, *et al.* High-dose estradiol improves cognition for women with AD: results of a randomised study. *Neurology* 2001;**57**:605–12	Not a disease modification trial
Atri A, Hendrix S, Pejovic V, Graham S. Extended-release daily memantine provides increasing cumulative benefits across clinical domains over 24 weeks in patients with moderate to severe Alzheimer's disease: an analysis of area under the curve. *Neurology* 2014;**82**:P1-006	Not published in a peer-reviewed journal article or is an ongoing trial
Atri A, Molinuevo JL, Lemming O, Wirth Y, Pulte I, Wilkinson D. Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy. *Alzheimers Res Ther* 2013;**5**:6	Not a disease modification trial
Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer disease. *Alzheimer Dis Assoc Disord* 2008;**22**:209–21	Not a disease modification trial
Auchus A, Brashear H, Salloway S, Korczyn A, De Deyn P, Gassmann-Mayer C. Galantamine treatment of vascular dementia: a randomised trial. *Neurology* 2007;**69**:448–58	Not a disease modification trial
Avila R, Carvalho IA, Bottino CM, Miotto EC. Neuropsychological rehabilitation in mild and moderate Alzheimer's disease patients. *Behav Neurol* 2007;**18**:225–33	Not a disease modification trial
Bachynsky J, McCracken P, Lier D, Alloul K, Jacobs P. Propentofylline treatment for Alzheimer disease and vascular dementia: an economic evaluation based on functional abilities. *Alzheimer Dis Assoc Disord* 2000;**14**:102–11	Not a disease modification trial
Bakchine S, Loft H. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. *J Alzheimers Dis* 2007;**11**:471–9	Not a disease modification trial
Ballard C, Sauter M, Scheltens P, He Y, Barkhof F, van Straaten ECW, *et al.* Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: the VantagE study. *Curr Med Res Opin* 2008;**24**:2561–74	Not a disease modification trial
Ban TA, Morey LC, Aguglia E, Batista R, Campanella G, Conti L, *et al.* Glycosaminoglycan polysulfate in the treatment of old age dementias. *Prog Neuropsychopharmacol Biol Psychiatry* 1991;**15**:323–42	Not a disease modification trial
Barak Y, Levine J, Glasman A, Elizur A, Belmaker RH. Inositol treatment of Alzheimer's disease: a double blind, cross-over placebo controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry* 1996;**20**:729–36	Not a disease modification trial
Barone P, Burn DJ, van Laar T, Hsu C, Poewe W, Lane RM. Rivastigmine versus placebo in hyperhomocysteinemic Parkinson's disease dementia patients. *Mov Disord* 2008;**23**:1532–40	Not a disease modification trial
Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the *Ginkgo biloba* extract EGb 761 in dementia. *Dement Geriatr Cogn Disord* 2000;**11**:230–7	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Batman MW. The effects of therapeutic aquatic exercise on patients with Alzheimer's Disease (elderly). *Diss Abstr Int B Sci Eng* 1999;**60**:2933	Not published in a peer-reviewed journal article or is an ongoing trial
Battaglia A, Annon K, Pamparana F, De Paolis C, Bonura ML, Stekke W, *et al.* P-8–11 Nicergoline in the long term treatment of mild or moderate senile dementia. A multicenter double-blind, randomised, placebo-controlled trial. *Eur Neuropsychopharmacol* 1995;**5**:383	Not published in a peer-reviewed journal article or is an ongoing trial
Baum L, Lam CWK, Cheung SKK, Kwok T, Lui V, Tsoh J, *et al.* Six-month randomised, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. *J Clin Psychopharmacol* 2008;**28**:110–13	Not published in a peer-reviewed journal article or is an ongoing trial
Bayer AJ, Bokonjic R, Booya NH, Demarin V, Ersmark B, Fairbairn AF, *et al.* European pentoxifylline multi-infarct dementia study. *Eur Neurol* 1996;**36**:315–21	Not a disease modification trial
Becker RE, Colliver JA, Markwell SJ, Moriearty PL, Unni LK, Vicari S. Double-blind, placebo-controlled study of metrifonate, an acetylcholinesterase inhibitor, for Alzheimer disease. *Alzheimer Dis Assoc Disord* 1996;**10**:124–31	Not a disease modification trial
Becker RE, Colliver JA, Markwell SJ, Moriearty PL, Unni LK, Vicari S. Effects of metrifonate on cognitive decline in Alzheimer disease: a double-blind, placebo-controlled, 6-month study. *Alzheimer Dis Assoc Disord* 1998;**12**:54–7	Not a disease modification trial
Belanoff JK, Jurik J, Schatzberg LD, DeBattista C, Schatzberg AF. Slowing the progression of cognitive decline in Alzheimer's disease using mifepristone. *J Mol Neurosci* 2002;**19**:201–6	Not a disease modification trial
Beller SA, Overall JE, Swann AC. Efficacy of oral physostigmine in primary degenerative dementia. A double-blind study of response to different dose level. *Psychopharmacology* 1985;**87**:147–51	Not a disease modification trial
Bentham PW. A double-blind placebo-controlled trial of L-tryptophan to assess the degree of cognitive and behavioural improvement in patients with Alzheimer-type dementia and to compare differential response in clinical sub-groups. *Int Clin Psychopharm* 1990;**5**:261–72	Not a disease modification trial
Bergamaschini LC, Scarpini E, Rossi E, Galimberti D, Case A, Lucca U, *et al.* [Randomised pilot study on the feasibility of Enoxaparin treatment in Alzheimer's disease.] *Neurodegener Dis* 2011;**8**:1	Full text unavailable in English
Bergamasco B, Scarzella L, La Commare P. Idebenone, a new drug in the treatment of cognitive impairment in patients with dementia of the Alzheimer type. *Funct Neurol* 1994;**9**:161–8	Not a disease modification trial
Bergamasco B, Villardita C, Coppi R. Idebenone in the treatment of multi-infarct dementia: a randomised, double-blind, placebo controlled multicentre trial. *Arch Gerontol Geriatr* 1992;**15**:271–8	Not a disease modification trial
Beversdorf DQ, Warner JL, Davis RA, Sharma UK, Nagaraja HN, Scharre DW. Donepezil in the treatment of dementia with Lewy bodies. *Am J Geriatr Psychiatry* 2004;**12**:542–3	Not a disease modification trial
Bierer LM, Aisen PS, Davidson M, Ryan TM, Schmeidler J, Davis KL. A pilot study of clonidine plus physostigmine in Alzheimer's disease. *Dementia* 1994;**5**:243–6	Not a disease modification trial
Black RS, Barclay LL, Nolan KA, Thaler HT, Hardiman ST, Blass JP. Pentoxifylline in cerebrovascular dementia. *J Am Geriatr Soc* 1992;**40**:237–44	Not a disease modification trial
Black S, Roman GC, Geldmacher DS, Salloway S, Hecker J, Burns A, *et al.* Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomised, placebo-controlled clinical trial. *Stroke* 2003;**34**:2323–30	Not a disease modification trial
Blass JP, Cyrus PA, Bieber F, Gulanski B. Randomised, double-blind, placebo-controlled, multicenter study to evaluate the safety and tolerability of metrifonate in patients with probable Alzheimer disease. The Metrifonate Study Group. *Alzheimer Dis Assoc Disord* 2000;**14**:39–45	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Blesa R, Bullock R, He Y, Bergman H, Gambina G, Meyer J, *et al.* Effect of butyrylcholinesterase genotype on the response to rivastigmine or donepezil in younger patients with Alzheimer's disease. *Pharmacogenet Genomics* 2006;**16**:771–4	Not a disease modification trial
Blesa R, Davidson M, Kurz A, Reichman W, van Baelen B, Schwalen S. Galantamine provides sustained benefits in patients with 'advanced moderate' Alzheimer's disease for at least 12 months. *Dement Geriatr Cogn Disord* 2003;**15**:79–87	Not a disease modification trial
Boada-Rovira M. [Human albumin grifols 5% in plasmapheresis: a new therapy involving beta-amyloid mobilisation in Alzheimer's disease.] *Rev Neurol* 2010;**50**(Suppl. 5):9–18	Full text unavailable in English
Boada-Rovira M, Lopez O, Nunez L, Ortiz P, Anaya F, Hernandez I, *et al.* A phase II study to evaluate the efficacy and safety of plasma replacement with 5% albumin in beta-amyloid peptide clearance in cerebrospinal fluid, and its effects in patients with mild–moderate Alzheimer's disease. *Alzheimers Dement* 2014;**10**:P274	Not published in a peer-reviewed journal article or is an ongoing trial
Bodick NC, Offen WW, Levey AI, Cutler NR, Gauthier SG, Satlin A, *et al.* Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioural symptoms in Alzheimer disease. *Arch Neurol* 1997;**54**:465–73	Not a disease modification trial
Bogaert P, Grinsven R, Tolson D, Wouters K, Engelborghs S, Mussele S. Effects of SolCos model-based individual reminiscence on older adults with mild to moderate dementia due to Alzheimer disease: a pilot study. *J Am Med Dir Assoc* 2013;**14**:528	Not a disease modification trial
Bokde ALW, Karmann M, Teipel SJ, Born C, Lieb M, Reiser MF, *et al.* Decreased activation along the dorsal visual pathway after a 3-month treatment with galantamine in mild Alzheimer disease: a functional magnetic resonance imaging study. *J Clin Psychopharmacol* 2009;**29**:147–56	Not a disease modification trial
Bottino CMC, Carvalho IAM, Alvarez AMM, Avila R, Zukauskas PR, Bustamante SEZ, *et al.* Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: a pilot study. *Clin Rehabil* 2005;**19**:861–9	Not a disease modification trial
Boxer A, Knopman D, Kaufer D, Grossman M, Onyike C, Graf-Radford N, *et al.* A randomised, multicenter, placebo controlled trial of memantine for behavioural variant FTD and semantic variant PPA. *Alzheimers Dement* 2012;**1**:P405	Not published in a peer-reviewed journal article or is an ongoing trial
Boxer A, Knopman D, Kaufer D, Grossman M, Onyike C, Graf-Radford N, *et al.* A 26-week, multicenter, randomised, double blind, placebo controlled trial of memantine for behavioural variant FTD and semantic variant PPA. *Dement Geriatr Cogn Disord* 2012;**34**:47–8	Not published in a peer-reviewed journal article or is an ongoing trial
Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, *et al.* Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2013;**12**:149–56	Not a disease modification trial
Boxer A, Tartaglia M, Koestler M, Lasky A, Fine E, Heuer H, *et al.* A 12 week, randomised, double-blind, placebo-controlled pilot clinical trial of davunetide 15 mg intranasally twice daily for FTLD with predicted tau pathology (CBD,PNFA, PSP). *Dement Geriatr Cogn Disord* 2010;**30**:28–9	Not published in a peer-reviewed journal article or is an ongoing trial
Breeze RW, Cox S, Rodgers-Cox J. Changes in P-300 latency as a result of co-dergocrine mesylate therapy in patients with senile dementia. *J Geriatr Psychiatry* 1988;**3**:263–6	Not a disease modification trial
Brem A-K, Atkinson NJ, Seligson EE, Pascual-Leone A. Differential pharmacological effects on brain reactivity and plasticity in Alzheimer's disease. *Front Psychiatry* 2013;**4**:124	Not a disease modification trial
Brem AK, Schilberg L, Freitas C, Atkinson N, Seligson E, Pascual-Leone A. Effects of cognitive training and rTMS in Alzheimer's disease. *Alzheimers Dement* 2013;**1**:664	Not published in a peer-reviewed journal article or is an ongoing trial
Brem AK, Schilberg L, Freitas C, Atkinson N, Seligson E, Pascual-Leone A. Synergistic effects of rTMS and cognitive training in Alzheimer's Disease. *J Neurol Sci* 2013;**333**:e343	Not published in a peer-reviewed journal article or is an ongoing trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Brodaty H, Corey-Bloom J, Potocnik FC, Truyen L, Gold M, Damaraju CR. Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease. *Dement Geriatr Cogn Disord* 2005;**20**:120–32	Not a disease modification trial
Brooks JO 3rd, Yesavage JA, Carta A, Bravi D. Acetyl L-carnitine slows decline in younger patients with Alzheimer's disease: a reanalysis of a double-blind, placebo-controlled study using the trilinear approach. *Int Psychogeriatr* 1998;**10**:193–203	Not a disease modification trial
Brown D, Spanjers K, Atherton N, Lowe J, Stonehewer L, Bridle C, *et al.* Development of an exercise intervention to improve cognition in people with mild to moderate dementia: Dementia And Physical Activity (DAPA) Trial, registration ISRCTN32612072. *Physiotherapy* 2015;**101**:126–34	Not a disease modification trial
Bullock R, Bergman H, Touchon J, Gambina G, He Y, Nagel J, *et al.* Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease. *Curr Med Res Opin* 2006;**22**:483–94	Not a disease modification trial
Bullock R, Touchon J, Bergman H, Gambina G, He Y, Rapatz G, *et al.* Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. *Curr Med Res Opin* 2005;**21**:1317–27	Not a disease modification trial
Burgener SC, Yang Y, Gilbert R, Marsh-Yant S. The effects of a multimodal intervention on outcomes of persons with early-stage dementia. *Am J Alzheimers Dis Other Demen* 2008;**23**:382–94	Not a disease modification trial
Burke D. Donepezil or memantine improved cognitive functioning in moderate-to-severe Alzheimer disease. *ACP J Club* 2012;**156**:1	Not published in a peer-reviewed journal article or is an ongoing trial
Burke WJ, Ranno AE, Roccaforte WH, Wengel SP, Bayer BL, Willcockson NK. L-deprenyl in the treatment of mild dementia of the Alzheimer type: preliminary results. *J Am Geriatr Soc* 1993;**41**:367–70	Not a disease modification trial
Burke WJ, Roccaforte WH, Wengel SP, Bayer BL, Ranno AE, Willcockson NK. L-deprenyl in the treatment of mild dementia of the Alzheimer type: results of a 15-month trial. *J Am Geriatr Soc* 1993;**41**:1219–25	Not a disease modification trial
Burn D, Emre M, McKeith I, De Deyn PP, Aarsland D, Hsu C, *et al.* Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. *Move Disord* 2006;**21**:1899–907	Not a disease modification trial
Burns A, Gauthier S, Perdomo C. Efficacy and safety of donepezil over 3 years: an open-label, multicentre study in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2007;**22**:806–12	Not a disease modification trial
Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, *et al.* The effects of donepezil in Alzheimer's disease – results from a multinational trial. *Dement Geriatr Cogn Disord* 1999;**10**:237–44	Not a disease modification trial
Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;**19**:243–9	Not a disease modification trial
Burns A GS, Perdomo C. Long-term use of donepezil may be safe and effective in elderly AD patients. *Brown Uni Geriatr Psychopharmacol Update* 2007;**11**:3–4	Not a disease modification trial
Buschert VC, Friese U, Teipel SJ, Schneider P, Merensky W, Rujescu D, *et al.* Effects of a newly developed cognitive intervention in amnestic mild cognitive impairment and mild Alzheimer's disease: a pilot study. *J Alzheimers Dis* 2011;**25**:679–94	Not a disease modification trial
Butchart J, Brook L, Hopkins V, Teeling J, Puntener U, Culliford D, *et al.* Etanercept in Alzheimer disease: a randomised, placebo-controlled, double-blind, phase 2 trial. *Neurology* 2015;**84**:2161–8	Not a disease modification trial
Camargo CH, Justus FF, Retzlaff G. The effectiveness of reality orientation in the treatment of Alzheimer's disease. *Am J Alzheimers Dis Other Dement* 2015;**30**:527–32	Not a disease modification trial
Canevelli M, Adali N, Kelaiditi E, Cantet C, Ousset PJ, Cesari M. Effects of *Ginkgo biloba* supplementation in Alzheimer's disease patients receiving cholinesterase inhibitors: data from the ICTUS study. *Phytomedicine* 2014;**21**:888–92	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Caramelli P, Laks J, Palmini ALF, Nitrini R, Chaves MLF, Forlenza OV, *et al.* Effects of galantamine and galantamine combined with nimodipine on cognitive speed and quality of life in mixed dementia: a 24-week, randomised, placebo-controlled exploratory trial (the REMIX study). *Arq Neuropsiquiatr* 2014;**72**:411–17	Not a disease modification trial
Carlson MC, Tschanz JT, Norton MC, Welsh-Bohmer K, Martin BK, Breitner JC. H2 histamine receptor blockade in the treatment of Alzheimer disease: a randomised, double-blind, placebo-controlled trial of nizatidine. *Alzheimer Dis Assoc Disord* 2002;**16**:24–30	Not a disease modification trial
Ceccato E, Vigato G, Bonetto C, Bevilacqua A, Pizziolo P, Crociani S, *et al.* STAM protocol in dementia: a multicenter, single-blind, randomised, and controlled trial. *Am J Alzheimers Dis Other Demen* 2012;**27**:301–10	Not a disease modification trial
Chan WC, Cheng ST, Shi L, Wang D, Lam LC-W. Would transcranial direct current stimulation (tDCS) enhance the effects of working memory training in older adults with mild neurocognitive disorder due to Alzheimer's disease: study protocol for a randomised controlled trial. *Trials* 2015;**16**:1–7	Not a disease modification trial
Chapman SB, Weiner MF, Rackley A, Hynan LS, Zientz J. Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. *J Speech Lang Hear R* 2004;**47**:1149–63	Not a disease modification trial
Chappell AS, Gonzales C, Williams J, Witte MM, Mohs RC, Sperling R. AMPA potentiator treatment of cognitive deficits in Alzheimer disease. *Neurology* 2007;**68**:1008–12	Not a disease modification trial
Chatellier G, Lacomblez L. Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: A multicentre trial. *BMJ* 1990;**300**:495–9	Not a disease modification trial
Chen J, Huang Y, Wang SX, Li QS, Liang YJ, Guo YN. [18FDG PET cerebral function imaging in 10 vascular dementia patients receiving needling at Baihui(DU20), Shuigou (DU26) and Shenmen(HT7).] *J South Med Uni* 2006;**26**:610–12	Full text unavailable in English
Chen TS, Lang HC. Cost-effectiveness analysis of donepezil and rivastigmine for mild to moderate Alzheimer's disease in Taiwan. *Value Health* 2013;**16**:A104	Not published in a peer-reviewed journal article or is an ongoing trial
Chen WW, Tian AL, Zhai L, Zhai XL, Zhang YL. [Effect of the xingding allied piracetam injection on improvement of cognitive function in patients with vascular dementia.] *Chin J Clin Rehabil* 2005;**9**:231–3	Full text unavailable in English
Cherrier MM, Matsumoto AM, Amory JK, Asthana S, Bremner W, Peskind ER, *et al.* Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology* 2005;**64**:2063–8	Not a disease modification trial
Cheung SK. The effects of the music-with-movement intervention of the cognitive functions of people with moderate dementia. *Diss Abstr Int B Sci Eng* 2014;**75**	Not published in a peer-reviewed journal article or is an ongoing trial
Chiu C-C, Su K-P, Cheng T-C, Liu H-C, Chang C-J, Dewey ME, *et al.* The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomised double-blind placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;**32**:1538–44	Not a disease modification trial
Choe YM, Kim KW, Jhoo JH, Ryu SH, Choo IH, Seo EH, *et al.* Multi-centre, randomised, placebo-controlled, double-blind clinical trial of escitalopram on the progression delaying effect in Alzheimer's disease: Anmri study for atrophy delaying effect. *Alzheimers Dement* 2014;**10**:P302	Not published in a peer-reviewed journal article or is an ongoing trial
Choi SH, Park KW, Na DL, Han HJ, Kim EJ, Shim YS, *et al.* Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomised, open-label, parallel-group study. *Curr Med Res Opin* 2011;**27**:1375–83	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Chua KK, Wong A, Kwan P-L, Song JX, Chen LL, Chan A-T, *et al.* The efficacy and safety of the Chinese herbal medicine Di-Tan decoction for treating Alzheimer's disease: protocol for a randomised controlled trial. *Trials* 2015;**16**:199	Not a disease modification trial
Clare L, Linden DEJ, Woods RT, Whitaker R, Evans SJ, Parkinson CH, *et al.* Goal-oriented cognitive rehabilitation for people with early-stage Alzheimer disease: a single-blind randomised controlled trial of clinical efficacy. *Am J Geriatr Psychiatry* 2010;**18**:928–39	Not a disease modification trial
Claus JJ, De Koning I, Van Harskamp F, Breteler MMB, Voet B, Gutzmann H, *et al.* Lisuride treatment of Alzheimer's disease: a preliminary placebo-controlled clinical trial of safety and therapeutic efficacy. *Clin Neuropharmacol* 1998;**21**:190–5	Not a disease modification trial
Claxton A, Baker L, Hanson A, Cholerton B, Trittschuh E, Morgan A, *et al.* Long-acting intranasal insulin detemir improves working memory for adults with mild cognitive impairment or early-stage Alzheimer's dementia. *Alzheimers Dement* 2013;**9**(Suppl. 1):P657	Not published in a peer-reviewed journal article or is an ongoing trial
Coelho FG, Andrade LP, Pedroso RV, Santos-Galduroz RF, Gobbi S, Costa JL, *et al.* Multimodal exercise intervention improves frontal cognitive functions and gait in Alzheimer's disease: a controlled trial. *Geriatr Gerontol Int* 2013;**13**:198–203	Not a disease modification trial
Coker E. High-dose vitamin B supplements did not slow cognitive decline in patients with mild to moderate Alzheimer disease. *Evid Based Nurs* 2009;**12**:57	Not published in a peer-reviewed journal article or is an ongoing trial
Comelli M, Lucca U, Spagnoli A. Statistical analysis of the clinical trial of a therapy for Alzheimer's disease. Univariate tests and logistic regression. *Acta Neurologica* 1990;**12**:222–30	Not a disease modification trial
Concari L, Gardini S, Dieci F, Copelli S, Ferrari Pellegrini F, Ghetti C, *et al.* Cognitive and brain metabolism improvement after cognitive stimulation therapy Functional. *Neurology* 2013;**28**:21–2	Not published in a peer-reviewed journal article or is an ongoing trial
Connelly P. High dose vitamin B supplementation does not slow cognitive decline in mild to moderate Alzheimer's disease. *Evid Based Ment Health* 2009;**12**:86	Not published in a peer-reviewed journal article or is an ongoing trial
Connelly PJ, Prentice NP, Cousland G, Bonham J. A randomised double-blind placebo-controlled trial of folic acid supplementation of cholinesterase inhibitors in Alzheimer's disease. *Int J Geriatr Psychiatry* 2008;**23**:155–60	Not a disease modification trial
Cook C, Fay S, Rockwood K. Decreased initiation of usual activities in people with mild to moderate Alzheimer's disease: a descriptive analysis from the VISTA clinical trial. *Int Psychogeriatr* 2008;**20**:952–63	Not a disease modification trial
Corey-Bloom J, Anand R, Veach J. A randomised trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatr Psychopharmacol* 1998;**1**:55–65	Not a disease modification trial
Cornelli U. Treatment of Alzheimer's disease with a cholinesterase inhibitor combined with antioxidants. *Neurodegen Dis* 2010;**7**:193–202	Not a disease modification trial
Corona GI SG, Frattini P, Cucchi ML, Zerbi F, Tosca P, Savoldi F. Preliminary data on monoamine metabolic levels in cerebrospinal fluid and in urine during therapy in dementia. *IRCS J Med Sci* 1983;**11**:923–4	Not a disease modification trial
Corona GL CM, Frattini P, Santagostino G, Schinelli S, Romani A, Pola A, *et al.* Clinical and biochemical responses to therapy in Alzheimer's disease and multi-infarct dementia. *Eur Arch Psychiatry Clin Neurosci* 1989;**239**:79–86	Not a disease modification trial
Corrigan FM VRA, Horrobin DF. Essential fatty acids in Alzheimer's disease. *Ann NY Acad Sci* 1991;**640**:250–2	Not a disease modification trial
Cotelli M, Calabria M, Manenti R, Rosini S, Zanetti O, Cappa SF, *et al.* Improved language performance in Alzheimer disease following brain stimulation. *J Neurol Neurosurg Psychiatry* 2011;**82**:794–7	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Courtney C, Farrell D, Grey R, Hills R, Lynch L, Sellwood E, *et al.* Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004;**363**:2105–15	Not a disease modification trial
Cove J, Jacobi N, Donovan H, Orrell M, Stott J, Spector A. Effectiveness of weekly cognitive stimulation therapy for people with dementia and the additional impact of enhancing cognitive stimulation therapy with a carer training program. *Clin Interv Ageing* 2014;**9**:2143–50	Not a disease modification trial
Craft S, Claxton A, Baker L, Cholerton B, Hanson A, Callaghan M, *et al.* Therapeutic effects of long-acting intranasal insulin detemir for Alzheimer's dementia or mild cognitive impairment. *Alzheimers Dement* 2013;**9**(Suppl. 1):139–40	Not published in a peer-reviewed journal article or is an ongoing trial
Crook T, Petrie W, Wells C, Massari DC. Effects of phosphatidylserine in Alzheimer's disease. *Psychopharmacol Bull* 1991;**28**:61–6	Unable to find a copy of the full text
Crook T, Wilner E, Rothwell A, Winterling D, McEntee W. Noradrenergic intervention in Alzheimer's disease. *Psychopharmacol Bull* 1991;**28**:67–70	Unable to find a copy of the full text
Crumpacker DW. Retrospective evaluation of constructional praxis measurements among APOE4(–) subjects enrolled in the study of AC-1202 (Axona) in mild to moderate Alzheimer's disease (AD). *Am J Geriatr Psychiatry* 2012;**1**:S129	Not published in a peer-reviewed journal article or is an ongoing trial
Cumbo E. Effects of levetiracetam, phenobarbital and lamotrigine on neuropsychological performance and moodin patients with Alzheimer's disease and epilepsy. *Epilepsia* 2009;**50**:101	Not published in a peer-reviewed journal article or is an ongoing trial
Cummings J, Cho W, Ward M, Friesenhahn M, Brunstein F, Honigberg L, *et al.* A randomised, double-blind, placebo-controlled phase 2 study to evaluate the efficacy and safety of crenezumab in patients with mild to moderate Alzheimer's disease. *Alzheimers Dement* 2014;**10**:P275	Not a disease modification trial
Cummings J, Froelich L, Black SE, Bakchine S, Bellelli G, Molinuevo JL, *et al.* Randomised, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm^2) in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2012;**33**:341–53	Not a disease modification trial
Cummings JL, Cyrus PA, Bieber F, Mas J, Orazem J, Gulanski B. Metrifonate treatment of the cognitive deficits of Alzheimer's disease. *Neurology* 1998;**50**:1214–21	Not a disease modification trial
Cummings JL, Farlow MR, Meng X, Tekin S, Olin JT. Rivastigmine transdermal patch skin tolerability: results of a 1-year clinical trial in patients with mild to moderate Alzheimers disease. *Clin Drug Investig* 2010;**30**:41–9	Not a disease modification trial
Cummings JL, Ferris SH, Farlow MR, Olin JT, Meng X. Effects of rivastigmine transdermal patch and capsule on aspects of clinical global impression of change in Alzheimer's disease: a retrospective analysis. *Dement Geriatr Cogn Disord* 2010;**29**:406–12	Not a disease modification trial
Cummings J, Grossberg G, Alva G, Caputo A, Downs P, Strohmaier C. High-dose 13.3 MG/24 h rivastigmine transdermal patch demonstrates efficacy on instrumental activities of daily living: individual item analysis. *Alzheimers Dement* 2012;**8**(Suppl. 1):P604	Not published in a peer-reviewed journal article or is an ongoing trial
Cummings J, Hendrix S, Miller M, Pejovic V, Graham S, Tocco M. Extended-release memantine (28 mg, once daily) and sustained behavioural improvement: post hoc responder analysis from a randomised trial in patients with moderate to severe Alzheimer's disease. *Neurology* 2012;**78**:P04.197	Not published in a peer-reviewed journal article or is an ongoing trial
Cutler NR, Sramek JJ, Murphy MF, Nash RJ. Implications of the study population in the early evaluation of anticholinesterase inhibitors for Alzheimer's disease. *Ann Pharmacother* 1992;**26**:1118–22	Not a disease modification trial
D'Amico F, Rehill A, Knapp M, Aguirre E, Donovan H, Hoare Z, *et al.* Maintenance cognitive stimulation therapy: an economic evaluation within a randomised controlled trial. *J Am Med Dir Assoc* 2015;**16**:63–70	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Darreh-Shori T, Kadir A, Almkvist O, Grut M, Wall A, Blomquist G, *et al.* Inhibition of acetylcholinesterase in CSF versus brain assessed by 11C-PMP PET in AD patients treated with galantamine. *Neurobiol Ageing* 2008;**29**:168–84	Not a disease modification trial
Darreh-Shori T ML, Pettersson T, Hugosson K, Hellstrom-Lindahl E, Andreasen N, Minthon L, *et al.* Changes in the activity and protein levels of CSF acetylcholinesterases in relation to cognitive function of patients with mild Alzheimer's disease following chronic donepezil treatment. *J Neural Transm* 2006;**113**:1791–801	Not a disease modification trial
Davidsson P, Blennow K, Andreasen N, Eriksson B, Minthon L, Hesse C. Differential increase in cerebrospinal fluid-acetylcholinesterase after treatment with acetylcholinesterase inhibitors in patients with Alzheimer's disease. *Neurosci Lett* 2001;**300**:157–60	Not a disease modification trial
Davis KL, Thal LJ, Gamzu ER, Davis CS, Woolson RF, Gracon SI, *et al.* A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group. *N Engl J Med* 1992;**327**:1253–9	Not a disease modification trial
Davis RN, Massman PJ, Doody RS. Cognitive intervention in Alzheimer disease: a randomised placebo-controlled study. *Alzheimer Dis Assoc Disord* 2001;**15**:1–9	Not a disease modification trial
de Waal H, Stam CJ, Lansbergen MM, Wieggers RL, Kamphuis PJ, Scheltens P, *et al.* The effect of Souvenaid on functional brain network organisation in patients with mild Alzheimer's disease: a randomised controlled study. *PLOS ONE* 2014;27;**9**:e86558	Not a disease modification trial
Dean R, Siemers E, Carlson C, Estergard W, Sundell K, Henley D, *et al.* Effects of solanezumab versus placebo administration on biomarkers in people with mild to moderate Alzheimer's disease: results from two phase III clinical trials. *Alzheimers Dement* 2013;**9**(Suppl. 1):P283	Not published in a peer-reviewed journal article or is an ongoing trial
Demarin V, Podobnik SS, Storga-Tomic D, Kay G. Treatment of Alzheimer's disease with stabilised oral nicotinamide adenine dinucleotide: a randomised, double-blind study. *Drugs Exp Clin Res* 2004;**30**:27–33	Not a disease modification trial
Derouesne C, Renault B, Gueguen B, Van Der Linden M, Lacomblez L, Homeyer P, *et al.* Neuropsychophysiological evaluation of three doses of S 12024–2 in mild to moderate Alzheimer's disease. *Clin Drug Investig* 1997;**14**:301–6	Not a disease modification trial
Desire L, Marcade M, Peillon H, Drouin D, Sol O, Pando M. Clinical trials of EHT 0202, a neuroprotective and procognitive alpha-secretase stimulator for Alzheimer's disease. *Alzheimers Dement* 2009;**1**:255–6	Not published in a peer-reviewed journal article or is an ongoing trial
Dichgans M, Markus HS, Salloway S, Verkkoniemi A, Moline M, Wang Q, *et al.* Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *The Lancet Neurol* 2008;**7**:310–18	Not a disease modification trial
Di Lorenzo F. D2 agonist administration restores altered cortical plasticity in Alzheimer's disease patients. *Clin Neurophysiol* 2014;**125**:S66	Not published in a peer-reviewed journal article or is an ongoing trial
Di Lorenzo F, Martorana A, Bonn S, Caltagirone C, Koch G. D2 agonist administration restores impaired LTP-like cortical plasticity in AD patients. *Clin Neurophysiol* 2013;**124**:e139–40	Not published in a peer-reviewed journal article or is an ongoing trial
Diehl-Schmid J, Hardlund J, Bentham P, Wischik CM. The first disease-modifying drug trial in frontotemporal dementia: initial experiences. *Alzheimers Dement* 2014;**10**:138	Not published in a peer-reviewed journal article or is an ongoing trial
Doggrell SA. Is memantine a breakthrough in the treatment of moderate-to-severe Alzheimer's disease? *Expert Opin Pharmacother* 2003;**4**:1857–60	Not a disease modification trial
Dong GS, Li X, Jiang QH, Yang HQ. [Effects of donepezil treatment on platelets and secretase activities in Alzheimer's disease patients.] *Zhonghua Yi Xue Za Zhi* 2011;**91**:3341–5	Full text unavailable in English
D'Onofrio G, Sancarlo D, Addante F, Ciccone F, Cascavilla L, Paris F, *et al.* A pilot randomised controlled trial evaluating an integrated treatment of rivastigmine transdermal patch and cognitive stimulation in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2015;**30**:965–75	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Doody R, Galvin J, Farlow M, Shah R, Doraiswamy PM, Ferris S, *et al.* A new 26-week, double-blind, randomised, placebo-controlled, study of AC-1204 (caprylic triglyceride) in mild to moderate Alzheimer's disease: presentation of study design. *J Nutr Health Ageing* 2012;**16**:868	Not published in a peer-reviewed journal article or is an ongoing trial
Doody RS, Geldmacher DS, Farlow MR, Sun Y, Moline M, Mackell J. Efficacy and safety of donepezil 23 mg versus donepezil 10 mg for moderate-to-severe Alzheimer's disease: a subgroup analysis in patients already taking or not taking concomitant memantine. *Dement Geriatr Cogn Disord* 2012;**33**:164–73	Not a disease modification trial
Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD. Open-label, multicenter, phase 3, extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol* 2001;**58**:427–33	Not a disease modification trial
Doody RS, Gavrilova SI, Sano M, Thomas RG, Aisen PS, Bachurin SO, *et al.* Dimebon found safe and effective in mild to moderate Alzheimer's disease. *Brown Uni Geriatr Psychopharmacol Update* 2008;**12**:1–6	Not a disease modification trial
Doran MD. *A Randomised 26 week Double-Blind Placebo Controlled Trial to Evaluate the Safety and Efficacy of Galantamine in the Treatment of Dementia Secondary to Cerebrovascular Disease*. London: National Research Register; 2003	Not published in a peer-reviewed journal article or is an ongoing trial
Dorn M. *Effect of Nimodipine on the Well-Being, Symptoms and Efficiency of Ambulatory Patients with Cerebrovascular Disorders*. Stuttgart: Schattauer; 1985	Not published in a peer-reviewed journal article or is an ongoing trial
Dubois B, McKeith I, Orgogozo J-M, Collins O, Meulien D. A multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy, tolerability and safety of two doses of metrifonate in patients with mild to moderate Alzheimer's disease: The MALT Study. *Int J Geriatr Psychiatry* 1999;**14**:973–82	Not a disease modification trial
Dubois B, Tolosa E, Katzenschlager R, Emre M, Lees AJ, Schumann G, *et al.* Donepezil in Parkinson's disease dementia: a randomised, double-blind efficacy and safety study. *Move Dis* 2012;**27**:1230–8	Not a disease modification trial
Dukoff R, Friz J, Lasser, Lev JPK, Sunderland T. *A Comparison of Effects of Tacrine with Scopolamine Versus Tacrine with Placebo in Patients with Alzheimer's Disease Conference Abstract.* 11th Annual Meeting of the American Association for Geriatric Psychiatry San Diego, CA, USA, 8–11 March 1998	Not published in a peer-reviewed journal article or is an ongoing trial
Dysken M, Kuskowski M, Love S. Ondansetron in the treatment of cognitive decline in Alzheimer dementia. *Am J Geriatr Psychiatry* 2002;**10**:212–15	Not a disease modification trial
Dysken MW, Guarino PD, Vertrees JE, Asthana S, Sano M, Llorente M, *et al.* Vitamin E and memantine in Alzheimer's disease: clinical trial methods and baseline data. *Alzheimers Dement* 2014;**10**:36–44	Not a disease modification trial
Dysken MW, Mendels J, LeWitt P, Reisberg B, Pomara N, Wood J, *et al.* Milacemide: a placebo-controlled study in senile dementia of the Alzheimer type. *J Am Geriatr Soc* 1992;**40**:503–6	Not a disease modification trial
Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, *et al.* Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomised trial. *JAMA* 2014;**311**:33–44	Not a disease modification trial
Eagger SA, Levy R, Sahakian BJ. Tacrine in Alzheimer's disease. *Acta Neurol Scand* 1992;**85**:75–80	Not a disease modification trial
Egan M, Yaari R, Liu L, Ryan M, Peng Y, Lines C, *et al.* Pilot randomised controlled study of a histamine receptor inverse agonist in the symptomatic treatment of Alzheimer's disease. *Alzheimers Dement* 2011;**1**:S300	Not published in a peer-reviewed journal article or is an ongoing trial
Eisdorfer CJ, Wilkie FL. The effect of magnesium pemoline on cognition and behaviour. *J Gerontol* 1968;**23**:283–8	Not a disease modification trial
Eliasova I, Anderkova L, Marecek R, Rektorova I. Non-invasive brain stimulation of the right inferior frontal gyrus may improve attention in early Alzheimer's disease: a pilot study. *J Neurol Sci* 2014;**346**:318–22	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Emeriau JP, Lehert P, Mosnier M. Efficacy of naftidrofuryl in patients with vascular or mixed dementia: results of a multicenter, double-blind trial. *Clin Ther* 2000;**22**:834–44	Not a disease modification trial
Emre M, Aarsland D, Albanese A, Byrne E, Deuschl G, De Deyn PP, *et al.* Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 2004;**351**:2509–18	Not a disease modification trial
Emre M, Poewe W, Deyn PP, Barone P, Kulisevsky J, Pourcher E, *et al.* Long-term safety of rivastigmine in Parkinson disease dementia: an open-label, randomised study. *Clin Neuropharmacol* 2014;**37**:9–16	Not a disease modification trial
Emre M, Tsolaki M, Bonuccelli U, Destee A, Tolosa E, Kutzelnigg A, *et al.* Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2010;**9**:969–77	Not a disease modification trial
Eriksdotter M, Vedin I, Falahati F, Freund-Levi Y, Hjorth E, Faxen-Irving G, *et al.* Plasma fatty acid profiles in relation to cognition and gender in Alzheimer's Disease patients during oral omega-3 fatty acid supplementation: The OmegAD Study. *J Alzheimers Dis* 2015;**48**:805–12	Not a disease modification trial
Erkinjuntti T, Gauthier S, Bullock R, Kurz A, Hammond G, Schwalen S, *et al.* Galantamine treatment in Alzheimer's disease with cerebrovascular disease: responder analyses from a randomised, controlled trial (GAL-INT-6). *J Psychopharmacol* 2008;**22**:761–8	Not a disease modification trial
Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002;**359**:1283–90	Not a disease modification trial
Erkinjuntti T, Kurz A, Small GW, Bullock R, Lilienfeld S, Damaraju CV, *et al.* An open-label extension trial of galantamine in patients with probable vascular dementia and mixed dementia. *Clin Ther* 2003;**25**:1765–82	Not a disease modification trial
Erkinjuntti T, Skoog I, Lane R, Andrews C. Rivastigmine in patients with Alzheimer's disease and concurrent hypertension. *Int J Clin Prac* 2002;**56**:791–6	Not a disease modification trial
Etienne P, Dastoor D, Gauthier S, Ludwick R, Collier B. Alzheimer disease: lack of effect of lecithin treatment for 3 months. *Neurology* 1981;**31**:1552–4	Not a disease modification trial
Fabbrini G, Martucci N, Battaglia A, Pamparana F, Annoni K. *Nicergoline in the Treatment of Dementia: The Effects on Cerebral Blood Flow Measured by SPECT Conference Abstract*. 8th European College of Neuropsychopharmacology Congress Venice, Italy, 30 September–4 October 1995	Not published in a peer-reviewed journal article or is an ongoing trial
Fakouhi TD, Jhee SS, Sramek JJ, Benes C, Schwartz P, Hantsburger G, *et al.* Evaluation of cycloserine in the treatment of Alzheimer's disease. *J Geriatr Psychiatry Neurol* 1995;**8**:226–30	Not a disease modification trial
Falsaperla A, Monici Preti PA, Oliani C. Selegiline versus oxiracetam in patients with Alzheimer-type dementia. *Clin Ther* 1990;**12**:376–84	Not a disease modification trial
Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J. A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. *JAMA* 1992;**268**:2523–9	Not a disease modification trial
Farlow MR. Rivastigmine three times daily improves cognition and response in Alzheimer's disease. *Evid Based Ment Health* 2007;**10**:116	Not a disease modification trial
Farlow MR, Alva G, Meng X, Olin JT. A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild to moderate Alzheimer's disease: a post hoc analysis. *Curr Med Res Opin* 2010;**26**:263–9	Not a disease modification trial
Farlow M, Anand R, Messina J Jr, Hartman R, Veach J. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. *Eur Neurol* 2000;**44**:236–41	Not a RCT/CCT
Farlow MR, Doraiswamy M, Meng X, Somogyi M. The effect of vascular risk factors on the efficacy of rivastigmine patch and capsule in Alzheimer's disease. *Am J Geriatr Psychiatry* 2011;**1**:S120	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Farlow MR, Salloway S, Tariot PN, Yardley J, Moline ML, Wang Q, *et al.* Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomised, double-blind study. *Clin Ther* 2010;**32**:1234–51	Not a disease modification trial
Farokhnia M, Shafiee Sabet M, Iranpour N, Gougol A, Yekehtaz H, Alimardani R, *et al.* Comparing the efficacy and safety of *Crocus sativus* L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomised clinical trial. *Hum Psychopharmacol* 2014;**29**:351–9	Not a disease modification trial
Feldman H, Coric V, Sperling R, Greenberg S, Bronen R, Sorensen AG, *et al.* Cerebral microbleeds in a phase 2 clinical trial of mild to moderate Alzheimer's disease with the gamma secretase inhibitor BMS-708163. *Alzheimers Dement* 2011;**1**:S375	Not published in a peer-reviewed journal article or is an ongoing trial
Feldman H, Gauthier S, Hecker J, Vellas B, Emir B, Mastey V, *et al.* Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden. *J Am Geriatr Soc* 2003;**51**:737–44	Not a disease modification trial
Feldman H, Gauthier S, Hecker J, Vellas B, Hux M, Xu Y, *et al.* Economic evaluation of donepezil in moderate to severe Alzheimer disease. *Neurology* 2004;**63**:644–50	Not a disease modification trial
Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomised, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001;**57**:613–20	Not a disease modification trial
Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, *et al.* Randomised controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology* 2010;**74**:956–64	Not a disease modification trial
Feldman HH, Lane R, Study G. Rivastigmine: a placebo controlled trial of twice daily and three times daily regimens in patients with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2007;**78**:1056–63	Not a disease modification trial
Feldman HH, Schmitt FA, Olin JT. Activities of daily living in moderate-to-severe Alzheimer disease: an analysis of the treatment effects of memantine in patients receiving stable donepezil treatment. *Alzheimer Dis Assoc Disord* 2006;**20**:263–8	Not a disease modification trial
Ferris SH, Schmitt FA, Saxton J, Richardson S, MacKell J, Sun Y. Analysing the impact of 23 mg/day donepezil on language dysfunction in moderate to severe Alzheimer's disease. *Alzheimers Res Ther* 2011;**3**:22	Not a disease modification trial
Finger EC, MacKinley J, Blair M, Oliver LD, Jesso S, Tartaglia MC, *et al.* Oxytocin for frontotemporal dementia: a randomised dose-finding study of safety and tolerability. *Neurology* 2015;**84**:174–81	Not a disease modification trial
Fischhof PK, Moslinger-Gehmayr R, Herrmann WM, Friedmann A, Russmann DL. Therapeutic efficacy of vincamine in dementia. *Neuropsychobiology* 1996;**34**:29–35	Not a disease modification trial
Fischhof PK, Saletu B, Ruther E, Litschauer G, Moslinger-Gehmayr R, Herrmann WM. Therapeutic efficacy of pyritinol in patients with senile dementia of the Alzheimer type (SDAT) and multi-infarct dementia (MID). *Neuropsychobiology* 1992;**26**:65–70	Not a disease modification trial
Fisman M. Double blind study of lecithin in patients with Alzheimer's disease. *Can J Psychiatry* 1981;**26**:426–8	Not a disease modification trial
Fleisher A, Tariot P, Truran D, Mai J, Aisen P, Cummings J, *et al.* Brain volume changes with divalproex sodium in Alzheimer's disease. *Neuropsychopharmacology* 2010;**35**:S318–19	Not published in a peer-reviewed journal article or is an ongoing trial
Flicker C, Ferris SH, Kalkstein D, Serby M. A double-blind, placebo–controlled crossover study of ganglioside GM1 treatment for Alzheimer's disease. *Am J Geriatr Psychiatry* 1994;**151**:126–9	Not a disease modification trial
Foerster S, Buschert VC, Buchholz HG, Teipel SJ, Zach C, Hampel H, *et al.* Positive effects of a 6-month stage-specific cognitive intervention program on brain metabolism in subjects with amnestic mild cognitive impairment (AMCI) and mild Alzheimer's disease (AD). *Alzheimers Dement* 2009;**1**:205–6	Not published in a peer-reviewed journal article or is an ongoing trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Forbes D. Cognitive stimulation therapy improved cognition and quality of life in dementia. *Evid Based Nurs* 2004;**7**:54–5	Not a disease modification trial
Forette F, Anand R, Gharabawi G. A phase II study in patients with Alzheimer's disease to assess the preliminary efficacy and maximum tolerated dose of rivastigmine (Exelon). *Eur J Neurol* 1999;**6**:423–9	Not a disease modification trial
Forette F, Gracon S, de Rotrou J, Hervy MP, Lechevalier B, Micas M, *et al.* A double-blind, placebo-controlled, enriched population study of tacrine in patients with Alzheimer's disease. *Eur J Neurol* 1995;**2**:229–38	Not a disease modification trial
Forster S, Buschert VC, Buchholz H-G, Teipel SJ, Friese U, Zach C, *et al.* Effects of a 6-month cognitive intervention program on brain metabolism in amnestic mild cognitive impairment and mild Alzheimer's disease. *J Alzheimers Dis* 2011;**25**:695–706	Not a disease modification trial
Forster S, Buschert VC, Buchholz HG, Teipel SJ, Rominger A, La Fougere C, *et al.* Attenuation of cerebral metabolic decline in patients with amnestic mild cognitive impairment (aMCI) or mild Alzheimers disease (AD) joining a six-month stage-specific cognitive intervention program. *Nuklear Medizin* 2010;**49**:A53	Not published in a peer-reviewed journal article or is an ongoing trial
Förster S, Buschert VC, Teipel SJ, Friese U, Buchholz HG, Drzezga A, *et al.* Effects of a 6-month cognitive intervention on brain metabolism in patients with amnestic MCI and mild Alzheimer's disease. *J Alzheimers Dis* 2011;**26**(Suppl. 3):337–48	Not a disease modification trial
Foroutanpour K. *A Phase II, Single Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Trial to Evaluate the Safety and Efficacy of Three Different Dosages of Cerebrolysin in Patients with Probable Alzheimer's Disease*. *PRA International Report prepared for EBEWE Pharma*. Vienna: EBEWE Pharma; 2003	Not published in a peer-reviewed journal article or is an ongoing trial
FORUM Pharmaceuticals Inc. *NCT02149160 Study to Assess the Safety, Tolerability, and Pharmacodynamic (PD) Effects of FRM-0334 in Subjects With Prodromal to Moderate Frontotemporal Dementia With Granulin Mutation.* URL: https://clinicaltrials.gov/ct2/show/NCT02149160 (accessed 29 January 2016)	No quantitative outcome relating to disease modification
Francois C, Sintonen H, Sulkava R, Rive B. Cost-effectiveness of memantine in moderately severe to severe Alzheimer's disease: a Markov model in Finland. *Clin Drug Investig* 2004;**24**:373–84	Not a disease modification trial
Freedman M, Rewilak D, Xerri T, Cohen S, Gordon A, Shandling M, *et al.* L-deprenyl in Alzheimer's disease: cognitive and behavioural effects. *Neurology* 1998;**50**:660–8	Not a disease modification trial
Freund-Levi Y, Vedin I, Hjorth E, Basun H, Faxen Irving G, Schultzberg M, *et al.* Effects of supplementation with omega-3 fatty acids on oxidative stress and inflammation in patients with Alzheimer's disease: the OmegAD study. *J Alzheimers Dis* 2014;**42**:823–31	Not a disease modification trial
Frolich L. High-dose rivastigmine patch: results from the optima study. *Neurobiol Ageing* 2012;**33**:S12	Not published in a peer-reviewed journal article or is an ongoing trial
Frolich L, Ashwood T, Nilsson J, Eckerwall G. Effects of AZD3480 on cognition in patients with mild to moderate Alzheimer's disease: a phase IIb dose-finding study. *J Alzheimers Dis* 2011;**24**:363–74	Not a disease modification trial
Gaitán A, Garolera M, Cerulla N, Chico G, Rodriguez-Querol M, Canela-Soler J. Efficacy of an adjunctive computer-based cognitive training program in amnestic mild cognitive impairment and Alzheimer's disease: a single-blind, randomised clinical trial. *Int J Geriatr Psychiatry* 2013;**28**:91–9	Not a disease modification trial
Galasko D, Kershaw PR, Schneider L, Zhu Y, Tariot PN. Galantamine maintains ability to perform activities of daily living in patients with Alzheimer's disease. *J Am Geriatr Soc* 2004;**52**:1070–6	Not a disease modification trial
Gang MG. Effect of the horticultural intervention program on cognitive function, emotion, communication and behaviour in the elderly with Alzheimer's disease. *Int Psychogeriatr* 2013;**25**:S140	Not published in a peer-reviewed journal article or is an ongoing trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Gault LM, Meier A, Florian H, Gauthier S, Lin Y, Tang Q, *et al.* A phase 2 trial of the efficacy and safety of the alpha7agonistabt-126 as an add-on treatment in mild to moderate Alzheimer's dementia. *Alzheimers Dement* 2014;**10**:917–18	Not a disease modification trial
Gauthier S. Dimebon improves cognitive function in people with mild to moderate Alzheimer's disease. *Evid Based Ment Health* 2009;**12**:21	Not published in a peer-reviewed journal article or is an ongoing trial
Gauthier S, Bouchard R, Lamontagne A, Bailey P, Bergman H, Ratner J, *et al.* Tetrahydroaminoacridine–lecithin combination treatment in patients with intermediate-stage Alzheimer's disease. Results of a Canadian double-blind, crossover, multicenter study. *N Engl J Med* 1990;**322**:1272–6	Not a disease modification trial
Gavrilova SI, Kalyn Ia B, Kolykhalov IV, Roshchina IF, Selezneva ND. [Acetyl-L-carnitine (carnicetine) in the treatment of early stages of Alzheimer's disease and vascular dementia.] *Zh Nevrol Psikhiatr Im S S Korsakova* 2011;**111**:16–22	Full text unavailable in English
Gejl M, Egejord L, Moller A, Hansen SB, Vang K, Rodell A, *et al.* GLP-1 analogue liraglutide prevents decline of brain glucose metabolism in Alzheimer's disease: randomised, placebo-controlled double-blinded clinical trial. *Eur J Nucl Med Mol Imaging* 2015;**1**:S132–3	Not published in a peer-reviewed journal article or is an ongoing trial
Gelmont D, Dyck-Jones J. Safety of intravenous immunoglobulin therapy in patients with probable Alzheimer's disease: a randomised, placebo-controlled clinical study. *J Allergy Clin Immunol* 2015;**135**(Suppl.1):Ab97	Not published in a peer-reviewed journal article or is an ongoing trial
Giordano M, Dominguez LJ, Vitrano T, Curatolo M, Ferlisi A, Di Prima A, *et al.* Combination of intensive cognitive rehabilitation and donepezil therapy in Alzheimer's disease (AD). *Arch Gerontol Geriatr* 2010;**51**:245–9	Not a disease modification trial
Gleason CE, Fischer BL, Dowling NM, Setchell KDR, Atwood CS, Carlsson CM, *et al.* Cognitive effects of soy isoflavones in patients with Alzheimer's disease. *J Alzheimers Dis* 2015;**47**:1009–19	Not a disease modification trial
Graham S, Hendrix S, Miller M, Pejovic V, Tocco M. Efficacy of high-dose, extended-release memantine (28 MG, once daily): post hoc responder analysis from a randomised trial in patients with moderate to severe Alzheimer's disease. *Alzheimers Dement* 2011;**1**:S782	Not published in a peer-reviewed journal article or is an ongoing trial
Graham S, Tocco M, Hendrix S, Hofbauer RK, Perhach JL. Functional communication in patients with moderate Alzheimer's disease treated with memantine. *Eur Neuropsychopharmacol* 2010;**20**:S557–8	Not published in a peer-reviewed journal article or is an ongoing trial
Graham SM, Hendrix S, Miller ML, Pejovic V, Tocco M. Extended-release memantine (28 mg, once daily) provides behavioural benefits across a wide range of disease severity in patients with moderate to severe Alzheimer's disease: post hoc analysis from a randomised trial. *Am J Geriatr Psychiatry* 2013;**1**:S139	Not published in a peer-reviewed journal article or is an ongoing trial
Graham SM, Tocco M, Hendrix S, Hofbauer RK, Miller ML, Perhach JL. Memantine prevents worsening across multiple domains in a trial of patients with moderate Alzheimer's disease. *Eur Neuropsychopharmacol* 2010;**20**:S557	Not published in a peer-reviewed journal article or is an ongoing trial
Green RC, Goldstein FC, Auchus AP, Presley R, Clark W, Van Tuyl L, *et al.* Treatment trial of oxiracetam in Alzheimer's disease. *Arch Neurol* 1992;**49**:1135–6	Not a disease modification trial
Greenberg SM, Tennis MK, Brown LB, Gomez-Isla T, Hayden DL, Schoenfeld DA, *et al.* Donepezil therapy in clinical practice: a randomised crossover study. *Arch Neurol* 2000;**57**:94–9	Not a disease modification trial
Grossberg G, Alva G, Hendrix S, Hofbauer R, Pejovic V, Graham S. Efficacy and tolerability of memantine extended release added to stable donepezil regimen in individuals with moderate to severe Alzheimer's disease: subset analysis of a randomised clinical trial. *Neurology* 2015;**84**:P7.101	Not published in a peer-reviewed journal article or is an ongoing trial

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TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Grossberg G, Alva G, Hendrix S, Hofbauer R, Pejovic V, Graham SM. Efficacy and tolerability of memantine extended release added to stable donepezil regimen in individuals with moderate to severe Alzheimer's disease: subset analysis of a randomised clinical trial. *Alzheimers Dement* 2014;**10**:P450	Not published in a peer-reviewed journal article or is an ongoing trial
Grossberg G, Cummings J, Frolich L, Bellelli G, Molinuevo JL, Krahnke T, *et al.* Efficacy of higher dose 13.3 mg/24 h rivastigmine patch on instrumental activities of daily living in patients with mild to moderate Alzheimer's disease. *AmJ Alzheimers Dis Other Dement* 2013;**28**:583–91	Not a disease modification trial
Grossberg G, Meng X, Olin JT. Impact of rivastigmine patch and capsules on activities of daily living in Alzheimer's disease. *Am J Alzheimers Dis Other Dement* 2011;**26**:65–71	Not a disease modification trial
Grossberg GT, Manes F, Allegri R, Robledo LMG, Gloger S, Xie L, *et al.* Extended-release memantine (28 mg, once daily) improves verbal fluency and behaviour in patients with moderate to severe Alzheimer's disease: results of a multinational, double-blind, placebo-controlled trial. *Am J Geriatr Psychiatry* 2009;**17**:A78	Not published in a peer reviewed journal article or an ongoing trial
Grossman H, Marzloff G, Luo X, LeRoith D, Sano M, Pasinetti G. NIC5–15 as a treatment for Alzheimer's: safety, pharmacokinetics and clinical variables. *Alzheimers Dement* 2009;**1**:259	Not published in a peer-reviewed journal article or is an ongoing trial
Grove RA, Harrington CM, Mahler A, Beresford I, Maruff P, Lowy MT, *et al.* A randomised, double-blind, placebo-controlled, 16-week study of the H3 receptor antagonist, GSK239512 as a monotherapy in subjects with mild to moderate Alzheimer's disease. *Curr Alzheimer Res* 2014;**11**:47–58	Not a disease modification trial
Growdon JH, Corkin S, Huff FJ, Rosen TJ. Piracetam combined with lecithin in the treatment of Alzheimer's disease. *Neurobiol Ageing* 1986;**7**:269–76	Not a disease modification trial
Gu C, Shen T, An H, Yuan C, Zhou J, Ye Q, *et al.* Combined therapy of di-huang-yi-zhi with donepezil in patients with Parkinson's disease dementia. *Neurosci Lett* 2015;**606**:13–17	Not a disease modification trial
Guekht A, Doppler E, Moessler H, Gusev E. Cerebrolysin improves clinical outcome in moderate to moderately severe vascular dementia: results from a randomised, double-blind, placebo-controlled, multicenter trial. *Eur J Neurol* 2009;**16**(Suppl. 3):391	Not published in a peer-reviewed journal article or is an ongoing trial
Guekht AB, Moessler H, Novak PH, Gusev EI. Cerebrolysin in vascular dementia: improvement of clinical outcome in a randomised, double-blind, placebo-controlled multicenter trial. *J Stroke Cerebrovasc Dis* 2011;**20**:310–18	Not a disease modification trial
Guimon J, Blanco J, Caso C. L-Dopa carbidopa treatment of senile dementia: a control study. *Eur J Psychiat* 1995;**9**:29–36	Not a disease modification trial
Gustafson L. Physostigmine and tetrahydroaminoacridine treatment of Alzheimer's disease. *Acta Neurol Scand Suppl* 1993;**149**:39–41	Not a disease modification trial
Gustafson L, Risberg J, Johanson M, Fransson M, Maximilian VA. Effects of piracetam on regional cerebral blood flow and mental functions in patients with organic dementia. *Psychopharmacology* 1978;**56**:115–17	Not a disease modification trial
Gustavsson A, Van Der Putt R, Jönsson L, McShane R. Economic evaluation of cholinesterase inhibitor therapy for dementia: comparison of Alzheimer's disease and Dementia with Lewy bodies. *Int J Geriatr Psychiatry* 2009;**24**:1072–8	Not a disease modification trial
Gutzmann H, Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. *J Neural Transm Supplementum* 1998;**54**:301–10	Not a disease modification trial
Haan J, Hörr R. [Delay in progression of dependency and need of care of dementia patients treated with Ginkgo special extract EGb 761.] *Wien Med Wochenschr* 2004;**154**:511–14	Full text unavailable in English
Haase J, Halama P, Horr R. [Efficacy of short-term treatment with intravenously administered *Ginkgo biloba* special extract EGb 761 in Alzheimer type and vascular dementia.] *Z Gerontol Geriatr* 1996;**29**:302–9	Full text unavailable in English

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Haase J, Halama P, Hörr R. [Effectiveness of brief infusions with *Ginkgo biloba* special extract EGb 761 in dementia of the vascular and Alzheimer type.] *Z Gerontol Geriatr* 1996;**29**:302–9	Full text unavailable in English
Hager K, Baseman AS, Han JH, Sano M, Richards HM. In a 2-year placebo-controlled randomised trial galantamine-treated patients had lower mortality rates and slower decline in cognition and activities of daily living. *Neuropsychopharmacology* 2012;**38**:S328	Not published in a peer-reviewed journal article or is an ongoing trial
Hager K, Baseman AS, Nye JS, Brashear H, Han J, Sano M, *et al.* Effects of galantamine in a 2-year, randomised, placebo-controlled study in Alzheimer's disease. *Neuropsychiat Dis Treat* 2014;**10**:391–401	Not a disease modification trial
Hagstadius S, Gustafson L, Risberg J. The effects of bromvincamine and vincamine on regional cerebral blood flow and mental functions in patients with multi-infarct dementia. *Psychopharmacology* 1984;**83**:321–6	Not a disease modification trial
Haig G, Meier A, Pritchett Y, Hall C, Gault L, Lenz R. Evaluation of the efficacy and safety of the H3 antagonist ABT-288 in mild to moderate Alzheimer's disease. *Alzheimers Dement* 2012;**1**:601–2	Not published in a peer-reviewed journal article or is an ongoing trial
Haig GM, Pritchett Y, Meier A, Othman AA, Hall C, Gault LM, *et al.* A randomised study of H3 antagonist ABT-288 in mild to moderate Alzheimer's dementia. *J Alzheimers Dis* 2014;**42**:959–71	Not a disease modification trial
Hancock G, Charlesworth G. Donepezil slows decline in daily life activities in people with moderate to severe Alzheimer's disease and alleviates caregiver burden. *Evid Based Ment Health* 2004;**7**:20–1	Not a disease modification trial
Hanney M, Prasher V, Williams N, Jones EL, Aarsland D, Corbett A, *et al.* Memantine for dementia in adults older than 40 years with Down's syndrome (MEADOWS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;**379**:528–36	Not a disease modification trial
Hanyu H, Sato T, Kiuchi A, Sakurai H, Iwamoto T. Pioglitazone improved cognition in a pilot study on patients with Alzheimer's disease and mild cognitive impairment with diabetes mellitus. *J Am Geriatr Soc* 2009;**57**:177–9	Not published in a peer-reviewed journal article or is an ongoing trial
Hara J, Shankle W. Long-term ivig treatment delays progression of Alzheimer's and Lewy body disease. *Alzheimers Dement* 2011;**1**:S461	Not published in a peer-reviewed journal article or is an ongoing trial
Hashimoto M, Kazui H, Matsumoto K, Nakano Y, Yasuda M, Mori E. Does donepezil treatment slow the progression of hippocampal atrophy in patients with Alzheimer's disease? *Am J Geriatr Psychiatry* 2005;**162**:676–82	Not a RCT/CCT
Hashimoto M, Yamashita K, Kato S, Tamai T, Matsumoto I, Tanabe Y, *et al.* Beneficial effects of dietary docosahexaenoic acid intervention on cognitive function in elderly people with very mild dementia in Japan. *Alzheimers Dement* 2011;**1**:610–11	Not published in a peer-reviewed journal article or is an ongoing trial
Hasselbalch SG, Hoffmann K, Frederiksen KS, Sobol NA, Beyer N, Vogel A, *et al.* A multicentre randomised clinical trial of physical exercise in Alzheimer's disease (AD): Rationale and design of the ADEX study. *Eur J Neurol* 2012;**19**:95	Not published in a peer-reviewed journal article or is an ongoing trial
Hauer K, Schwenk M, Zieschang T, Essig M, Becker C, Oster P. Physical training improves motor performance in people with dementia: a randomised controlled trial. *J Am Geriatr Soc* 2012;**60**:8–15	Not a disease modification trial
Heiss WD, Kessler J, Mielke R, Szelies B, Herholz K. Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation. *Dementia* 1994;**5**:88–98	Not a disease modification trial
Henderson ST, Barr LJ, Vogel JL, Garvin F. Evidence of an interaction between APOE and IDE in ketone body therapies in mild to moderate Alzheimer's disease. *J Neurol Sci* 2009;**285**:S277	Not published in a peer-reviewed journal article or is an ongoing trial
Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled, multicenter trial. *Nutri Metab* 2009;**6**:31	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Henderson VW, Ala T, Sainani KL, Bernstein AL, Stephenson BS, Rosen AC, *et al.* Raloxifene for women with Alzheimer disease: a randomised controlled pilot trial. *Neurology* 2015;**85**:1937–44	Not a disease modification trial
Herrmann WM, Stephan K. Moving from the question of efficacy to the question of therapeutic relevance: an exploratory reanalysis of a controlled clinical study of 130 inpatients with dementia syndrome taking piracetam. *Int Psychogeriatr* 1992;**4**:25–44	Not a disease modification trial
Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R, Schlaefke S. *Ginkgo biloba* extract EGb 761 in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. *J Psychiat Res* 2012;**46**:716–23	Not a disease modification trial
Heyman A, Schmechel D, Wilkinson W, Rogers H, Krishnan R, Holloway D, *et al.* Failure of long term high-dose lecithin to retard progression of early-onset Alzheimer's disease. *J Neural Transm Suppl* 1987;**24**:279–86	Not a disease modification trial
Hilt DC, Gawryl M, Koenig G, Dgetluck N, Harrison J, Moebius HJ, *et al.* Positive effects on cognition and clinical function in mild to moderate Alzheimer's disease patients with a selective alpha-7 nicotinic partial agonists: interpretation of effects based on a PK/PD model. *J Nutr Health Ageing* 2012;**16**:819	Not published in a peer-reviewed journal article or is an ongoing trial
Ho RT, Cheung JK, Chan WC, Cheung IK, Lam LC. A 3-arm randomised controlled trial on the effects of dance movement intervention and exercises on elderly with early dementia. *BMC Geriatr* 2015;**15**:127	Not a disease modification trial
Hofferberth B. The efficacy of EGb 761 in patients with senile dementia of the Alzheimer type, a double-blind, placebo-controlled study on different levels of investigation. *Hum Psychopharm* 1994;**9**:215–22	Not a disease modification trial
Hoffmann K, Frederiksen KS, Sobol NA, Beyer N, Vogel A, Simonsen AH, *et al.* Preserving cognition, quality of life, physical health and functional ability in Alzheimer's disease: the effect of physical exercise (ADEX trial): rationale and design. *Neuroepidemiology* 2013;**41**:198–207	Not a disease modification trial
Homma A, Takeda M, Imai Y, Udaka F, Hasegawa K, Kameyama M, *et al.* Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease: a 24-week, multicenter, double-blind, placebo-controlled study in Japan. *Dement Geriatr Cogn Disord* 2000;**11**:299–313	Not a disease modification trial
Hooghiemstra A, Eggermont L, Flier W, Marum R, Campen J, Koppe P, *et al.* Feasibility of an RCT on exercise interventions in early-onset dementia: let's move on! *Alzheimers Dement* 2013;**9**(Suppl. 1):P295	Not published in a peer-reviewed journal article or is an ongoing trial
Hooghiemstra AM, Eggermont LHP, Scheltens P, van der Flier WM, Bakker J, de Greef MHG, *et al.* Study protocol: EXERcise and Cognition In Sedentary adults with Early-ONset dementia (EXERCISE-ON). *BMC Neurol* 2012;**12**:75	Not a disease modification trial
Hoogveldt B, Rive B, Severens J, Maman K, Guilhaume C. Cost-effectiveness analysis of memantine for moderate-to-severe Alzheimer's disease in the Netherlands. *Neuropsychiatr Dis Treat* 2011;**7**:313–17	Not a disease modification trial
Howard R. Donepezil or memantine improved cognitive functioning in moderate-to-severe Alzheimer disease. *Ann Intern Med* 2012;**156**:JC6–10	Not a disease modification trial
Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, *et al.* Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med* 2012;**366**:893–903	Not a disease modification trial
Huang WW, Zhang LH, Zhang H, Kong L. [Effects of hydrochloric donepezil in improving cognition and daily life ability in patients with Alzheimer disease.] *Chin J Clin Rehabil* 2004;**8**:5378–9	Full text unavailable in English
Huang Y, Chen J, Htut WM, Lai X, Wik G. Acupuncture increases cerebral glucose metabolism in human vascular dementia. *Int J Neurosci* 2007;**117**:1029–37	Not a disease modification trial
Huff FJ. Preliminary evaluation of besipirdine for the treatment of Alzheimer's disease. Besipirdine Study Group. *Ann NY Acad Sci* 1996;**777**:410–14	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Huff FJ, Antuono P, Murphy M, Beyer J, Dobson C. Potential clinical use of an adrenergic/cholinergic agent (HP 128) in the treatment of Alzheimer's disease. *Ann NY Acad Sci* 1991;**640**:263–7	Not a disease modification trial
Hughes LE, Rittman T, Regenthal R, Robbins TW, Rowe JB. Improving response inhibition systems in frontotemporal dementia with citalopram. *Brain* 2015;**138**:1961–75	Not a disease modification trial
Hwang HR, Choi SH, Yoon DH, Yoon BN, Suh YJ, Lee D, *et al.* The effect of cognitive training in patients with mild cognitive impairment and early Alzheimer's disease: a preliminary study. *J Clin Neurol* 2012;**8**:190–7	Not a disease modification trial
Ihl R, Bachinskaya N, Korczyn AD, Vakhapova V, Tribanek M, Hoerr R, *et al.* Efficacy and safety of a once-daily formulation of *Ginkgo biloba* extract EGb 761 in dementia with neuropsychiatric features: a randomised controlled trial. *Int J Geriatr Psychiatry* 2011;**26**:1186–94	Not a disease modification trial
Ihl R, Tribanek M, Bachinskaya N. Baseline neuropsychiatric symptoms are effect modifiers in *Ginkgo biloba* extract (EGb 761®) treatment of dementia with neuropsychiatric features. Retrospective data analyses of a randomised controlled trial. *J Neurol Sci* 2010;**299**:184–7	Not a disease modification trial
Ihl R, Tribanek M, Bachinskaya N. Efficacy and tolerability of a once daily formulation of *Ginkgo biloba* extract EGb 761® in Alzheimer's disease and vascular dementia: results from a randomised controlled trial. *Pharmacopsychiatry* 2012;**45**:41–6	Not a disease modification trial
Ikeda M, Mori E, Kosaka K, Iseki E, Hashimoto M, Matsukawa N, *et al.* Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: Results from a 52-week, open-label, multicenter extension study. *Dement Geriatr Cogn Disord* 2013;**36**:229–41	Not a disease modification trial
Imbimbo BP, Lucca U, Lucchelli F, Alberoni M, Thal L. A 25-week placebo-controlled study of eptastigmine in patients with Alzheimer disease. *Alzheimer Dis Assoc Disord* 1998;**12**:313–22	Not published in a peer-reviewed journal article or is an ongoing trial
Imbimbo BP, Lucchelli PE. Chronic low dose eptastigmine in Alzheimer patients: Relationship between acetylcholinesterase inhibition and cognitive effects. *Neurobiol Ageing* 1994;**15**(Suppl. 1):100	Not published in a peer-reviewed journal article or is an ongoing trial
Imbimbo BP, Martelli P, Troetel WM, Lucchelli F, Lucca U, Thal LJ. Efficacy and safety of eptastigmine for the treatment of patients with Alzheimer's disease. *Neurology* 1999;**52**:700–8	Not a disease modification trial
Imbimbo BP, Nicoli M, Martini C, Tomelleri GP, Martelli P, Ferrari GP, *et al.* Acetylcholinesterase assay may predict cognitive response of Alzheimer patients to eptastigmine treatment. *Eur J Clin Pharmacol* 1998;**54**:809–10	Not a disease modification trial
Imbimbo BP, Troetel WM, Martelli P, Lucchelli F. A 6-month, double-blind, placebo-controlled trial of eptastigmine in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2000;**11**:17–24	Not a disease modification trial
Imbimbo BP, Verdelli G, Martelli P, Marchesini D. Two-year treatment of Alzheimer's disease with eptastigmine. *Dement Geriatr Cogn Disord* 1999;**10**:139–46	Not a disease modification trial
Imbriano L, Podda L, Rendace L, Lucchese F, Campanelli A, D'Antonio F, *et al.* Long-lasting cognitive stimulation temporary improves cognitive impairment in patients with Alzheimer's disease: the results from a 6-months follow-up controlled clinical study. *Funct Neurol* 2013;**28**:36–7	Not published in a peer-reviewed journal article or is an ongoing trial
Ishizaki J, Meguro K, Ohe K, Kimura E, Tsuchiya E, Ishii H, *et al.* Therapeutic psychosocial intervention for elderly subjects with very mild Alzheimer disease in a community: the tajiri project. *Alzheimer Dis Assoc Disord* 2002;**16**:261–9	Not a disease modification trial
Isik AT, Bozoglu E. Acetylcholinesterase inhibition and insulin resistance in late onset Alzheimer's disease. *Int Psychogeriatr* 2009;**21**:1127–33	Not a disease modification trial
Ito T, Meguro K, Akanuma K, Ishii H, Mori E. A randomised controlled trial of the group reminiscence approach in patients with vascular dementia. *Dement Geriatr Cogn Disord* 2007;**24**:48–54	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Jack C, Slomkowski M, Gracon S, Hoover T, Felmlee J, Stewart K, *et al.* MRI as a biomarker of disease progression in a therapeutic trial of milameline for AD. *Neurology* 2003;**60**:253–60	Not a disease modification trial
Jack CRSM, Gracon S, Hoover TM, Felmlee JP, Stewart K, Xu YC, *et al. MRI as a Surrogate End Point for Disease Progression in a Therapeutic Trial of Milameline for Alzheimer's Disease*. Proceedings of the 8th International Conference on Alzheimer's Disease and Related Disorders, Stockholm, Sweden, 20–25 July 2002	Not published in a peer-reviewed journal article or is an ongoing trial
Jacoby R. Rofecoxib or naproxen do not slow progression of mild to moderate Alzheimer's disease. *Evid Based Ment Health* 2003;**6**:110	Not published in a peer-reviewed journal article or is an ongoing trial
Jann MW, Cyrus PA, Eisner LS, Margolin DI, Griffin T, Gulanski B. Efficacy and safety of a loading-dose regimen versus a no-loading-dose regimen of metrifonate in the symptomatic treatment of Alzheimer's disease: a randomised, double-masked, placebo-controlled trial. Metrifonate Study Group. *Clin Ther* 1999;**21**:88–102	Not a disease modification trial
Jelcic N, Agostini M, Meneghello F, Busse C, Parise S, Galano A, *et al.* Feasibility and efficacy of cognitive telerehabilitation in early Alzheimer's disease: a pilot study. *Clin Interv Ageing* 2014;**9**:1605–11	Not a disease modification trial
Jelcic N, Cagnin A, Meneghello F, Turolla A, Ermani M, Dam M. Effects of lexical-semantic treatment on memory in early Alzheimer disease: an observer-blinded randomised controlled trial. *Neurorehabil Neural Repair* 2012;**26**:949–56	Not a disease modification trial
Jeong YH WR, Park CH, Suh YH. Therapeutic potentials of mefenamic acid for the treatment of Alzheimer's disease. *Neurobiol Ageing* 2004;**25**:s589	Not published in a peer-reviewed journal article or is an ongoing trial
Jesso S, Diodati D, Morlog D, Pasternak S, Kertesz A, Finger E. A randomised, double-blind, placebo controlled, cross-over study of the effects of oxytocin in patients with frontotemporal dementia. *Dement Geriatr Cogn Disord* 2010;**30**:98	Not a disease modification trial
Jhee SS, Fabbri L, Piccinno A, Monici P, Moran S, Zarotsky V, *et al.* First clinical evaluation of ganstigmine in patients with probable Alzheimer's disease. *Clin Neuropharmacol* 2003;**26**:164–9	Not a disease modification trial
Joffres C, Bucks RS, Haworth J, Wilcock GK, Rockwood K. Patterns of clinically detectable treatment effects with galantamine: a qualitative analysis. *Dement Geriatr Cogn Disord* 2003;**15**:26–33	Not a disease modification trial
Johansson C, Ballard C, Hansson O, Palmqvist S, Minthon L, Aarsland D, *et al.* Efficacy of memantine in PDD and DLB: an extension study including washout and open-label treatment. *Int J Geriatr Psychiatry* 2011;**26**:206–13	Not a RCT/CCT
Johannsen P, Salmon E, Hampel H, Xu Y, Richardson S, Qvitzau S, *et al.* Assessing therapeutic efficacy in a progressive disease: a study of donepezil in Alzheimer's disease. *CNS drugs* 2006;**20**:311–25	Not a disease modification trial
Johnsen K, Brynne N, Annas P, Hannesdottir K, Alexander R, Segerdahl M. The effects of AZD1446 (A neuronal nicotinic receptor agonist) on quantified electroencephalography (QEEG) in patients with mild to moderate Alzheimer's disease. Quantitative measurements using a QEEG cholinergic index. *J Nutr Health Ageing* 2013;**17**:834	Not published in a peer-reviewed journal article or is an ongoing trial
Johnson KH. Donepezil minimally effective for patients with vascular dementia. *J Fam Pract* 2004;**53**:181–2	Not a disease modification trial
Johnson NA, Rademaker A, Weintraub S, Gitelman D, Wienecke C, Mesulam M. Pilot trial of memantine in primary progressive aphasia. *Alzheimer Dis Assoc Disord* 2010;**24**:308	Not published in a peer-reviewed journal article or is an ongoing trial
Jolkkonen JT, Soininen HS, Riekkinen PJ. The effect of an ACTH4–9 analogue (Org2766) on some cerebrospinal fluid parameters in patients with Alzheimer's disease. *Life Sci* 1985;**37**:585–90	Not a disease modification trial
Jones RW, McCrone P, Guilhaume C. Cost-effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. *Drugs Ageing* 2004;**21**:607–20	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Jones RW, Soininen H, Hager K, Aarsland D, Passmore P, Murthy A, *et al.* A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;**19**:58–67	Not a disease modification trial
Jorgenson S BA, Andersen J, Jensen HV, Olafsson K, Arup P, Moller SE. Fluvoxamine treatment of dementia: tryptophan levels. *Biol Psychiatry* 1993;**34**:587–8	Not published in a peer-reviewed journal article or is an ongoing trial
Jubert J, Navarra J, Canals R, Balaguer M. [Neuropsychologic evaluation of the action of oxovinca in the syndrome of diffuse deterioration of vascular origin.] *Med Clín* 1980;**75**:115–21	Full text unavailable in English
Kadir A, Darreh-Shori T, Almkvist O, Wall A, Grut M, Strandberg B, *et al.* PET imaging of the in vivo brain acetylcholinesterase activity and nicotine binding in galantamine-treated patients with AD. *Neurobiol Ageing* 2008;**29**:1204–17	Not a disease modification trial
Kalman J, Juhasz A, Rimanoczy A, Palotas A, Palotas M, Szabo Z, *et al.* Lack of influence of the apolipoprotein E genotype on the outcome of selegiline treatment in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2003;**16**:31–4	Not a disease modification trial
Kamphuis P, Verhey F, Olde Rikkert M, Twisk J, Swinkels S, Scheltens P. Efficacy of a medical food on cognition in Alzheimer's disease: results from secondary analyses of a randomised, controlled trial. *J Nutr Health Ageing* 2011;**15**:720–4	Not a disease modification trial
Kanowski S, Hoerr R. *Ginkgo biloba* extract EGb 761 in dementia: intent-to-treat analyses of a 24-week, multi-centre, double-blind, placebo-controlled, randomised trial. *Pharmacopsychiatry* 2003;**36**:297–303	Not a disease modification trial
Karaman Y, Erdogan F, Köseoglu E, Turan T, Ersoy AO. A 12-month study of the efficacy of rivastigmine in patients with advanced moderate Alzheimer's disease. *Dement Geriatr Cogn Disord* 2005;**19**:51–6	Not a disease modification trial
Keller C, Kadir A, Forsberg A, Porras O, Nordberg A. Long-term effects of galantamine treatment on brain functional activities as measured by PET in Alzheimer's disease patients. *J Alzheimers Dis* 2011;**24**:109–23	Not a disease modification trial
Kemp PM, Holmes C, Hoffmann S, Wilkinson S, Zivanovic M, Thom J, *et al.* A randomised placebo controlled study to assess the effects of cholinergic treatment on muscarinic receptors in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2003;**74**:1567–70	Not a disease modification trial
Kennelly S, Abdullah L, Crawford F, Mullan M, Kenny RA, Lawlor B. APOE E4 genotype-specific short-term cognitive benefits of treatment with the antihypertensive nilvadipine in Alzheimer's patients-an open-label trial. *Ir J Med Sci* 2011;**180**:S325	Not published in a peer-reviewed journal article or is an ongoing trial
Kennelly S, Abdullah L, Paris D, Parish J, Mathura V, Mullan M, *et al.* Demonstration of safety in Alzheimer's patients for intervention with an anti-hypertensive drug nilvadipine: results from a 6-week open label study. *Int J Geriatr Psychiatry* 2011;**26**:1038–45	Not a disease modification trial
Kertesz A, Morlog D, Light M, Blair M, Davidson W, Jesso S, *et al.* Galantamine in frontotemporal dementia and primary progressive aphasia. *Dement Geriatr Cogn Disord* 2008;**25**:178–85	Not a disease modification trial
Kim SY, Choi SH, Rollema H, Schwam EM, McRae T, Dubrava S, *et al.* Phase II crossover trial of varenicline in mild to moderate Alzheimer's disease. *Dement Geriatr Cogn Disord* 2014;**37**:232–45	Not a disease modification trial
Koch HJ, Szecsey A. A randomised controlled trial of prednisone in Alzheimer's disease. *Neurology* 2000;**55**:1067	Not published in a peer-reviewed journal article or is an ongoing trial
Knapp MJ, Gracon SI, Davis CS, Solomon PR, Pendlebury WW, Knopman DS. Efficacy and safety of high-dose tacrine: a 30-week evaluation. *Alzheimer Dis Assoc Disord* 1994;**8**(Suppl. 2):22–31	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-week randomised controlled trial of high-dose tacrine in patients with Alzheimer's disease. *JAMA* 1994;**271**:985–91	Not a disease modification trial
Knopman D, Schneider L, Davis K, Talwalker S, Smith F, Hoover T, *et al.* Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality, Tacrine Study Group. *Neurology* 1996;**47**:166–77	Not a disease modification trial
Knott V, Engeland C, Mohr E, Mahoney C, Ilivitsky V. Acute nicotine administration in Alzheimer's disease: an exploratory EEG study. *Neuropsychobiology* 2000;**41**:210–20	Not a disease modification trial
Knott V, Mohr E, Mahoney C, Engeland C, Ilivitsky V. Effects of acute nicotine administration on cognitive event-related potentials in tacrine-treated and non-treated patients with Alzheimer's disease. *Neuropsychobiology* 2002;**45**:156–60	Not a disease modification trial
Kolykhalov IV, Gavrilova SI, Kalyn Ia B, Selezneva ND, Fedorova Ia B. [Efficacy, safety and tolerability of a single dose of akatinol memantine in comparison to two-doses in patients with moderately expressed and moderately severe dementia in Alzheimer's disease.] *Zh Nevrol Psikhiatr Im S S Korsakova* 2012;**112**:35–9	Full text unavailable in English
Krishnan K, Charles H, Doraiswamy P, Mintzer J, Weisler R, Yu X, *et al.* Randomised, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. *Am J Geriatr Psychiatry* 2003;**160**:2003–11	Not a disease modification trial
Kruntoradova K, Mandelikova M, Mlcoch T, Dolezal T. Cost-effectiveness analysis of *Ginkgo biloba* extract (EGB761-tanakan) for the treatment of dementia in the Czech Republic. *Value Health* 2015;**18**:A756	Not published in a peer-reviewed journal article or is an ongoing trial
Kumar V, Anand R, Messina J, Hartman R, Veach J. An efficacy and safety analysis of Exelon in Alzheimer's disease patients with concurrent vascular risk factors. *Eur J Neurol* 2000;**7**:159–69	Not a disease modification trial
Kwak YS, Um SY, Son TG, Kim DJ. Effect of regular exercise on senile dementia patients. *Int J Sports Med* 2008;**29**:471–4	Not a disease modification trial
Kwok T, Lee J, Law CB, Pan PC, Yung CY, Choi KC, *et al.* A randomised placebo controlled trial of homocysteine lowering to reduce cognitive decline in older demented people. *Clinical Nutrition* 2011;**30**:297–302	Not a disease modification trial
Kwon JC, Kim EG, Kim JW, Kwon Oh D, Yoo BG, Yi HA, *et al.* A multicenter, open-label, 24-week follow-up study for efficacy on cognitive function of donepezil in Binswanger-type subcortical vascular dementia. *Am J Alzheimers Dis Other Demen* 2009;**24**:293–301	Not a disease modification trial
Kyowa Hakko Kirin Pharma, Inc. *NCT02127476 A Study of Single and Multiple Doses of KHK6640 in Subjects With Prodromal or Mild to Moderate Alzheimer's Disease.* URL: https://clinicaltrials.gov/ct2/show/NCT02127476 (accessed 29 January 2016)	No quantitative outcome relating to disease modification
Kyowa Hakko Kirin Pharma, Inc. *NCT02377713 A Single Dose Study of KHK6640 in Japanese Patients With Alzheimer's Disease*. URL: https://clinicaltrials.gov/ct2/show/NCT02377713 (accessed 29 January 2016)	No quantitative outcome relating to disease modification
Lanier ER, Sturge G, McClernon D, Brown S, Halman M, Sacktor N, *et al.* HIV-1 reverse transcriptase sequence in plasma and cerebrospinal fluid of patients with AIDS dementia complex treated with abacavir. *AIDS* 2001;**15**:747–51	Not a disease modification trial
Larsson V, Engedal K, Aarsland D, Wattmo C, Minthon L, Londos E. Quality of life and the effect of memantine in dementia with Lewy bodies and Parkinson's disease dementia. *Dement Geriatr Cogn Disord* 2011;**32**:227–34	Not a disease modification trial
Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, *et al.* A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Annals Neurol* 2010;**68**:521–34	Not a disease modification trial
Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomised trial of an extract of *Ginkgo biloba* for dementia. *JAMA* 1997;**278**:1327–32	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Leach L. Cognitive stimulation therapy improves cognition and quality of life in older people with dementia. *Evid Based Ment Health* 2004;**7**:19	Not a disease modification trial
Lee DA, Ngo LY, Adamiak B, Gelmont D. A confirmatory phase 3 randomised, double-blind, placebo-controlled study of the safety and effectiveness of immune globulin intravenous (human), 10% solution (gammagard liquid/kiovig) for the treatment of mild to moderate Alzheimer's disease. *Alzheimers Dement* 2011;**1**:S783–4	Not published in a peer-reviewed journal article or is an ongoing trial
Lee DY, Kim KW, Jhoo JH, Ryu SH, Choo H, Seo EH, *et al.* A multicenter, randomised, placebo-controlled, double-blind clinical trial of escitalopram on its atrophydelaying effect in Alzheimer's disease. *Alzheimers Dement* 2012;**8**(Suppl. 1):603	Not published in a peer-reviewed journal article or is an ongoing trial
Lee GY, Yip CC, Yu EC, Man DW. Evaluation of a computer-assisted errorless learning-based memory training program for patients with early Alzheimer's disease in Hong Kong: a pilot study. *Clin Interv Ageing* 2013;**8**:623–33	Not a disease modification trial
Lefevre G, Sedek G, Jhee SS, Leibowitz MT, Huang HL, Enz A, *et al.* Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in Alzheimer's disease patients. *Clin Pharmacol Ther* 2008;**83**:106–14	Not a disease modification trial
Lenz RA, Pritchett YL, Berry SM, Llano DA, Han S, Berry DA, *et al.* Adaptive, dose-finding Phase 2 trial evaluating the safety and efficacy of ABT-089 in mild to moderate Alzheimer disease. *Alzheimer Dis Assoc Disord* 2015;**29**:192–9	Not a disease modification trial
Leroi I, Atkinson R, Overshott R. Memantine improves goal attainment and reduces caregiver burden in Parkinson's disease with dementia. *Int J Geriatr Psychiatry* 2014;**29**:899–905	Not a disease modification trial
Leroi I, Brandt J, Reich SG, Lyketsos CG, Grill S, Thompson R, *et al.* Randomised placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. *Int J Geriatr Psychiatry* 2004;**19**:1–8	Not a disease modification trial
Leroi I, Overshott R, Byrne EJ, Daniel E, Burns A. Randomised controlled trial of memantine in dementia associated with Parkinson's disease. *Move Dis* 2009;**24**:1217–21	Not a disease modification trial
Levin OS, Batukaeva LA, Smolentseva IG, Amosova NA. [Efficacy and safety of memantine in dementia with Lewy bodies.] *Zh Nevrol Psikhiatr Im S S Korsakova* 2008;**108**:39–46	Full text unavailable in English
Levin OS, Batukaeva LA, Smolentseva IG, Amosova NA. Efficacy and safety of memantine in Lewy body dementia. *Neurosci Behav Physiol* 2009;**39**:597–604	Not a disease modification trial
Levy A, Brandeis R, Treves TA, Meshulam Y, Mawassi F, Feiler D, *et al.* Transdermal physostigmine in the treatment of Alzheimer's disease. *Alzheimer Dis Assoc Disord* 1994;**8**:15–21	Not a disease modification trial
Li CH, Liu CK, Yang YH, Chou MC, Chen CH, Lai CL. Adjunct effect of music therapy on cognition in Alzheimer's disease in Taiwan: a pilot study. *Neuropsychiatr Dis Treat* 2015;**11**:291–6	Not a disease modification trial
Liang E, Wagg J, Kurth M, Abushakra S. Effects of ELND005 (scyllo-inositol) on neuropsychiatric symptoms (NPS) in mild/moderate AD: correlations of ELND005 exposures to neuropsychiatric outcomes in a 78-week phase 2 study. *J Nutr Health Ageing* 2012;**16**:839	Not published in a peer-reviewed journal article or is an ongoing trial
Liang J, Li F, Wei C, Song H, Wu L, Tang Y, *et al.* Rationale and design of a multicenter, phase 2 clinical trial to investigate the efficacy of traditional Chinese medicine SaiLuoTong in vascular dementia. *J Stroke Cerebrovasc Dis* 2014;**23**:2626–34	Not a disease modification trial
Liang P, Wang Z, Qian T, Li K. Acupuncture stimulation of Taichong (Liv3) and Hegu (LI4) modulates the default mode network activity in Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 2014;**29**:739–48	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Likitjaroen Y, Meindl T, Friese U, Wagner M, Buerger K, Hampel H, *et al.* Longitudinal changes of fractional anisotropy in Alzheimer's disease patients treated with galantamine: a 12-month randomised, placebo-controlled, double-blinded study. *Eur Arch Psychiatry Clin Neurosci* 2012;**262**:341–50	Not a disease modification trial
Lin CH, Chen PK, Chang YC, Chuo LJ, Chen YS, Tsai GE, *et al.* Benzoate, a D-amino acid oxidase inhibitor, for the treatment of early-phase Alzheimer disease: a randomised, double-blind, placebo-controlled trial. *Biol Psychiatry* 2014;**75**:678–85	Not a disease modification trial
Lin CH, Chen PK, Chang YC, Chuo LJ, Chen YS, Tsai GE, *et al.* Enhancement of NMDA neurotransmission for the treatment of early-phase Alzheimer's disease. *J Neurochem* 2014;**130**:34	Not published in a peer-reviewed journal article or is an ongoing trial
Litvan I, Phipps M, Pharr VL, Hallett M, Grafman J, Salazar A. Randomised placebo-controlled trial of donepezil in patients with progressive supranuclear palsy. *Neurology* 2001;**57**:467–73	No participants with mild or moderate dementia
Liu X, Zhang J, Sun D, Fan Y, Zhou H, Fu B. Effects of fluoxetine on brain-derived neurotrophic factor serum concentration and cognition in patients with vascular dementia. *Clin Interv Ageing* 2014;**9**:411–18	Not a disease modification trial
Liu-Seifert H, Andersen S, Holdridge K, Siemers E. Delayed-start analyses of solanezumab phase 3 studies in mild Alzheimer's disease. *Neurology* 2015;**84**:P7.108	Not published in a peer-reviewed journal article or is an ongoing trial
Livingston GA, Sax KB, McClenahan Z, Blumenthal E, Foley K, Willison J, *et al.* Acetyl-l-carnitine in dementia. *Int J Geriatr Psychiatry* 1991;**6**:853–60	Not a disease modification trial
Lloret A, Badía MC, Mora NJ, Pallardó FV, Alonso MD, Viña J. Vitamin E paradox in Alzheimer's disease: it does not prevent loss of cognition and may even be detrimental. *J Alzheimers Dis* 2009;**17**:143–9	Not a disease modification trial
Loeb MB, Molloy D, Smieja M, Standish T, Goldsmith CH, Mahony J, *et al.* A randomised, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. *J Am Geriatr Soc* 2004;**52**:381–7	Not a disease modification trial
Lojkowska W, Ryglewicz D, Jedrzejczak T, Minc S, Jakubowska T, Jarosz H, *et al.* The effect of cholinesterase inhibitors on the regional blood flow in patients with Alzheimer's disease and vascular dementia. *J Neurol Sci* 2003;**216**:119–26	Not a disease modification trial
Lopez-Pousa S, Turon-Estrada A, Garre-Olmo J, Pericot-Nierga I, Lozano-Gallego M, Vilalta-Franch M, *et al.* Differential efficacy of treatment with acetylcholinesterase inhibitors in patients with mild and moderate Alzheimer's disease over a 6-month period. *Dement Geriatr Cogn Disord* 2005;**19**:189–95	Not a disease modification trial
Lott IT, Doran E, Nguyen VQ, Tournay A, Head E, Gillen DL. Down syndrome and dementia: a randomised, controlled trial of antioxidant supplementation. *Am J Med Genet A* 2011;**155A**:1939–48	Not a disease modification trial
Lu PH, Masterman DA, Mulnard R, Cotman C, Miller B, Yaffe K, *et al.* Preliminary results suggest testosterone therapy may benefit older patients with AD. *Brown Uni Geriatr Psychopharmacol Update* 2006;**10**:1–7	Not a disease modification trial
Lucas P, Li D, Lobello K, Liu E, Brashear HR, Styren S. Intravenous bapineuzumab in mild to moderate Alzheimer's disease: results from two double-blind, placebo-controlled phase 3 trials. *J Nutr Health Ageing* 2013;**17**:806–7	Not published in a peer-reviewed journal article or is an ongoing trial
Lucca U TM, Forloni G, Spagnoli A. Nonsteroidal antiinflammatory drug use in Alzheimer's disease. *Biol Psychiatry* 1994;**36**:854–6	Not a disease modification trial
Lyketsos CG, Reichman WE, Kershaw P, Zhu Y. Long-term outcomes of galantamine treatment in patients with Alzheimer disease. *Am J Geriatr Psychiatry* 2004;**12**:473–82	Not a disease modification trial
Magdolna P, Anna J, Agnes F, Gergely D, Csilla FO, Tamas HL, *et al.* [Achetylcholinesterase (AchE) inhibition and serum lipokines in Alzheimer's disease: Friend or foe?] *Neuropsychopharmacol Hung* 2012;**14**:19–27	Full text unavailable in English

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Maher-Edwards G, Watson C, Ascher J, Barnett C, Boswell D, Davies J, *et al.* Two randomised controlled trials of SB742457 in mild to moderate Alzheimer's disease. *Alzheimers Dement* 2015;**1**:23–36	Not a disease modification trial
Maher-Edwards G, Zvartau-Hind M, Hunter A, Gold M, Hopton G, Jacobs G, *et al.* Double-blind, controlled phase II study of a 5-HT6 receptor antagonist, SB-742457, in Alzheimer's disease. *Curr Alzheimer Res* 2010;**7**:374–85	Not a disease modification trial
Maina G, Fiori L, Torta R, Fagiani M, Ravizza L, Bonavita E, *et al.* Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study. *Neuropsychobiology* 1989;**21**:141–5	Not a disease modification trial
Maltby N, Broe GA, Creasey H, Jorm AF, Christensen H, Brooks WS. Efficacy of tacrine and lecithin in mild to moderate Alzheimer's disease: double blind trial. *BMJ* 1994;**308**:879–83	Not a disease modification trial
Marek GJ, Katz DA, Meier A, Greco NT, Zhang W, Liu W, *et al.* Efficacy and safety evaluation of HSD-1 inhibitor ABT-384 in Alzheimer's disease. *Alzheimers Dement* 2014;**10**(Suppl.):364–73	Not a disease modification trial
Marek G, Katz D, Meier A, Greco N, Zhang W, Liu W, *et al.* Evaluation of the efficacy and safety of the HSD-1 inhibitor ABT-384 in mild to moderate Alzheimer's disease. *Alzheimers Dement* 2012;**8**(Suppl. 1):602	Not published in a peer-reviewed journal article or is an ongoing trial
Marin DB, Bierer LM, Lawlor BA, Ryan TM, Jacobson R, Schmeidler J, *et al.* L-deprenyl and physostigmine for the treatment of Alzheimer's disease. *Psychiatry Res* 1995;**58**:181–9	Not a disease modification trial
Marsh L, Biglan K, Williams JR. Randomised placebo-controlled trial of memantine for dementia in Parkinson's disease. *Parkinsonism Relat Disord* 2009;**15**:S82	Not published in a peer-reviewed journal article or is an ongoing trial
Maruyama M, Tomita N, Iwasaki K, Ootsuki M, Matsui T, Nemoto M, *et al.* Benefits of combining donepezil plus traditional Japanese herbal medicine on cognition and brain perfusion in Alzheimer's disease: a 12-week observer-blind, donepezil monotherapy controlled trial. *J Am Geriatr Soc* 2006;**54**:869–71	Not published in a peer-reviewed journal article or is an ongoing trial
Masterman D, Awipi T, Ashford E, Nave S, Yoo K, Vellas B, *et al.* A nicotinic-alpha-7 partial agonist as adjunctive therapy to stable donepezil. *J Nutr Health Ageing* 2012;**16**:838–9	Not published in a peer-reviewed journal article or is an ongoing trial
Matsuda O. Cognitive stimulation therapy for Alzheimer's disease: the effect of cognitive stimulation therapy on the progression of mild Alzheimer's disease in patients treated with donepezil. *Int Psychogeriatr* 2007;**19**:241–52	Not a disease modification trial
Matsuda O, Shido E, Hashikai A, Shibuya H, Kouno M, Hara C, *et al.* Short-term effect of combined drug therapy and cognitive stimulation therapy on the cognitive function of Alzheimer's disease. *Psychogeriatrics* 2010;**10**:167–72	Not a disease modification trial
Maurer K, Ihl R, Dierks T, Frolich L. Clinical efficacy of *Ginkgo biloba* special extract EGb 761 in dementia of the Alzheimer type. *J Psychiat Res* 1997;**31**:645–55	Not a disease modification trial
McCarney R, Fisher P, Iliffe S, Haselen R, Griffin M, Meulen J, *et al. Ginkgo biloba* for mild to moderate dementia in a community setting: a pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. *Int J Geriatr Psychiatry* 2008;**23**:1222–30	Not a disease modification trial
McCarney R, Warner J, Iliffe S, Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol* 2007;**7**:30	Not a disease modification trial
McKeith I, Ser T, Spano P, Emre M, Wesnes K, Anand R, *et al.* Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000;**356**:2031–6	Not a disease modification trial
McKeith IG. The clinical trial protocol of the Metrifonate in Alzheimer's Trial (MALT). *Dement Geriatr Cogn Disord* 1998;**9**(Suppl. 2):2–7	Not a disease modification trial
McShane RH. Memantine plus donepezil improves physical and mental health in people with Alzheimer's disease. *Evid Based Ment Health* 2004;**7**:76	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Mellow AM, Sunderland T, Cohen RM, Lawlor BA, Hill JL, Newhouse PA, *et al.* Acute effects of high-dose thyrotropin releasing hormone infusions in Alzheimer's disease. *Psychopharmacology* 1989;**98**:403–7	Not a disease modification trial
Meyer JS, Chowdhury MH, Xu G, Li YS, Quach M. Donepezil treatment of vascular dementia. *Ann NY Acad Sci* 2002;**977**:482–6	Not a disease modification trial
Meyer JS, Rogers RL, McClintic K, Mortel KF, Lotfi J. Randomised clinical trial of daily aspirin therapy in multi-infarct dementia. A pilot study. *J Am Geriatr Soc* 1989;**37**:549–55	Not a disease modification trial
Minthon L, Edvinsson L, Gustafson L. Tacrine treatment modifies cerebrospinal fluid neuropeptide levels in Alzheimer's disease. *Dementia* 1994;**5**:295–301	Not a disease modification trial
Minthon L, Gustafson L, Dalfel G, Hagberg B, Nilsson K, Risberg J, *et al.* Oral tetrahydroaminoacridine treatment of Alzheimer's disease evaluated clinically and by regional cerebral blood flow and EEG. *Dementia* 1993;**4**:32–42	Not a disease modification trial
Mintzer JE, Kershaw P. The efficacy of galantamine in the treatment of Alzheimer's disease: comparison of patients previously treated with acetylcholinesterase inhibitors to patients with no prior exposure. *Int J Geriatr Psychiatry* 2003;**18**:292–7	Not a disease modification trial
Modrego PJ, Fayed N, Errea JM, Rios C, Pina MA, Sarasa M. Memantine versus donepezil in mild to moderate Alzheimer's disease: a randomised trial with magnetic resonance spectroscopy. *Eur J Neurol* 2010;**17**:405–12	Not a disease modification trial
Modrego PJ, Pina MA, Fayed N, Díaz M. Changes in metabolite ratios after treatment with rivastigmine in Alzheimer's disease: a nonrandomised controlled trial with magnetic resonance spectroscopy. *CNS Drugs* 2006;**20**:867–77	Not a disease modification trial
Moebius H, Loewen G, Dgetluck N, Hilt D. A randomised, double-blind, placebo-controlled, 24-week, phase 2b outcomes study of 3 different doses of encenicline or placebo in subjects with mild to moderate probable Alzheimer's disease. *Neurology* 2015;**84**:P7.100	Not published in a peer-reviewed journal article or is an ongoing trial
Mohr E, Knott V, Sampson M, Wesnes K, Herting R, Mendis T. Cognitive and quantified electroencephalographic correlates of cycloserine treatment in Alzheimer's disease. *Clin Neuropharmacol* 1995;**18**:28–38	Not a disease modification trial
Mohr E, Nair NP, Sampson M, Murtha S, Belanger G, Pappas B, *et al.* Treatment of Alzheimer's disease with sabeluzole: functional and structural correlates. *Clin Neuropharmacol* 1997;**20**:338–45	Not a disease modification trial
Mohs RC, Doody R, Morris J, Ieni J, Rogers S, Perdomo C, *et al.* A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* 2001;**57**:481–8	Not a disease modification trial
Mohs RC, Shiovitz TM, Tariot PN, Porsteinsson AP, Baker KD, Feldman PD. Atomoxetine augmentation of cholinesterase inhibitor therapy in patients with Alzheimer disease: 6-month, randomised, double-blind, placebo-controlled, parallel-trial study. *Am J Geriatr Psychiatry* 2009;**17**:752–9	Not a disease modification trial
Mok V, Wong A, Ho S, Leung T, Lam WWM, Wong KS. Rivastigmine in Chinese patients with subcortical vascular dementia. *Neuropsychiatr Dis Treat* 2007;**3**:943–8	Not a disease modification trial
Molinuevo JL, Berthier ML, Rami L. Donepezil provides greater benefits in mild compared to moderate Alzheimer's disease: implications for early diagnosis and treatment. *Geriatric Arch Gerontol Geriatr* 2011;**52**:18–22	Not a disease modification trial
Moller HJ, Hampel H, Hegerl U, Schmitt W, Walter K. Double-blind, randomised, placebo-controlled clinical trial on the efficacy and tolerability of a physostigmine patch in patients with senile dementia of the Alzheimer type. *Pharmacopsychiatry* 1999;**32**:99–106	Not a disease modification trial
Moller HJ, Maurer I, Saletu B. Placebo-controlled trial of the xanthine derivative propentofylline in dementia. *Pharmacopsychiatry* 1994;**27**:159–65	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Molloy DW, Standish TI, Almeida E, DiLoreto P, Lam-Au C, Guyatt GH. Doxycycline and rifampin for Alzheimer's disease – The DARAD clinical trial. *Eur Geriatr Med* 2010;**1**:S3	Not published in a peer-reviewed journal article or is an ongoing trial
Moreno Moreno MDJ. Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomised, placebo-controlled trial. *Clin Ther* 2003;**25**:178–93	Not a disease modification trial
Moretti DV. Alpha rhythm oscillations and MMSE scores are differently modified by transdermal or oral rivastigmine in patients with Alzheimer's disease. *Am J Neurodegener Dis* 2014;**3**:72–83	Not a disease modification trial
Moretti DV, Frisoni GB, Giuliano B, Zanetti O. Comparison of the effects of transdermal and oral rivastigmine on cognitive function and EEG markers in patients with Alzheimer's disease. *Front Ageing Neurosci* 2014;**6**:179	Not a disease modification trial
Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: an open 22-month study. *J Neurol Sci* 2002;**203–204**:141–6	Not published in a peer-reviewed journal article or is an ongoing trial
Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: a randomised, controlled, open 12-month study in 208 patients. *Am J Alzheimers Dis Other Demen* 2003;**18**:265–72	Not a disease modification trial
Moretti R, Torre P, Antonello RM, Cazzato G, Griggio S, Ukmar M, *et al.* Rivastigmine superior to aspirin plus nimodipine in subcortical vascular dementia: an open, 16-month, comparative study. *Int J Clin Pract* 2004;**58**:346–53	Not a disease modification trial
Moretti R, Torre P, Antonello RM, Cazzato G, Pizzolato G. Different responses to rivastigmine in subcortical vascular dementia and multi-infarct dementia. *Am J Alzheimers Dis Other Demen* 2008;**23**:167–76	Not a disease modification trial
Morgan J, Sethi KD. Rivastigmine for dementia associated with Parkinson's disease. *Curr Neurol Neurosci Rep* 2005;**5**:263–5	Not a disease modification trial
Mori E, Ikeda M, Kosaka K. Donepezil for dementia with Lewy bodies: a randomised, placebo-controlled trial. *Annals Neurol* 2012;**72**:41–52	Not a disease modification trial
Mori E, Ikeda M, Nagai R, Matsuo K, Nakagawa M, Kosaka K. Long-term donepezil use for dementia with Lewy bodies: results from an open-label extension of Phase III trial. *Alzheimers Res Ther* 2015;**7**:5	Not a disease modification trial
Mori S, Mori E, Iseki E, Kosaka K. Efficacy and safety of donepezil in patients with dementia with Lewy bodies: preliminary findings from an open-label study. *Psychiatry Clin Neurosci* 2006;**60**:190–5	Not a disease modification trial
Morillas-Ruiz JM, Rubio-Perez JM, Albaladejo MD, Zafrilla P, Parra S, Vidal-Guevara ML. Effect of an antioxidant drink on homocysteine levels in Alzheimer's patients. *J Neurol Sci* 2010;**299**:175–8	Not a disease modification trial
Morris JC, Cyrus PA, Orazem J, Mas J, Bieber F, Ruzicka BB, *et al.* Metrifonate benefits cognitive, behavioural, and global function in patients with Alzheimer's disease. *Neurology* 1998;**5**:1222–30	Not a disease modification trial
Moss DE, Berlanga P, Hagan MM, Sandoval H, Ishida C. Methanesulfonyl fluoride (MSF): a double-blind, placebo-controlled study of safety and efficacy in the treatment of senile dementia of the Alzheimer type. *Alzheimer Dis Assoc Disord* 1999;**13**:20–5	Not a disease modification trial
Mossello E, Tonon E, Caleri V, Tilli S, Cantini C, Cavallini MC, *et al.* Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a 'real world' study. *Arch Gerontol Geriatr* 2004;**38**(Suppl.):297–307	Not a disease modification trial
Mowla A, Mosavinasab M, Haghshenas H, Haghighi AB. Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial. *J Clin Psychopharmacol* 2007;**27**:484–7	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Mulnard RA, Cotman CW, Kawas C, Dyck CH, Sano M, Doody R, *et al.* Oestrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomised controlled trial. *JAMA* 2000;**283**:1007–15	Not a disease modification trial
Muniza R, Serraa CM, Reisberga B, Rojo JM, del Ser T, Casanova JP, *et al.* Cognitive-motor intervention in Alzheimer's disease: long-term results from the Maria Wolff trial. *J Alzheimers Dis* 2015;**45**:295–304	Not a disease modification trial
Muratorio A, Bonuccelli U, Nuti A, Battistini N, Passero S, Caruso V, *et al.* A neurotropic approach to the treatment of multi-infarct dementia using L-alpha-glycerylphosphorylchlorine. *Curr Ther Res Clin Exp* 1992;**52**:741–52	Not a disease modification trial
Na HR, Kim S, Choi SH, Yang DW, Bae HJ, Kim JE, *et al.* Donepezil treatment in Alzheimer's disease patients with and without cerebrovascular lesions: a preliminary report. *Geriatr Gerontol Int* 2011;**11**:90–7	Not a disease modification trial
Naber D, Greenspan A, Schreiner A. Efficacy and safety of risperidone in the treatment of elderly patients suffering from organic brain disease (organic brain syndrome): results from a double-blind, randomised, placebo-controlled clinical trial. *Psychopharmacology* 2007;**191**:1027–9	No participants with mild or moderate dementia
Nadeau SE, Malloy PF, Andrew ME. A crossover trial of bromocriptine in the treatment of vascular dementia. *Ann Neurol* 1988;**24**:270–2	Not a disease modification trial
Nakamura Y, Strohmaier C, Tamura K, Kataoka N, Nakano M, Oda S, *et al.* A 24-week, randomised, controlled study to evaluate the tolerability, safety and efficacy of 2 different titration schemes of the rivastigmine patch in Japanese patients with mild to moderate Alzheimer's disease. *Dement Geriatr Cogn Disord Extra* 2015;**5**:361–74	Not a disease modification trial
Nakano S, Asada T, Matsuda H, Uno M, Takasaki M. Donepezil hydrochloride preserves regional cerebral blood flow in patients with Alzheimer's disease. *J Nucl Med* 2001;**42**:1441–5	Not a disease modification trial
Nakasujja N, Miyahara S, Evans S, Lee A, Musisi S, Katabira E, *et al.* Randomised trial of minocycline in the treatment of HIV-associated cognitive impairment. *Neurology* 2013;**80**:196–202	Not a disease modification trial
Nakatsuka M, Nakamura K, Hamanosono R, Takahashi Y, Kasai M, Sato Y, *et al.* A cluster randomised controlled trial of nonpharmacological interventions for old-old subjects with a clinical dementia rating of 0.5: The Kurihara Project. *Dement Geriatr Cogn DisordExtra* 2015;**5**:221–32	Not a disease modification trial
Nappi G, Bono G, Merlo P, Borromei A, Caltagirone C, Lomeo C, *et al.* Long-term nicergoline treatment of mild to moderate senile dementia. Results of a multicentre, double-blind, placebo-controlled study. *Clin Drug Investig* 1997;**13**:308–16	Not a disease modification trial
Napryeyenko O, Borzenko I. *Ginkgo biloba* special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. *Arzneimittelforschung* 2007;**57**:4–11	Not a disease modification trial
Napryeyenko O, Sonnik G, Tartakovsky I. Efficacy and tolerability of *Ginkgo biloba* extract EGb 761 by type of dementia: analyses of a randomised controlled trial. *J Neurol Sci* 2009;**283**:224–9	Not a disease modification trial
Nasab NM, Bahrammi MA, Nikpour MR, Rahim F, Naghibis SN. Efficacy of rivastigmine in comparison to ginkgo for treating Alzheimer's dementia. *J Pak Med Assoc* 2012;**62**:677–80	Not a disease modification trial
Nascimento CMC, Teixeira CVL, Gobbi LTB, Gobbi S, Stella F. [A controlled clinical trial on the effects of exercise on neuropsychiatric disorders and instrumental activities in women with Alzheimer's disease.] *Braz J Phys Ther* 2012;**16**:197–204	Not a disease modification trial
Navia BA, Dafni U, Simpson D, Tucker T, Singer E, McArthur JC, *et al.* A phase I/II trial of nimodipine for HIV-related neurological complications. *Neurology* 1998;**51**:221–8	Not a disease modification trial
Neumann PJ, Hermann RC, Kuntz KM, Araki SS, Duff SB, Leon J, *et al.* Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology* 1999;**52**:1138–45	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Nicholas T, Knebel W, Gastonguay MR, Bednar MM, Billing CB, Landen JW, *et al.* Preliminary population pharmacokinetic modelling of pf-04360365, a humanised anti-amyloid monoclonal antibody, in patients with mild to moderate Alzheimer's disease. *Alzheimers Dement* 2009;**1**:253	Not published in a peer-reviewed journal article or is an ongoing trial
Nordberg A, Darreh-Shori T, Peskind E, Soininen H, Mousavi M, Eagle G, *et al.* Different cholinesterase inhibitor effects on CSF cholinesterases in Alzheimer patients. *Curr Alzheimer Res* 2009;**6**:4–14	Not a disease modification trial
Novak G, Brashear HR, Di J, Werth J, Booth K, Margolin R, *et al.* Efficacy and safety of monthly subcutaneous bapineuzumab. *Alzheimers Dement* 2014;**10**:25	Not published in a peer-reviewed journal article or is an ongoing trial
Novak PH, Moessler H, Gusev EI, Guekht AB. Cerebrolysin in vascular dementia: a randomised, placebo controlled study. *Alzheimers Dement* 2009;**1**:249	Not published in a peer-reviewed journal article or is an ongoing trial
O'Brien BJ, Goeree R, Hux M, Iskedjian M, Blackhouse G, Gagnon M, *et al.* Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. *J Am Geriatr Soc* 1999;**47**:570–8	Not a disease modification trial
O'Caoimh R, Healy L, Gao Y, Svendrovski A, Kerins DM, Eustace J, *et al.* Effects of centrally acting angiotensin-converting enzyme inhibitors on functional decline in patients with Alzheimer's disease. *J Alzheimers Dis* 2014;**40**:595–603	Not a disease modification trial
Ohnishi T, Sakiyama Y, Okuri Y, Kimura Y, Sugiyama N, Saito T, *et al.* The prediction of response to galantamine treatment in patients with mild to moderate Alzheimer's disease. *Curr Alzheimer Res* 2014;**11**:110–18	Not a disease modification trial
Olazarán J, Muñiz R. Cognitive intervention in the initial stages of Alzheimer's disease. *Res Pract Alzheimers Dis* 2006;**11**:376–80	Not a disease modification trial
Olazarán J, Muñiz R, Reisberg B, Peña-Casanova J, Ser T, Cruz-Jentoft AJ, *et al.* Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. *Neurology* 2004;**63**:2348–53	Not a disease modification trial
Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, *et al.* Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. *Br J Psychiatry* 2005;**187**:450–5	Not a disease modification trial
Orgeta V, Leung P, Yates L, Kang S, Hoare Z, Henderson C, *et al.* Individual cognitive stimulation therapy for dementia: a clinical effectiveness and cost-effectiveness pragmatic, multicentre, randomised controlled trial. *Health Technol Assess* 2015;**19**(64)	Not a disease modification trial
Orgogozo JM, Rigaud AS, Stöffler A, Möbius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomised, placebo-controlled trial (MMM 300). *Stroke* 2002;**33**:1834–9	Not a disease modification trial
Orrell M, Aguirre E, Spector A, Hoare Z, Woods RT, Streater A, *et al.* Maintenance cognitive stimulation therapy for dementia: single-blind, multicentre, pragmatic randomised controlled trial. *Br J Psychiatry* 2014;**204**:454–61	Not a disease modification trial
Orrell M, Yates LA, Burns A, Russell I, Woods RT, Hoare Z, *et al.* Individual cognitive stimulation therapy for dementia (iCST): study protocol for a randomised controlled trial. *Trials* 2012;**13**:172	Not a disease modification trial
Ortega L, Yassuda M, Nunes P, Aprahamian I, Santos F, Santos G, *et al.* The effects of a multiprofessional cognitive and functional rehabilitation program for patients with mild Alzheimer's disease. *Alzheimers Dement* 2011;**1**:S660–1	Not published in a peer-reviewed journal article or is an ongoing trial
Othman A, Meier A, William Ritchie C, Florian H, Gault LM, Tang Q. Efficacy and safety of the ALPHA7 agonist ABT-126 as a monotherapy treatment in mild to moderate Alzheimer's dementia: results of a phase 2b trial. *Alzheimers Dement* 2014;**10**:P137	Not published in a peer-reviewed journal article or is an ongoing trial
Ott BR, Blake LM, Kagan E, Resnick M. Open label, multicenter, 28-week extension study of the safety and tolerability of memantine in patients with mild to moderate Alzheimer's disease. *J Neurol* 2007;**254**:351–8	Not a disease modification trial

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TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Paasschen J, Clare L, Yuen KS, Woods RT, Evans SJ, Parkinson CH, *et al.* Cognitive rehabilitation changes memory-related brain activity in people with Alzheimer disease. *Neurorehabil Neural Repair* 2013;**27**:448–59	Not a disease modification trial
Panisset M, Gauthier S, Moessler H, Windisch M. Cerebrolysin in Alzheimer's disease: a randomised, double-blind, placebo-controlled trial with a neurotrophic agent. *J Neural Transm* 2002;**109**:1089–104	Not a disease modification trial
Pantoni L, Bianchi C, Beneke M, Inzitari D, Wallin A, Erkinjuntti T. The Scandinavian Multi-Infarct Dementia Trial: a double-blind, placebo-controlled trial on nimodipine in multi-infarct dementia. *J Neurol Sci* 2000;**175**:116–23	Not a disease modification trial
Pantoni L, Rossi R, Inzitari D, Bianchi C, Beneke M, Erkinjuntti T, *et al.* Efficacy and safety of nimodipine in subcortical vascular dementia: a subgroup analysis of the Scandinavian Multi-Infarct Dementia Trial. *J Neurol Sci* 2000;**175**:124–34	Not a disease modification trial
Pantoni L, Ser T, Soglian AG, Amigoni S, Spadari G, Binelli D, *et al.* Efficacy and safety of nimodipine in subcortical vascular dementia: a randomised placebo-controlled trial. *Stroke* 2005;**36**:619–24	Not a disease modification trial
Parnetti L, Ambrosoli L, Abate G, Azzini C, Balestreri R, Bartorelli L, *et al.* Posatirelin for the treatment of late-onset Alzheimer's disease: a double-blind multicentre study vs citicoline and ascorbic acid. *Acta Neurol Scand* 1995;**92**:135–40	Not a disease modification trial
Parnetti L, Chiasserini D, Andreasson U, Ohlson M, Huls C, Zetterberg H, *et al.* Changes in CSF acetyl- and butyrylcholinesterase activity after long-term treatment with AChE inhibitors in Alzheimer's disease. *Acta Neurol Scand* 2011;**124**:122–9	Not a disease modification trial
Paskavitz JF, Gunstad JJ, Samuel JE. Clock drawing and frontal lobe behavioural effects of memantine in Alzheimer's disease: a rater-blinded study. *Am J Alzheimers Dis Other Dement* 2006;**21**:454–9	Not a disease modification trial
Pasinetti G, Rosenberg P. Repurposing anti-hypertensive drugs for Alzheimer's disease. *Alzheimers Dement* 2012;**1**:707–P8	Not published in a peer-reviewed journal article or is an ongoing trial
Pasinetti GM, Rosenberg P. Repurposing cardiovascular drugs as Alzheimer's disease modifying agents. *J Nutr Health Ageing* 2012;**16**:822	Not published in a peer reviewed journal article or an ongoing trial
Patel KR. Biogen's Aducanumab raises hope that Alzheimer's can be treated at its source. *Manag Care* 2015;**24**:19	Not published in a peer-reviewed journal article or is an ongoing trial
Peng DT, Xu XH, Wang LN. [Efficiency and safety assessment of donepezil for treating mild and moderate Alzheimer disease.] *Chin J Clin Rehabil* 2005;**9**:170–2	Full text unavailable in English
Perryman KM, Fitten LJ. Quantitative EEG during a double-blind trial of THA and lecithin in patients with Alzheimer's disease. *J Geriatr Psychiatry Neurol* 1991;**4**:127–33	Not a disease modification trial
Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, *et al.* Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomised, controlled trial. *Am J Geriatr Psychiatry* 2006;**14**:704–15	Not a disease modification trial
Petit H, Doody RS, Pratt RD. *Donepezil Improves Cognition and Global Function in Alzheimer's Disease: Results from us and Multinational Phase III Clinical Trials*. 11th European College of Neuropsychopharmacology Congress Paris, France, 31 October–4 November 1998	Not published in a peer-reviewed journal article or is an ongoing trial
Pettegrew JW, Klunk WE, Panchalingam K, Kanfer JN, McClure RJ. Clinical and neurochemical effects of acetyl-L-carnitine in Alzheimer's disease. *Neurobiol Aging* 1995;**16**:1–4	Not a disease modification trial
Pfizer. *NCT00912288 A Phase 3, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled 26-Week Trial to Evaluate the Efficacy and Safety of Dimebon in Patients with Moderate-to-Severe Alzheimer's Disease.* URL: http://clinicaltrials.gov/show/NCT00912288 (accessed 29 January 2016)	Not published in a peer-reviewed journal article or is an ongoing trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Phillips MA, Childs CE, Calder PC, Rogers PJ. No effect of omega-3 fatty acid supplementation on cognition and mood in individuals with cognitive impairment and probable Alzheimer's disease: a randomised controlled trial. *Int J Mol Sci* 2015;**16**:24600–13	Not a disease modification trial
Pirttilä T, Wilcock G, Truyen L, Damaraju CV. Long-term efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicenter trial. *Eur J Neurol* 2004;**11**:734–41	Not a disease modification trial
Pitkälä KH, Pöysti MM, Laakkonen M-L, Tilvis RS, Savikko N, Kautiainen H, *et al.* Effects of the Finnish Alzheimer Disease Exercise Trial (FINALEX): a randomised controlled trial. *JAMA Intern Med* 2013;**173**:894–901	Not a disease modification trial
Pitkala K, Raivio M, Laakkonen ML, Tilvis R, Kautiainen H, Strandberg T. Effects of intensive exercise intervention on Alzheimer's patients – a randomised, controlled trial. *Eur Geriatr Med* 2011;**2**:S59	Not published in a peer-reviewed journal article or is an ongoing trial
Pitkala KH, Raivio MM, Laakkonen ML, Tilvis RS, Savikko N, Kautiainen H, *et al.* Effectiveness and costs of intensive exercise intervention on Alzheimer's patients – a randomised, controlled trial. *Eur Geriatr Med* 2013;**4**:S8	Not published in a peer-reviewed journal article or is an ongoing trial
Poewe W, Wolters E, Emre M, Onofrj M, Hsu C, Tekin S, *et al.* Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: an active treatment extension study. *Move Dis* 2006;**21**:456–61	Not a disease modification trial
Pomara N, Block R, Abraham J. Combined cholinergic precursor treatment and dihydroergotoxine mesylate in Alzheimer's disease. *IRCS J Med Sci* 1983;**11**:1048–9	Not a disease modification trial
Pomara N, Ott BR, Peskind E, Resnick E. Memantine treatment of cognitive symptoms in mild to moderate Alzheimer disease: secondary analyses from a placebo-controlled randomised trail. *Alzheimer Dis Assoc Disord* 2007;**21**:60–4	Not a disease modification trial
Poole Hoffmann V, Case M, Hake AM. Effects of treatment with solanezumab in patients with Alzheimer's disease who receive current standard of care. *J Nutr Health Ageing* 2013;**17**:847–8	Not published in a peer-reviewed journal article or is an ongoing trial
Poon P, Hui E, Dai D, Kwok T, Woo J. Cognitive intervention for community-dwelling older persons with memory problems: telemedicine versus face-to-face treatment. *Int J Geriatr Psychiatry* 2005;**20**:285–6	Not a disease modification trial
Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomised, double-blind, placebo-controlled trial. *Curr Alzheimer Res* 2008;**5**:83–9	Not a disease modification trial
Potkin SG, Alva G, Gunay I, Koumaras B, Chen M, Mirski D. A pilot study evaluating the efficacy and safety of rivastigmine in patients with mixed dementia. *Drugs Ageing* 2006;**23**:241–9	Not a disease modification trial
Prasher VP, Huxley A, Haque MS. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Down syndrome and Alzheimer's disease – pilot study. *Int J Geriatr Psychiatry* 2002;**17**:270–8	Not a disease modification trial
Pratt RD. Patient populations in clinical studies of donepezil in vascular dementia. *Int Psychogeriatr* 2003;**15**(Suppl. 1):195–200	Not a disease modification trial
Prentice N, Van Beck M, Dougall NJ, Moffoot APR, O'Carroll RE, Goodwin GM, *et al.* A double-blind, placebo-controlled study of tacrine in patients with Alzheimer's disease using SPET. *J Psychopharmacol* 1996;**10**:175–81	Not a disease modification trial
Pressman P, Gottfried JA. Journal Club: a randomised, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology* 2012;**79**:33–6	Not published in a peer-reviewed journal article or is an ongoing trial
Rabey J, Dobronevsky E, Marton RG, Aichenbau S, Khaigrech M. Improved cognitive function following treatment of Alzheimer's patients with repetitive transcranial magnetic stimulation (rTMS) interlaced with cognitive learning treatment. *Alzheimers Dement* 2011;**1**:S694–5	Not published in a peer-reviewed journal article or is an ongoing trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Rafii MS, Walsh S, Little JT, Behan K, Reynolds B, Ward C, *et al.* A phase II trial of huperzine A in mild to moderate Alzheimer disease. *Neurology* 2011;**76**:1389–94	Not a disease modification trial
Rankinen T. *NCT00083811 A Phase 3, Multi-Centre, Randomised, Double-Blind Placebo-Controlled Study to Evaluate the Safety and Tolerability of Dimebon (PF-01913539) for up to 26-Weeks in Patients with Mild to Moderate Alzheimer's Disease.* URL: http://clinicaltrials.gov/ct2/show/NCT0083811 (accessed 29 January 2016)	Not published in a peer-reviewed journal article or is an ongoing trial
Randolph C, Roberts JW, Tierney MC, Bravi D, Mouradian MM, Chase TN. D-cycloserine treatment of Alzheimer disease. *Alzheimer Dis Assoc Disord* 1994;**8**:198–205	Not a disease modification trial
Raskind M, Liang E, Sperling R, Boxer A, Ross J, Brody M, *et al.* Pharmacokinetics and pharmacodynamics of bapineuzumab following multiple intravenous infusions in patients with mild to moderate Alzheimer's disease. *Alzheimers Dement* 2009;**1**:415–16	Not published in a peer-reviewed journal article or is an ongoing trial
Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. *Arch Neurol* 2004;**61**:252–6	Not a disease modification trial
Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: a 6-month randomised, placebo-controlled trial with a 6-month extension. *Neurology* 2000;**54**:2261–8	Not a disease modification trial
Ravina B, Putt M, Siderowf A, Farrar JT, Gillespie M, Crawley A, *et al.* Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. *J Neurol Neurosurg Psychiatry* 2005;**76**:934–9	Not a disease modification trial
Rebok GW, Ball K, Guey LT, Jones RN, Kim H-Y, King JW, *et al.* Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. *J Am Geriatr Soc* 2014;**62**:16–24	Not a disease modification trial
Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ. A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch Neurol* 2006;**63**:49–54	Not a disease modification trial
Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ, *et al.* Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* 2003;**348**:1333–41	Not a disease modification trial
Reisberg B, Kenowsky S, Boksay I, Golomb J, Heller S, Ghimire S, *et al.* Memantine and comprehensive, individualised, person-centred management (CI-PCM) of Alzheimer's disease: a randomised controlled trial. *Alzheimers Dement* 2013;**1**:295–6	Not published in a peer-reviewed journal article or is an ongoing trial
Riekkinen M, Laakso MP, Jakala P, Riekkinen P Jr. Clonidine impairs sustained attention and memory in Alzheimer's disease. *Neuroscience* 1999;**92**:975–82	Not a disease modification trial
Riekkinen P, Kuikka J, Soininen H, Helkala EL, Hallikainen M, Riekkinen P. Tetrahydroaminoacridine modulates technetium-99 m labelled ethylene dicysteinate retention in Alzheimer's disease measured with single photon emission computed tomography imaging. *Neurosci Lett* 1995;**195**:53–6	Not a disease modification trial
Riekkinen P, Riekkinen M. THA improves word priming and clonidine enhances fluency and working memory in Alzheimer's disease. *Neuropsychopharmacology* 1999;**20**:357–64	Not a disease modification trial
Riekse RG, Li G, Petrie EC, Leverenz JB, Vavrek D, Vuletic S, *et al.* Effect of statins on Alzheimer's disease biomarkers in cerebrospinal fluid. *J Alzheimers Dis* 2006;**10**:399–406	No participants with mild or moderate dementia
Rigaud AS, André G, Vellas B, Touchon J, Pere JJ, Loria-Kanza Y. [Oestro-progestagen treatment combined with rivastigmine in menopausal women suffering from Alzheimer's disease. The results of a 28-weeks controlled study.] *Presse Med* 2003;**32**:1649–54	Full text unavailable in English
Rijpma A, Meulenbroek O, Van Hees AM, Sijben JW, Scheltens P, Olde Rikkert MG. Effects of a medical food on plasma micronutrient and fatty acid levels in mild to moderate Alzheimer's disease. *Clin Nutr* 2014;**33**:S193	Not published in a peer-reviewed journal article or is an ongoing trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Rijpma A, Meulenbroek O, van Hees AM, Sijben JW, Vellas B, Shah RC, *et al.* Effects of Souvenaid on plasma micronutrient levels and fatty acid profiles in mild and mild to moderate Alzheimer's disease. *Alzheimers Res Ther* 2015;**7**:51	Not a disease modification trial
Risner ME, Saunders AM, Altman JFB, Ormandy GC, Craft S, Foley IM, *et al.* Efficacy of rosiglitazone in a genetically defined population with mild to moderate Alzheimer's disease. *Pharmacogenomics J* 2006;**6**:246–54	Not a disease modification trial
Rive B, Vercelletto M, Damier FD, Cochran J, Francois C. Memantine enhances autonomy in moderate to severe Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;**19**:458–64	Not a disease modification trial
Rockwood K, Dai D, Mitnitski A. Patterns of decline and evidence of subgroups in patients with Alzheimer's disease taking galantamine for up to 48 months. *Int J Geriatr Psychiatry* 2008;**23**:207–14	Not a disease modification trial
Rockwood K, Fay S, Gorman M. The ADAS-Cog and clinically meaningful change in the VISTA clinical trial of galantamine for Alzheimer's disease. *Int J Geriatr Psychiatry* 2010;**25**:191–201	Not a disease modification trial
Rockwood K, Fay S, Song X, MacKnight C, Gorman M. Video-imaging synthesis of treating Alzheimer's disease I attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomised controlled trial. *CMAJ* 2006;**174**:1099–105	Not a disease modification trial
Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. *J Neurol Neurosurg Psychiatry* 2001;**71**:589–95	Not a disease modification trial
Rodriguez-Sanchez E, Criado-Gutierrez JM, Mora-Simon S, Muriel-Diaz MP, Gomez-Marcos MA, Recio-Rodriguez JI, *et al.* Physical activity program for patients with dementia and their relative caregivers: randomised clinical trial in primary health care (AFISDEMyF study). *BMC Neurol* 2014;**14**:63	Not a disease modification trial
Rogers J, Kirby LC, Hempelman SR, Berry DL, McGeer PL, Kaszniak AW, *et al.* Clinical trial of indomethacin in Alzheimer's disease. *Neurology* 1993;**43**:1609	Not a disease modification trial
Rogers S, Perdomo C, Friedhoff L. *Clinical Benefits are Maintained During Long-term Treatment of Alzheimer's Disease with the Acetylcholinesterase Inhibitor, E2020*. 8th European College of Neuropsychopharmacology Congress Venice, Italy, 30 September–4 October 1995	Not published in a peer-reviewed journal article or is an ongoing trial
Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. *Arch Intern Med* 1998;**158**:1021–31	Not a disease modification trial
Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;**50**:136–45	Not a disease modification trial
Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, Ieni J, *et al.* Donepezil improved cognitive and global function in mild to moderate Alzheimer disease. *Evid Based Med* 1998;**3**:155	Not a disease modification trial
Rogers SL, Friedhoff LT. *Donepezil Improves Cognition in Patients with Mild to Moderate AD: Results of ADAS-Cog Analysis in a 30-Week Phase III Study*. 10th European College of Neuropsychopharmacology Congress Vienna, Austria, 13–17 September 1997	Not published in a peer-reviewed journal article or is an ongoing trial
Rogers SL, Mohs RC, Friedhoff LT. *Donepezil (E2020) Improves Cognition and Function in Patients with Mild to Moderately Severe Alzheimer's Disease Results from Phase*. 150th Annual Meeting of the American Psychiatric Association San Diego, CA, 17–22 May 1997	Not published in a peer-reviewed journal article or is an ongoing trial
Román GC, Salloway S, Black SE, Royall DR, Decarli C, Weiner MW, *et al.* Randomised, placebo-controlled, clinical trial of donepezil in vascular dementia: differential effects by hippocampal size. *Stroke* 2010;**41**:1213–21	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Román GC, Wilkinson DG, Doody RS, Black SE, Salloway SP, Schindler RJ. Donepezil in vascular dementia: combined analysis of two large-scale clinical trials. *Dement Geriatr Cogn Disord* 2005;**20**:338–44	Not a disease modification trial
Rosenbloom MH, Barclay TR, Pyle M, Owens BL, Cagan AB, Anderson CP, *et al.* A single-dose pilot trial of intranasal rapid-acting insulin in apolipoprotein E4 carriers with mild-moderate Alzheimer's disease. *CNS Drugs* 2014;**28**:1185–9	Not a disease modification trial
Rosengarten B, Paulsen S, Molnar S, Kaschel R, Gallhofer B, Kaps M. Acetylcholine esterase inhibitor donepezil improves dynamic cerebrovascular regulation in Alzheimer patients. *J Neurol* 2006;**253**:58–64	Not a disease modification trial
Roshchina IF, Kolykhalov IV, Selezneva ND, Zharikov GA, Gerasimov NP, Gavrilova SI. [The influence of Cerebrolysin on the efficiency of subsequent therapy with amiridine++ in Alzheimer's disease patients (neuropsychological investigation).] *Zh Nevrol Psikhiatr Im S S Korsakova* 1999;**99**:43–6	Full text unavailable in English
Rosler M, Anand R, Cincin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, *et al.* Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ* 1999;**318**:633–40	Not a disease modification trial
Sabbagh M, Cummings J, Christensen D, Doody R, Farlow M, Liu L, *et al.* Evaluating the cognitive effects of donepezil 23 mg/d in moderate and severe Alzheimer's disease: analysis of effects of baseline features on treatment response. *BMC Geriatr* 2013;**13**:56	Not a disease modification trial
Sacktor N, Kieburtz K, Schifitto G, McDermott M, Bourgeois K, Palumbo D, *et al.* A randomised, double-blind, placebo-controlled trial of deprenyl and thioctic acid in human immunodeficiency virus-associated cognitive impairment. *Neurology* 1998;**50**:645–51	No participants with mild or moderate dementia
Sadowsky CH, Grossberg GT, Somogyi M, Meng X. Predictors of sustained response to rivastigmine in patients with Alzheimer's disease: a retrospective analysis. *Prim Care Companion J Clin Psychiatry* 2011;**13**:PCC.10m01101	Not a disease modification trial
Sahakian BJ, Coull JT. Tetrahydroaminoacridine (THA) in Alzheimer's disease: an assessment of attentional and mnemonic function using CANTAB. *Acta Neurol Scand Suppl* 1993;**149**:29–35	Not a disease modification trial
Sahakian BJ, Coull JT. Nicotine and tetrahydroaminoacradine: evidence for improved attention in patients with dementia of the Alzheimer type. *Drug Develop Res* 1994;**31**:80–8	Not a disease modification trial
Sainati SM ID, Talwalker S, Geis GS. *Results of a Double-Blind, Randomised, Placebo-Controlled Study of Celecoxib in the Treatment of Progression of Alzheimer's Disease.* Proceedings of the 6th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy, Stockholm, Sweden, 5–8 April 2000	Not published in a peer-reviewed journal article or is an ongoing trial
Saletu B, Anderer P, Fischhof PK, Lorenz H, Barousch R, Böhmer F. EEG mapping and psychopharmacological studies with denbufylline in SDAT and MID. *Biol Psychiatry* 1992;**32**:668–81	Not a disease modification trial
Saletu B, Hochmayer I, Grunberger J, Bohmer F, Paroubek J, Wicke L, *et al.* [Therapy of multi-infarct-dementia with nicergoline: double-blind, clinical, psychometric and EEG-imaging-investigation with two different drug administration schedules.] *Wien Med Wochenschr* 1987;**137**:513–24	Full text unavailable in English
Salloway S, Sperline R, Gregg K, Black R, Grundman M. Cognitive and functional outcomes from a phase II trial of bapineuzumab in mid to moderate Alzheimer's disease. *Neurology* 2009;**72**(Suppl. 3):A271	Not published in a peer-reviewed journal article or is an ongoing trial
Salloway S, Sperling R, Gregg K, Yu P, Joshi A, Lu M, *et al.* Incidence and clinical progression of placebo-treated amyloidnegative subjects with mild to moderate Alzheimer's disease (AD): results from the phase III PET substudies of bapineuzumab and solanezumab. *Alzheimers Dement* 2013;**9**(Suppl. 1):888–9	Not published in a peer-reviewed journal article or is an ongoing trial
Salloway S, Sperling R, Honig L, Porsteinsson A, Sabbagh M, Liu E, *et al.* A randomised, double-blind, placebo-controlled clinical trial of intravenous bapineuzumab in patients with Alzheimer's disease who are apolipoprotein E 4 non-carriers. *Eur J Neurol* 2012;**19**:70	Not published in a peer-reviewed journal article or is an ongoing trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Salotti P, De Sanctis B, Clementi A, Fernandez Ferreira M, De Silvestris T. Evaluation of the efficacy of a cognitive rehabilitation treatment on a group of Alzheimer's patients with moderate cognitive impairment: a pilot study. *Aging Clin Exp Res* 2013;**25**:403–9	Not a disease modification trial
Salva A, Andrieu S, Fernandez E, Schiffrin E, Moulin J, Decarli B, *et al.* Health and nutrition promotion program for patients with dementia (NutriAlz): cluster randomised trial. *J Nutr Health Aging* 2011;**15**:822–30	Not a disease modification trial
Salva A, Andrieu S, Fernandez E, Schiffrin EJ, Moulin J, Decarli B, *et al.* Health and nutritional promotion program for patients with dementia (NutriAlz Study): design and baseline data. *J Nutr Health Aging* 2009;**13**:529–37	Not a disease modification trial
Samorajski T, Vroulis GA, Smith RC. Piracetam plus lecithin trials in senile dementia of the Alzheimer type. *Ann NY Acad Sci* 1985;**444**:478–81	Not a disease modification trial
Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med* 1997;**336**:1216–22	Not a disease modification trial
Sanofi, ICD CSD. *NCT00104013 A Randomised, Multicenter, Double-Blind, Placebo-Controlled, 18-Month Study of the Efficacy of SR57746A in Patients with Mild to Moderate Dementia of the Alzheimer.* URL: https://clinicaltrials.gov/ct2/show/NCT00104013 (accessed 29 January 2016)	Not published in a peer-reviewed journal article or is an ongoing trial
Sanofi, ICD CSD. *NCT00103649 18-month Study of the Efficacy of Xaliproden (SR57746A) in Patients with Mild to Moderate Dementia of the Alzheimer.* URL: https://clinicaltrials.gov/ct2/show/NCT00103649 (accessed 29 January 2016)	Not published in a peer-reviewed journal article or is an ongoing trial
Santens P, Ventura M. Donepezil in the treatment of mild to moderate Alzheimer's disease: report of a Belgian multicenter study. *Acta Neurol Belg* 2003;**103**:159–63	Not a disease modification trial
Saxton J, Hofbauer RK, Woodward M, Gilchrist NL, Potocnik F, Hsu HA, *et al.* Memantine and functional communication in Alzheimer's disease: results of a 12-week, international, randomised clinical trial. *J Alzheimers Dis* 2012;**28**:109–18	Not a disease modification trial
Schecker M, Pirnay-Dummer P, Schmidtke K, Hentrich-Hesse T, Borchardt D. Cognitive interventions in mild Alzheimer's disease: a therapy-evaluation study on the interaction of medication and cognitive treatment. *Dement Geriatr Cogn Disord Extra* 2013;**3**:301–11	Not a disease modification trial
Scheltens NME, Van Berckel BNM, Boellaard R, Barkhof F, Van Der Flier WM, Kamphuis PJGH, *et al.* A Dutch 24-week randomised controlled study exploring the effect of a nutritional intervention on brain glucose metabolism in early Alzheimer's disease (NL-ENIGMA); rationale and design. *Eur Geriatr Med* 2014;**5**:91	Not published in a peer-reviewed journal article or is an ongoing trial
Scheltens P, Kamphuis PJGH, Verhey FRJ, Olde Rikkert MGM, Wurtman RJ, Wilkinson D, *et al.* Efficacy of a medical food in mild Alzheimer's disease: a randomised, controlled trial. *Alzheimers Dement* 2010;**6**:1–10.e1	Not a disease modification trial
Scheltens P, Sperling R, Salloway S, Fox N. Bapineuzumab IV phase 3 results. *J Nutr Health Aging* 2012;**16**:797	Not published in a peer-reviewed journal article or is an ongoing trial
Scheltens P, Stam C, Shah R, Bennett D, Wieggers R, Hartmann T, *et al.* Medical nutrition in disease management of Alzheimer's patients. *Clin Nutr* 2013;**32**:35	Not published in a peer-reviewed journal article or is an ongoing trial
Scheltens P, Verhey FRJ, Rikkert MGMO, Kamphuis PJGH, Wilkinson D, Kurz A. The efficacy of a medical food (Souvenaid) in Alzheimer's disease: results from the first trial and design of future trials. *Alzheimers Dement* 2009;**1**:258–9	Not published in a peer-reviewed journal article or is an ongoing trial
Scherder E, Knol D, van Tol MJ, van Someren E, Deijen JB, Swaab D, *et al.* Effects of high-frequency cranial electrostimulation on the rest-activity rhythm and salivary cortisol in Alzheimer's disease: a pilot study. *Dement Geriatr Cogn Disord* 2006;**22**:267–72	Not a disease modification trial
Scherder EJ, Tol MJ, Swaab DF. High-frequency cranial electrostimulation (CES) in patients with probable Alzheimer's disease. *Am J Phys Med Rehabil* 2006;**85**:614–18	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Schiffczyk C, Romero B, Jonas C, Muller F, Riepe MW. Efficacy of multimodal intervention for people with Alzheimer's disease. *Alzheimers Dement* 2013;**1**:654	Not published in a peer-reviewed journal article or is an ongoing trial
Schifitto G, Navia BA, Yiannoutsos CT, Marra CM, Chang L, Ernst T, *et al.* Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study. *AIDS* 2007;**21**:1877–86	Not a disease modification trial
Schifitto G, Zhang J, Evans SR, Sacktor N, Simpson D, Millar LL, *et al.* A multicenter trial of selegiline transdermal system for HIV-associated cognitive impairment. *Neurology* 2007;**69**:1314–21	Not a disease modification trial
Schmidt R, Ropele S, Pendl B, Ofner P, Enzinger C, Schmidt H, *et al.* Longitudinal multimodal imaging in mild to moderate Alzheimer disease: a pilot study with memantine. *J Neurol Neurosurg Psychiatry* 2008;**79**:1312–17	Not a disease modification trial
Schmitt F, Farlow M, Olin J. Effects of rivastigmine on executive function in Parkinson's disease dementia: results from a 24-week placebo-controlled clinical trial. *Ann Neurol* 2009;**66**:48	Not published in a peer-reviewed journal article or is an ongoing trial
Schmitt FA, Aarsland D, Bronnick KS, Meng X, Tekin S, Olin JT. Evaluating rivastigmine in mild to moderate Parkinson's disease dementia using ADAS-Cog items. *Am J Alzheimers Dis Other Demen* 2010;**25**:407–13	Not a disease modification trial
Schmitt FA, Aarsland D, Bronnick KS, Olin JT, Meng X. Evaluating cognitive effects of oral rivastigmine using subscales and items of the ADAS-Cog in patients with mild to moderate Parkinson's disease dementia. *Am J Geriatr Psychiatry* 2010;**1**:79	Not published in a peer-reviewed journal article or is an ongoing trial
Schmitt FA, Farlow MR, Meng X, Tekin S, Olin JT. Efficacy of rivastigmine on executive function in patients with Parkinson's disease dementia. *CNS Neurosci Ther* 2010;**16**:330–6	Not a disease modification trial
Schmitt FA, Saxton J, Ferris SH, Mackell J, Sun Y. Evaluation of an 8-item Severe Impairment Battery (SIB-8) vs. the full SIB in moderate to severe Alzheimer's disease patients participating in a donepezil study. *J Clin Pract* 2013;**67**:1050–6	Not a disease modification trial
Schneider L, Porsteinsson A, Farlow M, Shimakura A, Nakagawa M, Iwakami N. The neuroprotective and neurotrophic agent T-817MA for Alzheimer's disease: randomised, double-blind, placebo controlled proof-of-concept trial outcomes. *Alzheimers Dement* 2013;**1**:530–1	Not published in a peer-reviewed journal article or is an ongoing trial
Schneider LS, DeKosky ST, Farlow MR, Tariot PN, Hoerr R, Kieser M. A randomised, double-blind, placebo-controlled trial of two doses of *Ginkgo biloba* extract in dementia of the Alzheimer's type. *Curr Alzheimer Res* 2005;**2**:541–51	Not a disease modification trial
Schneider LS, Farlow M. Combined tacrine and oestrogen replacement therapy in patients with Alzheimer's disease. *Ann NY Acad Sci* 1997;**826**:317–22	Not a disease modification trial
Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of oestrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. *Neurology* 1996;**46**:1580–4	Not a disease modification trial
Schneider LS, Farlow MR, Pogoda JM. Potential role for oestrogen replacement in the treatment of Alzheimer's dementia. *Am J Med* 1997;**103**:46–50	Not a disease modification trial
Schwam E, Evans R, Nicholas T, Chew R, Davidson W, Ambrose D, *et al.* PF-04447943: A phase II controlled clinical trial of a selective pde9a inhibitor in Alzheimer's disease. *Alzheimers Dement* 2011;**1**:695	Not published in a peer-reviewed journal article or is an ongoing trial
Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, *et al.* Efficacy of donepezil in early-stage Alzheimer disease: a randomised placebo-controlled trial. *Arch Neurol* 2004;**61**:1852–6	Not a disease modification trial
Seltzer B, Zolnouni P, Nunez M, Goldman R, Noble Y, Kumar D, *et al. Donepezil Treatment Improves Cognitive Performance in Patients with Very Mild Alzheimer's Disease*. European Neuropsychopharmacology; 15th International Congress of the European College of Neuropsychopharmacology, Barcelona, Spain, 5–9 October, 2002	Not published in a peer-reviewed journal article or is an ongoing trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Ser T, Lovestone S, Boada-Rovira M, Dubois B, Hull M, Rinne J, *et al.* A phase II randomised, double-blind, parallel group, 26-week study of GSK-3 inhibitor tideglusib in Alzheimer's disease (argo trial). *Alzheimers Dement* 2013;**1**:689–90	Not published in a peer-reviewed journal article or is an ongoing trial
Ser TD, Lovestone S, Rovira MB, Dubois B, Hull M, Rinne J, *et al.* Argo trial. *Alzheimers Dement* 2012;**1**:455–6	Not published in a peer-reviewed journal article or is an ongoing trial
Shah RC, Matthews DC, Andrews RD, Capuano AW, Fleischman DA, VanderLugt JT, *et al.* An evaluation of MSDC-0160, a prototype mTOT modulating insulin sensitiser, in patients with mild Alzheimer's disease. *Curr Alzheimer Res* 2014;**11**:564–73	Not a disease modification trial
Shankle WR, Hara J. Longitudinal measure of IVIG treatment effect in patients with Alzheimer's and Lewy body disease. *Alzheimers Dement* 2009;**1**:430	Not published in a peer-reviewed journal article or is an ongoing trial
Shatenstein B, Kergoat M, Reid I, Chicoine ME. Dietary intervention in older adults with early-stage Alzheimer dementia: early lessons learned. *J Nutr Health Ageing* 2008;**12**:461–9	Not a disease modification trial
Sheehan B, Phillips P, Juszczak E, Adams J, Baldwin A, Ballard C, *et al.* DOMINO-AD protocol: donepezil and memantine in moderate to severe Alzheimer's disease – a multicentre RCT. *Trials* 2009;**10**:57	Not a disease modification trial
Shifu X, Heqin Y, Peifen Y, Luning W, Jianjun J, Xin M, *et al.* Efficacy of FPF 1070 (Cerebrolysin) in patients with Alzheimer's disease. A multicentre, randomised, double-blind, placebo-controlled trial. *Clin Drug Investig* 2000;**19**:43–53	Not a disease modification trial
Shikiar R, Shakespeare A, Sagnier PP, Wilkinson D, McKeith I, Dartigues JF, *et al.* The impact of metrifonate therapy on caregivers of patients with Alzheimer's disease: results from the MALT clinical trial. Metrifonate in Alzheimer's Disease Trial. *J Am Geriatr Soc* 2000;**48**:268–74	Not a disease modification trial
Shimizu S, Kanetaka H, Hirose D, Sakurai H, Hanyu H. Differential effects of acetylcholinesterase inhibitors on clinical responses and cerebral blood flow changes in patients with Alzheimer's disease: a 12-month, randomised, and open-label trial. *Dement Geriatr Cogn Disord Extra* 2015;**5**:135–46	Not a disease modification trial
Shinto L, Quinn J, Montine T, Dodge HH, Woodward W, Baldauf-Wagner S, *et al.* A randomised placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. *J Alzheimers Dis* 2014;**38**:111–20	Not a disease modification trial
Shrotriya RC, Cutler NR, Sramek JJ, Veroff AE, Hironaka DY. Efficacy and safety of BMY 21,502 in Alzheimer disease. *Ann Pharmacother* 1996;**30**:1376–80	Not a disease modification trial
Sidtis JJ, Gatsonis C, Price RW, Singer EJ, Collier AC, Richman DD, *et al.* Zidovudine treatment of the AIDS dementia complex: results of a placebo-controlled trial. *Ann Neurol* 1993;**33**:343–9	Not a disease modification trial
Siemers E, Henley D, Sundell K, Sethuraman G, Dean R, Wrobleski K, *et al.* Evaluating semagacestat, a gammasecretase inhibitor, in a phase iii trial. *Alzheimers Dement* 2011;**1**:484–5	Not published in a peer-reviewed journal article or is an ongoing trial
Silva HA, Pathmeswaran A, Gunatilake SB. Efficacy of rivastigmine on activities of daily living in Sri Lankan patients with Alzheimer disease and on improving caregiver burden: a prospective study. *Ceylon Med J* 2005;**50**:106–9	Not a disease modification trial
Sinforiani E, Iannuccelli M, Mauri M, Costa A, Merlo P, Bono G, Nappi G. Neuropsychological changes in demented patients treated with acetyl-L-carnitine. *Int J Clin Pharmacol Res* 1989;**10**:69–74	Unable to find a copy of the full text
Small G, Erkinjuntti T, Kurz A, Lilienfeld S. Galantamine in the treatment of cognitive decline in patients with vascular dementia or Alzheimer's disease with cerebrovascular disease. *CNS Drugs* 2003;**17**:905–14	Not a disease modification trial
Spagnoli A, Lucca U, Menasce G, Bandera L, Cizza G, Forloni G, *et al.* Long-term acetyl-L-carnitine treatment in Alzheimer's disease. *Neurology* 1991;**41**:1726–32	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Spector A, Orrell M, Woods B. Cognitive Stimulation Therapy (CST): effects on different areas of cognitive function for people with dementia. *Int J Geriatr Psychiatry* 2010;**25**:1253–8	Not a disease modification trial
Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, Butterworth M, *et al.* Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia. *Br J Psychiatry* 2003;**183**:248–54	Not a disease modification trial
Spector A, Woods B, Orrell M. Cognitive stimulation for the treatment of Alzheimer's disease. *Expert Rev Neurother* 2008;**8**:751–7	Not a disease modification trial
Spilich GJ, Wannenmacher W, Duarte A, Buendia R, Gomez JT, Ramirez S, *et al.* Efficacy of pyritinol versus hydergine upon cognitive performance in patients with senile dementia of the Alzheimer's type: a double-blind multi-centre trial. *Alzheimers Res* 1996;**2**:79–84	Not a disease modification trial
Sramek JJ, Viereck C, Huff FJ, Wardle T, Hourani J, Stewart JA, *et al.* A 'bridging' (safety/tolerance) study of besipirdine hydrochloride in patients with Alzheimer's disease. *Life Sci* 1995;**57**:1241–8	Not a disease modification trial
Standridge JB. Donepezil did not reduce the rate of institutionalisation or disability in people with mild to moderate Alzheimer's disease. *Evid Based Ment Health* 2004;**7**:112	Not a disease modification trial
Steele LS, Glazier RH. Is donepezil effective for treating Alzheimer's disease? *Can Fam Physician*1999;**45**:917–19	Not a disease modification trial
Stein MS, Scherer SC, Ladd KS, Harrison LC. A randomised controlled trial high-dose vitamin D2 followed by intranasal insulin in Alzheimer's disease. *J Alzheimers Dis* 2011;**26**:477–84	Not a disease modification trial
Stein AM, Vital TM, Coelho FGM, Andrade LP, Pereira JR, Garuffi M, *et al.* Aerobic exercise training effect on cognitive functions, neuropsychiatric disorders, functionality, quality of life and lipid profile in elderly with Alzheimer's disease. *Eur Geriatr Med* 2014;**5**:105–6	Not published in a peer-reviewed journal article or is an ongoing trial
Stern Y, Sano M, Mayeux R Long-term administration of oral physostigmine in Alzheimer's disease. *Neurology* 1988;**38**:1837–41	Not a disease modification trial
Storey P HL, Duke L, Callaway R, Marson D. Does chronic oral physostigmine alter the course of Alzheimer's disease? *Neurobiol Ageing* 1992;**13**(Suppl. 1):126	Not published in a peer-reviewed journal article or is an ongoing trial
Stott DJ, MacIntosh G, Lowe GDO, Rumley A, McMahon AD, Langhorne P, *et al.* Randomised controlled trial of homocysteine-lowering vitamin treatment in elderly patients with vascular disease. *Am J Clin Nutr* 2005;**82**:1320–6	Not a disease modification trial
Streater A, Spector A, Aguirre E, Hoe J, Hoare Z, Woods R, *et al.* Maintenance cognitive stimulation therapy (CST) in practice: study protocol for a randomised controlled trial. *Trials* 2012;**13**:91	Not a disease modification trial
Stubendorff K, Larsson V, Ballard C, Minthon L, Aarsland D, Londos E. Treatment effect of memantine on survival in dementia with Lewy bodies and Parkinson's disease with dementia: a prospective study. *BMJ Open* 2014;**4**:e005158	Not a RCT/CCT
Suh GH, Jung HY, Lee CU, Choi S, Korean Galantamine Study G. Economic and clinical benefits of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population: a 52-week prospective study. *J Korean Med Sci* 2008;**23**:10–17	Not a disease modification trial
Suh GH, Jung HY, Lee CU, Lee SK, Lee NJ, Kim JH. [Effect of galantamine on caregiver time and activities of daily living in mild to moderate Alzheimer's disease: a 1-year prospective study.] *J Korean Geriatr Soc* 2007;**11**:74–82	Full text unavailable in English
Suh GH, Jung HY, Lee CU, Oh BH, Lee SK, Lee N, *et al.* Effect of the apolipoprotein E epsilon4 allele on the efficacy and tolerability of galantamine in the treatment of Alzheimer's disease. *Dement Geriatr Cogn Disord* 2006;**21**:33–9	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Suh GH, Yeon Jung H, Uk Lee C, Hoon Oh B, Nam Bae J, Jung HY, *et al.* A prospective, double-blind, community-controlled comparison of three doses of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population. *Clinical Therapeutics* 2004;**26**:1608–18	Not a disease modification trial
Sun Y, Lu C-J, Chien K-L, Chen S-T, Chen R-C. Efficacy of multivitamin supplementation containing vitamins B6 and B12 and folic acid as adjunctive treatment with a cholinesterase inhibitor in Alzheimer's disease: a 26-week, randomised, double-blind, placebo-controlled study in Taiwanese patients. *Clin Ther* 2007;**29**:2204–14	Not a disease modification trial
Suzuki T, Futami S, Igari Y, Matsumura N, Watanabe K, Nakano H, *et al.* A Chinese herbal medicine, choto-san, improves cognitive function and activities of daily living of patients with dementia: a double-blind, randomised, placebo-controlled study. *J Am Geriatr Soc* 2005;**53**:2238–40	Not a disease modification trial
Tadaka E, Kanagawa K. A randomised controlled trial of a group care program for community-dwelling elderly people with dementia. *Jpn J Nurs Sci* 2004;**1**:19–25	Not a disease modification trial
Tadaka E, Kanagawa K. Effects of reminiscence group in elderly people with Alzheimer disease and vascular dementia in a community setting. *Geriatr Gerontol Int* 2007;**7**:167–73	Not a disease modification trial
Tajadini H, Saifadini R, Choopani R, Mehrabani M, Kamalinejad M, Haghdoost AA. Herbal medicine Davaie Loban in mild to moderate Alzheimer's disease: a 12-week randomised double-blind placebo-controlled clinical trial. *Complement Ther Med* 2015;**23**:767–72	Not a disease modification trial
Takahashi T, Matsushita H. Long-term effects of music therapy on elderly with moderate/severe dementia. *J Music Ther* 2006;**43**:317–33	Not a disease modification trial
Tariot P, Sabbagh M, Flitman S, Reyes P, Taber I, Seely L. A safety, tolerability and pharmacokinetic study of Dimebon in patients with Alzheimer's disease already receiving donepezil. *Alzheimers Dement* 2009;**5**:251	Not published in a peer-reviewed journal article or is an ongoing trial
Tariot P, Salloway S, Yardley J, Mackell J, Moline M. Long-term safety and tolerability of donepezil 23 mg in patients with moderate to severe Alzheimer's disease. *BMC Res Notes* 2012;**5**:283	Not a disease modification trial
Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomised controlled trial. *JAMA* 2004;**291**:317–24	Not a disease modification trial
Tariot PN, Goldstein B, Podgorski CA, Cox C, Frambes N. Short-term administration of selegiline for mild to moderate dementia of the Alzheimer's type. *Am J Geriatr Psychiatry* 1998;**6**:145–54	Not a disease modification trial
Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomised, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 2000;**54**:2269–76	Not a disease modification trial
Tarraga L, Boada M, Modinos G, Espinosa A, Diego S, Morera A, *et al.* A randomised pilot study to assess the efficacy of an interactive, multimedia tool of cognitive stimulation in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2006;**77**:1116–21	Not a disease modification trial
Teipel SJ, Drzezga A, Bartenstein P, Moller HJ, Schwaiger M, Hampel H. Effects of donepezil on cortical metabolic response to activation during 18FDG-PET in Alzheimer's disease: a double-blind cross-over trial. *Psychopharmacology* 2006;**187**:86–94	Not a disease modification trial
Thai LJ, Carta A, Clarke WR, Ferris SH, Friedland RP, Petersen RC, *et al.* A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. *Neurology* 1996;**47**:705–11	Not a disease modification trial
Thal L, Grundman M, Berg J, Ernstrom K, Margolin R, Pfeiffer E, *et al.* Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology* 2003;**61**:1498–502	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Thal LJ, Calvani M, Amato A, Carta A. A 1-year controlled trial of acetyl-l-carnitine in early-onset AD. *Neurology* 2000;**55**:805–10	Not a disease modification trial
Thal LJ, Ferguson JM, Mintzer J, Raskin A, Targum SD. A 24-week randomised trial of controlled-release physostigmine in patients with Alzheimer's disease. *Neurology* 1999;**52**:1146–52	Not a disease modification trial
Thal LJ, Forrest M, Loft H, Mengel H. Lu 25–109, a muscarinic agonist, fails to improve cognition in Alzheimer's disease. Lu25–109 Study Group. *Neurology* 2000;**54**:421–6	Not a disease modification trial
Thal LJ, Fuld PA, Masur DM, Sharpless NS. Oral physostigmine and lecithin improve memory in Alzheimer disease. *Ann Neurol* 1983;**13**:491–6	Not a disease modification trial
Thal LJ, Masur DM, Sharpless NS. Acute and chronic effects of oral physostigmine and lecithin in Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 1986;**10**:627–36	Not a disease modification trial
Thal LJ, Schwartz G, Sano M, Weiner M, Knopman D, Harrell L, *et al.* A multicenter double-blind study of controlled-release physostigmine for the treatment of symptoms secondary to Alzheimer's disease. Physostigmine Study Group. *Neurology* 1996;**47**:1389–95	Not a disease modification trial
Thomas AJ, Burn DJ, Rowan EN, Littlewood E, Newby J, Cousins D, *et al.* A comparison of the efficacy of donepezil in Parkinson's disease with dementia and dementia with Lewy bodies. *Int J Geriatr Psychiatry* 2005;**20**:938–44	Not a disease modification trial
Thompson ITL, Filley CM, Mitchell WD, Culig KM, LoVerde M, Byyny RL. Lack of efficacy of hydergine in patients with Alzheimer's disease. *N Engl J Med* 1990;**323**:445–8	Not a disease modification trial
Tian J, Shi J, Miao Y, Wei M. Efficacy and safety of an herbal therapy in patients with early stage of Alzheimer's disease: a 24-week randomised phase III trial. *Alzheimers Dement* 2011;**1**:790	Not a disease modification trial
Tian J, Shi J, Wei M, Qin R, Chen Y, Wang Y. Efficacy and safety of FFDS tablets in people with mild to moderate vascular dementia: a 24-week randomised, double-blind, placebo, parallel-controlled trial. *Alzheimers Dement* 2013;**1**:670–1	Not published in a peer-reviewed journal article or is an ongoing trial
Tinklenberg JR, Kraemer HC, Yaffe K, Ross L, Sheikh J, Ashford JW, *et al.* Donepezil treatment and Alzheimer disease: can the results of randomised clinical trials be applied to Alzheimer disease patients in clinical practice? *Am J Geriatr Psychiatry* 2007;**15**:953–60	Not a disease modification trial
Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Effects of extended-release memantine (28 MG/DAY) on activities of daily living in patients with moderate to severe Alzheimer's disease: post hoc factor analysis of a randomised trial. *Alzheimers Dement* 2011;**1**:790–1	Not published in a peer-reviewed journal article or is an ongoing trial
Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Effects of extended-release memantine (28 MG/day) on cognitive domains in patients with moderate to severe Alzheimer's disease: post hoc analysis of a randomised trial. *Alzheimers Dement* 2011;**1**:784–5	Not published in a peer-reviewed journal article or is an ongoing trial
Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Clinical benefits of extended-release memantine (28 mg, once daily) as a function of disease severity in people with moderate to severe Alzheimer's disease: post hoc analysis from a randomised trial. *Alzheimers Dement* 2013;**1**:655	Not published in a peer-reviewed journal article or is an ongoing trial
Tocco M, Hendrix S, Miller ML, Pejovic V, Graham SM. Effects of extended-release memantine (28 mg, once daily) on language and communication abilities in patients with moderate to severe Alzheimer's disease. *Ann Neurol* 2012;**72**:S52–3	Not published in a peer-reviewed journal article or is an ongoing trial
Tollefson GD. Short-term effects of the calcium channel blocker nimodipine (Bay-e-9736) in the management of primary degenerative dementia. *Biol Psychiatry* 1990;**27**:1133–42	Not a disease modification trial
Trollor JN SP, Haindl W, Brodaty H, Wen W, Walker BM. Combined cerebral blood flow effects of a cholinergic agonist (milameline) and a verbal recognition task in early Alzheimer's disease. *Psychiatry Clin Neurosci* 2006;**60**:616–25	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Tsai GE, Falk WE, Gunther J. A preliminary study of D-cycloserine treatment in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 1998;**10**:224–6	Not a disease modification trial
Tzimopoulou S, Cunningham VJ, Nichols TE, Searle G, Bird NP, Mistry P, *et al.* A multi-centre randomised proof-of-concept clinical trial applying [18F]FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate Alzheimer's disease. *J Alzheimers Dis* 2010;**22**:1241–56	Not a disease modification trial
Van de Winckel A, Fey H, De Weerdt W, Dom R. Cognitive and behavioural effects of music-based exercises in patients with dementia. *Clin Rehabil* 2004;**18**:253–60	Not a disease modification trial
van Dongen M, van Rossum E, Kessels A, Sielhorst H, Knipschild P. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomised clinical trial. *J Clin Epidemiol* 2003;**56**:367–76	Not a disease modification trial
Van Dyck CH, Lin CH, Robinson R, Cellar J, Smith EO, Nelson JC, *et al.* The acetylcholine releaser linopirdine increases parietal regional cerebral blood flow in Alzheimer's disease. *Psychopharmacology* 1997;**132**:217–26	Not a disease modification trial
van Dyck CH, Newhouse P, Falk WE, Mattes JA. Extended-release physostigmine in Alzheimer disease: a multicenter, double-blind, 12-week study with dose enrichment. Physostigmine Study Group. *Arch Gen Psychiatry* 2000;**57**:157–64	Not a disease modification trial
van Dyck CH, Tariot PN, Meyers B, Resnick E. A 24-week randomised, controlled trial of memantine in patient with moderate-to-severe Alzheimer disease. *Alzheimer Dis Assoc Disord* 2007;**21**:136–43	Not a disease modification trial
Venneri A, Shanks MF, Staff RT, Pestell SJ, Forbes KE, Gemmell HG, *et al.* Cerebral blood flow and cognitive responses to rivastigmine treatment in Alzheimer's disease. *Neuroreport* 2002;**13**:83–7	Not a disease modification trial
Vereschagin NV NY, Lebedeva NV, Suslina ZA, Solovyev OI, Piradov MA, *et al.* [Mild forms of multiinfarct dementia – effectiveness of Cerebrolysin.] *Sov Meditsina* 1991;**11**:6–8	Full text unavailable in English
Veroff AE, Bodick NC, Offen WW, Sramek JJ, Cutler NR. Efficacy of xanomeline in Alzheimer disease: cognitive improvement measured using the Computerised Neuropsychological Test Battery (CNTB). *Alzheimer Dis Assoc Disord* 1998;**12**:304–12	Not a disease modification trial
Villardita C, Grioli S, Lomeo C, Cattaneo C, Parini J. Clinical studies with oxiracetam in patients with dementia of Alzheimer type and multi-infarct dementia of mild to moderate degree. *Neuropsychobiology* 1992;**25**:24–8	Not a disease modification trial
Villardita C, Parini J, Grioli S, Quattropani M, Lomeo C, Scapagnini U. Clinical and neuropsychological study with oxiracetam versus placebo in patients with mild to moderate dementia. *J Neural Transm Suppl* 1987;**24**:293–8	Not a disease modification trial
Villemagne VL, Rowe CC, Barnham KJ, Cherny R, Woodward M, Pejoska S, *et al.* A 52-week pilot study targeting abeta with PBT2: neuroimaging results. *Neurodegen Dis* 2015;**15**:308	Not published in a peer-reviewed journal article or is an ongoing trial
Viola LF, Nunes PV, Yassuda MS, Aprahamian I, Santos FS, Santos GD, *et al.* Effects of a multidisciplinary cognitive rehabilitation program for patients with mild Alzheimer's disease. *Clinics* 2011;**66**:1395–400	Not a disease modification trial
Vreugdenhil A, Cannell J, Davies A, Razay G. A community-based exercise programme to improve functional ability in people with Alzheimer's disease: a randomised controlled trial. *Scand J Caring Sci* 2012;**26**:12–19	Not a disease modification trial
Wade AG, Farmer M, Harari G, Fund N, Laudon M, Nir T, *et al.* Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomised, placebo-controlled, multicenter trial. *Clin Interv Ageing* 2014;**9**:947–61	Not a disease modification trial
Waldemar G, Hoffmann K, Sobol N, Frederiksen K, Beyer N, Vogel A, *et al.* Effect of moderate-to-high intensity endurance exercise in elderly community-dwelling persons with mild-moderate Alzheimer's disease. *Eur J Neurol* 2015;**22**:95	Not published in a peer-reviewed journal article or an ongoing trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Walzl M, Walzl B, Kleinert G, Schied G, Lechner H. [Heparin-induced extracorporeal LDL precipitation (HELP). A new therapeutic possibility in cerebral multi-infarct dementia.] *Der Nervenarzt* 1993;**64**:648–52	Full text unavailable in English
Wang P, Yang J, Liu G, Chen H, Yang F. [Effects of moxibustion at head-points on levels of somatostatin and arginine vasopressin from cerebrospinal fluid in patients with vascular dementia: a randomised controlled trial.] *Chin J Integr Med* 2010;**8**:636–40	Full text unavailable in English
Wang PN, Liao SQ, Liu RS, Liu CY, Chao HT, Lu SR, *et al.* Effects of oestrogen on cognition, mood, and cerebral blood flow in AD: a controlled study. *Neurology* 2000;**54**:2061–6	Not a disease modification trial
Warner J. Donepezil is more effective than galantamine for mild to moderate Alzheimer's disease. *Evid Based Ment Health* 2004;**7**:77	Not published in a peer-reviewed journal article or is an ongoing trial
Watkins PB, Zimmerman HJ, Knapp MJ, Gracon SI, Lewis KW. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA* 1994;**271**:992–8	Not a disease modification trial
Wattmo C, Wallin AK, Londos E, Minthon L. Predictors of long-term cognitive outcome in Alzheimer's disease. *Alzheimers Res Ther* 2011;**3**:23	Not a disease modification trial
Wei MQ, Tian JZ, Shi J, Ma FY, Miao YC, Wang YY. Effects of Chinese medicine for promoting blood circulation and removing blood stasis in treating patients with mild to moderate vascular dementia: a randomised, double-blind and parallel-controlled trial. *Chin J Integr Med* 2012;**10**:1240–6	Not a disease modification trial
Weiner MF, Bonte FJ, Tintner R, Ford N, Svetlik D, Riall T. ACE inhibitor lacks acute effect on cognition or brain blood flow in Alzheimer's disease. *Drug Dev Res* 1992;**26**:467–71	Not a disease modification trial
Weinstein HC, Teunisse S, van Gool WA. Tetrahydroaminoacridine and lecithin in the treatment of Alzheimer's disease. Effect on cognition, functioning in daily life, behavioural disturbances and burden experienced by the carers. *J Neurol* 1991;**238**:34–8	Not a disease modification trial
Wesnes KA, Aarsland D, Ballard C, Londos E. Improvements to attention and verbal episodic memory with memantine in Parkinson's disease dementia and dementia with Lewy bodies. *J Nutr Health Aging* 2013;**17**:781–2	Not published in a peer-reviewed journal article or is an ongoing trial
Wesnes K, Aarsland D, Ballard C, Londos E. Memantine improves attention and verbal episodic memory in Parkinson's disease dementia and dementia with Lewy bodies: a double-blind, placebo-controlled multicentre trial. *Alzheimers Dement* 2013;**1**:890	Not a disease modification trial
Wesnes KA, McKeith IG, Ferrara R, Emre M, Ser T, Spano PF, *et al.* Effects of rivastigmine on cognitive function in dementia with Lewy bodies: a randomised placebo-controlled international study using the cognitive drug research computerised assessment system. *Dement Geriatr Cogn Disord* 2002;**13**:183–92	Not a disease modification trial
Weyer G, Babej-Dölle RM, Hadler D, Hofmann S, Herrmann WM. A controlled study of 2 doses of idebenone in the treatment of Alzheimer's disease. *Neuropsychobiology* 1997;**36**:73–82	Not a disease modification trial
Weyer G, Erzigkeit H, Hadler D, Kubicki S. Efficacy and safety of idebenone in the long-term treatment of Alzheimer's disease: a double-blind, placebo controlled multicentre study. *Hum Psychopharmacol* 1996;**11**:53–65	Not a disease modification trial
Weyer G, Eul A, Milde K, Wierich W, Herrmann WM. Cyclandelate in the treatment of patients with mild to moderate primary degenerative dementia of the Alzheimer type or vascular dementia: experience from a placebo controlled multi-centre study. *Pharmacopsychiatry* 2000;**33**:89–97	Not a disease modification trial
White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. *Psychopharmacology* 1999;**143**:158–65	Not a disease modification trial
Wieggers RL, Kamphuis P, Stam C, Shah R, Bennett D, Hartmann T, *et al.* An overview of the medical food Souvenaid clinical trial program. *Alzheimers Dement* 2013;**9**(Suppl. 1):669	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, *et al.* A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* 2003;**20**:777–89	Not a disease modification trial
Wilcock G, Möbius HJ, Stöffler A. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharm* 2002;**17**:297–305	Not a disease modification trial
Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. *BMJ* 2000;**321**:1445–9	Not a disease modification trial
Wilcock GK, Surmon DJ, Scott M, Boyle M, Mulligan K, Neubauer KA, *et al.* An evaluation of the efficacy and safety of tetrahydroaminoacridine (THA) without lecithin in the treatment of Alzheimer's disease. *Age Ageing* 1993;**22**:316–24	Not a disease modification trial
Wilkinson D, Colding-Jorgensen E, Windfeld K. A clinical phase II study of LU AE58054 added to stable donepezil treatment in patients with moderate Alzheimer's disease. *Alzheimers Dement* 2013;**9**(Suppl. 1):P529	Not published in a peer-reviewed journal article or is an ongoing trial
Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, *et al.* Donepezil in vascular dementia: a randomised, placebo-controlled study. *Neurology* 2003;**61**:479–86	Not a disease modification trial
Wilkinson D, Fox NC, Barkhof F, Phul R, Lemming O, Scheltens P. Memantine and brain atrophy in Alzheimer's disease: a 1-year randomised controlled trial. *J Alzheimers Dis* 2012;**29**:459–69	Not a disease modification trial
Wilkinson D, Murray J. Galantamine: a randomised, double-blind, dose comparison in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2001;**16**:852–7	Not a disease modification trial
Wilkinson D, Róman G, Salloway S, Hecker J, Boundy K, Kumar D, *et al.* The long-term efficacy and tolerability of donepezil in patients with vascular dementia. *Int J Geriatr Psychiatry* 2010;**25**:305–13	Not a disease modification trial
Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, *et al.* A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *Int J Clin Pract* 2002;**56**:441–6	Not a disease modification trial
Willan AR, Goeree R, Pullenayegum EM, McBurney C, Blackhouse G. Economic evaluation of rivastigmine in patients with Parkinson's disease dementia. *Pharmacoeconomics* 2006;**24**:93–106	Not a disease modification trial
Wimo A, Gaudig M, Schauble B, Jedenius E. The economic impact of galantamine vs placebo: an analysis based on functional capacity in a Swedish cohort study. *J Med Econ* 2012;**15**:1019–24	Not a disease modification trial
Wimo A, Winblad B, Shah SN, Chin W, Zhang R, McRae T. Impact of donepezil treatment for Alzheimer's disease on caregiver time. *Curr Med Res Opin* 2004;**20**:1221–5	Not a disease modification trial
Wimo A, Winblad B, Soininen H, Verhey F, Waldemar G, Wetterholm AL, *et al.* An economic evaluation of donepezil in mild to moderate Alzheimer's disease: results of a 1-year, double-blind, randomised trial. *Dement Geriatr Cogn Disord* 2003;**15**:44–54	Not a disease modification trial
Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, *et al.* A 1-year, randomised, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001;**57**:489–95	Not a disease modification trial
Winblad B, Giacobini E, Frölich L, Friedhoff LT, Bruinsma G, Becker RE, *et al.* Phenserine efficacy in Alzheimer's disease. *J Alzheimers Dis* 2010;**22**:1201–8	Not a disease modification trial
Winblad B, Grossberg G, Frolich L, Farlow M, Zechner S, Nagel J, *et al.* A 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology* 2007;**69**(Suppl. 1):14–22	Not a disease modification trial

continued

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, *et al.* 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. *Dement Geriatr Cogn Disord* 2006; **21**:353–63	Not a disease modification trial
Wirth Y, Rive B. Memantine enhances autonomy in moderate to severe Alzheimer's disease patients already receiving donepezil. *Eur J Neurol* 2012;**19**:474	Not a disease modification trial
Wolters E, Riekkinen P, Lowenthal A, Van der Plaats J, Zwart J, Sennef C. DGAVP (Org 5667) in early Alzheimer's disease patients: an international double-blind, placebo-controlled, multicenter trial. *Neurology* 1990;**40**:1099–101	Not a disease modification trial
Wong WJ, Liu HC, Fuh JL, Wang SJ, Hsu LC, Wang PN, *et al.* A double-blind, placebo-controlled study of tacrine in Chinese patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 1999;**10**:289–94	Not a disease modification trial
Woods B, Thorgrimsen L, Spector A, Royan L, Orrell M. Improved quality of life and cognitive stimulation therapy in dementia. *Ageing Ment Health* 2006;**10**:219–26	Not a disease modification trial
Wouters CJ, Dautzenberg L, Thissen A, Dautzenberg PL. [Oral galantamine versus rivastigmine transdermal patch: a descriptive study at a memory clinic in The Netherlands.] *Tijdschr Gerontol Geriatr* 2010;**41**:146–50	Full text unavailable in English
Xiao S, Wang T, Huang Q, Chen K, Reiman E. Changes of biological markers and brain PET imaging and clinical effects of memantine for patients with moderate to severe Alzheimer's disease: a 24 week double-blind, randomised, placebo-controlled study. *J Nutr Health Aging* 2012;**16**:855	Not published in a peer-reviewed journal article or is an ongoing trial
Xiao S, Yan H, Yao P. The efficacy of Cerebrolysin in patients with vascular dementia: results of a Chinese multicentre, randomised, double-blind, placebo-controlled trial. The Cerebrolysin Study Group. *Hong Kong J Psychiatry* 1999;**9**:13–9	Unable to find a copy of the full text
Xu SS, Gao ZX, Weng Z, Du ZM, Xu WA, Yang JS, *et al.* Efficacy of tablet huperzine-A on memory, cognition, and behaviour in Alzheimer's disease. *Zhongguo Yao Li Xue Bao* 1995;**16**:391–5	Not a disease modification trial
Xue SW, Ding JM, Zhong P, Liang K, An HY, Bo Y. Impacts of huperzine A on the level of Fas, Apo2.7 and Bcl-2 on the platelet membrane and the cognitive function in patients with Alzheimer disease. *Chin J Clin Rehabil* 2005;**9**:188–9	Full text unavailable in English
Yamanaka K, Kawano Y, Noguchi D, Nakaaki S, Watanabe N, Amano T, *et al.* Effects of cognitive stimulation therapy Japanese version (CST-J) for people with dementia: a single-blind, controlled clinical trial. *Aging Ment Health* 2013;**17**:579–86	Not a disease modification trial
Yan YX, Liang LZ, Zhou ZL. Clinical study of combined treatment with compound reinhartdt and sea cumber capsule and donepezil for vascular dementia. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2007;**27**:887–90	Full text unavailable in English
Yancheva S, Ihl R, Nikolova G, Panayotov P, Schlaefke S, Hoerr R, *et al. Ginkgo biloba* extract EGb 761(R), donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomised, double-blind, exploratory trial. *Aging Ment Health* 2009;**13**:183–90	Not a disease modification trial
Yoo HB, Choi JS, Yoon EJ, Lee HY, Kim YK, Lee H, *et al.* Efficacy of cilostazol augmentation treatment in Alzheimer's disease with white matter lesion by FDG PET. *Int Psychogeriatr* 2013;**25**:S58	Not published in a peer-reviewed journal article or is an ongoing trial
Yoon BK, Kim DK, Kang Y, Kim JW, Shin MH, Na DL. Hormone replacement therapy in postmenopausal women with Alzheimer's disease: a randomised, prospective study. *Fertil Steril* 2003;**79**:274–80	Not a disease modification trial
Yu F, Bronas U, Nelson N, Dysken M, Jack C, Konety S, *et al.* Aerobic exercise in Alzheimer's disease: The FIT-AD trial. *Alzheimers Dement* 2014;**10**:851–2	Not a disease modification trial
Yu F, Bronas UG, Konety S, Nelson NW, Dysken M, Jack C Jr, *et al.* Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer's disease: study protocol of a randomised controlled trial (The FIT-AD trial). *Trials* 2014;**15**:394	Not a disease modification trial
Yu J, Zhang X, Liu C, Meng Y, Han J. Effect of acupuncture treatment on vascular dementia. *Neurol Res* 2006;**28**:97–103	Not a disease modification trial

TABLE 15 Excluded studies and reasons for exclusion ($n = 748$) (*continued*)

Reference	Reason for exclusion
Yu L, Lin SM, Zhou RQ, Tang WJ, Huang PX, Dong Y, *et al.* Chinese herbal medicine for patients with mild to moderate Alzheimer disease based on syndrome differentiation: a randomised controlled trial. *Chin J Integr Med* 2012;**10**:766–76	Full text unavailable in English
Zamfirescu A, Capisizu A, Slavila M, Capisizu AA, Romila A. Physical exercise training in older adults diagnosed with mild to moderate dementia. *J Nutr Health Aging* 2012;**16**:861–2	Not published in a peer-reviewed journal article or is an ongoing trial
Zanetti O, Frisoni GB, De Leo D, Dello Buono M, Bianchetti A, Trabucchi M. Reality orientation therapy in Alzheimer disease: useful or not? A controlled study. *Alzheimer Dis Assoc Disord* 1995;**9**:132–8	Not a disease modification trial
Zemlan FP, Keys M, Richter RW, Strub RL. Double-blind placebo-controlled study of velnacrine in Alzheimer's disease. *Life Sci* 1996;**58**:1823–32	Not a disease modification trial
Zhang FR. Observation of Chinese herb kangnaoling in improving cognitive and daily living ability of patients with vascular dementia. *Chin J Clin Rehabil* 2006;**10**:161–3	Full text unavailable in English
Zhang MZ, Dong ZX, Mao YJ, Du F. Effect of yizhi capsule on the intelligence of patient with multi-infarct dementia. *Chin J Clin Rehabil* 2005;**9**:155–7	Full text unavailable in English
Zhang Y, Lin C, Zhang L, Cui Y, Gu Y, Guo J, *et al.* Cognitive improvement during treatment for mild Alzheimer's disease with a Chinese herbal formula: a randomised controlled trial. *PLOS ONE* 2015;**10**:e0130353	Not a disease modification trial
Zhang YX, Luo G, Guo ZJ, Cui RY, Wang LQ, Zhou CL. Quantitative evaluation of the interventional effect of oestrogen on Alzheimer disease. *Chin J Clin Rehabil* 2006;**10**:37–9	Full text unavailable in English
Zhang YY, Yang LQ, Guo LM. Effect of phosphatidylserine on memory in patients and rats with Alzheimer's disease. *Genet Mol Res* 2015;**14**:9325–33	Not a disease modification trial
Zhou BR XZ, Kuang YF, Deng YH, Liu ZF. Effectiveness of polydrug therapy for senile dementia. *Chin J Clin Rehabil* 2004;**8**:1214	Full text unavailable in English
Zhu M, Xiao S, Li G, Li X, Tang M, Yang S, *et al.* Effectiveness and safety of generic memantine hydrochloride manufactured in China in the treatment of moderate to severe Alzheimer's disease: a multicenter, double-blind randomised controlled trial. *Shanghai Jingshen Yixue* 2013;**25**:244–53	Not a disease modification trial
Zieschang T, Schwenk M, Oster P, Hauer K. Long-term effect of a standardised motor training on cognition in patients with dementia: results of a RCT. *Eur Geriatr Med* 2013;**4**:S211	Not published in a peer-reviewed journal article or is an ongoing trial

Appendix 4 Information sheet for focus group participants

Summary of Research:

What is the problem being addressed?

In the UK, the numbers living with dementia are expected to rise to over a million people with dementia by 2020. There are currently no disease modifying treatments available for the common dementias, and our research knowledge and funding on dementia lagging behind other major diseases such as cancer or heart disease. The National Institute of Health Research (NIHR) has identified the area of disease modification in dementia as important, particularly in the mild and moderate stages, and are supporting trials evaluating potential disease modifying treatments.

However, across previous and current disease modification trials various measurements of outcome are used, making it difficult to compare trials of the same or different types of potential treatments in modifying the disease course of dementia. A standardised set of the most valid and appropriate outcome measures for use in disease modification trials in dementia would improve the efficiency of future trials, and enhance the interpretation of data across studies; enabling meta-analyses combining small data sets that could inform practice.

What does this study aim to do?

The aim of this project is to identify outcome measures for all disease modification trials in mild (including early) and moderate dementia. This is in order to report which outcomes are used in trials, and to assess the frequency of outcome use. We will then examine validation measures and use this information to determine possible standardised 'core set' of health outcome measures for trials of disease modification treatments in mild and moderate dementia. We will consult with focus groups from the Alzheimer's society and then present possible measures at a consensus conference to decide upon agreed measures. This will allow direct comparison of future trials of such treatments and will shape and optimise the design of future NIHR and other funders' dementia trials.

Why is the research needed now?

The National Institute of Health Research (NIHR) has already identified this as an important area of research. Current trials are developed, funded and set up without any liaison between the trial teams with different choice of outcome measures so that these cannot be compared. Researchers do not agree on which measures should be used. Use

of an agreed set of outcome measures would improve efficiency. This applies to both drugs and non-pharmacological interventions so that the efficacy of, for example, exercise or diet changes, could be compared to new drugs.

Study Design

There are four stages to this project.

1. Use of current knowledge:

We will use any relevant data from existing systematic reviews by co-applicants of the group, including reference lists, to inform the design of this study and avoid duplication.

2. Systematic review:

We will conduct a brief systematic review of literature available to date. The review will focus on trials involving people with mild to moderate dementia, aiming to develop a disease modifying therapy. We will exclude studies set in a care home, as very few people resident in care homes will have mild to moderate dementia, and studies where all patients have severe dementia. We will also exclude outcomes that are qualitative, economic, only about carers or those where there are no validation data in people with mild to moderate dementia published or known to the group. This review will inform a list of most frequently used trial measures, including information about the therapy under investigation, the acceptability of the test and the length time associated with the measure.

3. Patient and Public Involvement (PPI consultation):

We will conduct three to four focus groups, in partnership with the Alzheimer's Society involving people with dementia, and family carers, to assess which of the included outcomes are most important and appropriate to both people with dementia and carers.

4. Consensus conference:

Towards the end of the project all researchers involved in the study will be invited to a consensus conference. This meeting will agree a core set of outcomes to be recommended for use in NIHR applications for trials of disease modification in mild to moderate dementia.

Why have you been invited to take part?

An important part of this research is to seek the advice of people with dementia and carers on the measures and tests used during clinical trials. You have been invited to participate in a focus group as you have direct experience of dementia as part of the third stage of the project.

You do not have to take part, and if you do decide to join a focus group you are free to withdraw at any time. If you withdraw during the research, we will ask to use the information you gave during any group you have attended, unless you request that it is destroyed.

What will happen during the focus group?

The focus groups will last between 2 and 2.5 hours. The discussion will be recorded and transcribed – recordings will be destroyed after transcription. All your contributions will be strictly confidential.

Expenses and refreshments will be provided for all focus group participants. We will also offer you a £30 voucher as a token of our appreciation of you giving up your time to take part.

What are the possible benefits of taking part?

There will be no direct benefit but your experience and knowledge could influence future trials to help provide more consistent clinical trials in dementia and thus improve knowledge of the effect of disease modifying treatments.

Are there any risks involved?

We don't anticipate any harm as a result of taking part. However, discussions about research participation may raise potentially distressing subjects relating to medical testing. A trained clinician will be part of the meeting and support will be available if any aspect of the discussion causes distress.

Further Information

The dissemination policy:

We will draft a press release with the UCL media office and the Alzheimer's Society. We have previously worked together in disseminating published work of interest in dementia and have had results in national, international and local press as well as

interviews on TV and the radio. The communications departments of the institutions to which the expert group members belong will be invited to help disseminate the findings.

Approval by ethics committees

This project will not be using individual or identifiable patient data, so we do not envisage ethical problems in the carrying out of this research. We have not required research ethics committee permission as the data is in the public domain and we are not engaged in any primary research. We will draw conclusions about outcomes. We will discuss with our research team if any of the interventions included in the review raise ethical dilemmas, and discuss these in the final report.

Further Questions

If you have any further questions about this research, please contact

Anna Grinbergs-Saull (Research Engagement Officer, Alzheimer's Society)

[redacted]

Lucy Webster (Research Assistant, UCL Division of Psychiatry)

[redacted]

Appendix 5 First e-mail consultation

Thank you again for taking part in a focus group as part of the Core Outcomes for Dementia project. Discussing the measures used during clinical trials with you was very helpful and your thoughts and ideas will make a hugely valuable contribution to the final report.

As discussed after your meeting, I would like to ask for your advice on the report we will be submitting in two weeks, summarising our discussions. This will be presented at a conference with the co-applicants from the study to ensure that your views are included in the final recommendations for future trial design. The aim of the conference is to produce a list of 'core' outcomes, to be adopted by all future trials. It is important to ensure that this list is feasible and acceptable to people with dementia. So, I would particularly like to know what you think of the package of measures we have suggested at the bottom of p3, and how often you think the combined measures could be taken (e.g. all tests during one day a year or different tests every few weeks).

If you would be willing to help in this stage of the project, please read the attached report and send me your answers to the following questions by next **Wednesday 30th March**. I am sorry to give such a short time, this is because we need to finalise the report before the conference, which is taking place the following week.

1. Do you agree that biological measures are the main core outcome measure for dementia? If not, please suggest which measure you prefer.
2. Do you agree that a potential combination of measures should include biological, cognitive and behavioural tests?
3. Are there any other combinations of tests that would be feasible for people with dementia? Are there any measures that should not be used together?
4. Do you have any other comments on this report?

Many thanks again for participating in this project. If you have any questions, please don't hesitate to contact me.

Appendix 6 Second e-mail consultation

I am writing to invite you to take part in a consultation, as part of a research project we are supporting through our research partnerships programme.

Core Outcomes for Dementia

The National Institute of Health Research (NIHR) HTA funded project, *Core Outcomes for Dementia*, is led by Prof. Gill Livingston at University College London, and involves a large multi-disciplinary team from around the UK. This is a 6 month project collating data on how results have been measured from all clinical trials over 30 years, looking for disease modifying treatments for dementia. That is, treatments that alter the underlying brain changes rather than the symptoms. The aim of the whole project is to develop a consensus on the 'Core' set of measures that should be used in these trials in the future. This will make it easier to compare or add together the results of different trials.

The research team conducted a systematic literature review to find the different outcome measures that trials have used in dementia research to test whether a therapy or drug was successful. These included cognitive tests, biological tests, behavioural measures and quality of life measures. We then spoke to people affected by dementia to find out if the measures identified by the research were acceptable and feasible. The recommendations made by people affected by dementia are summarised in the attached focus group report. This also gives an overview of the outcome measures we discussed.

The final stage was a consensus conference, which brought together the views of people affected by dementia and research experts to try to decide which measures should be core (used in all future trials). Those present at the conference recommended that cognitive measures should be considered 'core', with others used depending on the aim of each trial. As a secondary measure, researchers suggested that MRI scans should be used only with small groups of people, not for all participants in a trial.

How can you be involved?

To help the production of the final report, we would like to ask for your advice and feedback on the results of the conference, as well as the report on our focus group meetings. We would particularly like to know your thoughts on the following questions:

1. Do you agree that cognitive tests (e.g. memory, language, logic) should be the core measure in dementia research?

2. Researchers suggested that MRI scans are important, but should be optional for trial participants. This would mean that not everyone in a trial would have an MRI - only those who agreed to it. What do you think of this suggestion?
3. Based on your experience, do you agree that a 1.5 hour time limit should be set for completing a set of measures or tests?
4. Do you have any additional comments to add to the discussion summarised in the Focus Group Report? (e.g. on the acceptability of different measures, or the general recommendations for research)

If you would like to take part in this project, please send me your responses by **Monday 25th April**. Your feedback will be anonymised and incorporated into the final report sent to the NIHR in June.

I have attached an information sheet on the project to give you some more information on the research. If you have any questions about this project, please don't hesitate to contact me.

Appendix 7 List of consensus conference attendees

Twenty-seven attendees:

1. Sube Banerjee
2. Frances Bunn
3. David Challis
4. Georgina Charlesworth
5. Alison Evans
6. Katie Featherstone
7. Chris Fox
8. Claire Goodman
9. Anna Grinbergs-Saull
10. Derek Groskreutz
11. Rob Howard
12. Roy Jones
13. Louise Lafortune
14. Sallie Lamb
15. Gill Livingston
16. Esme Moniz-Cook
17. Gail Mountain
18. John O'Brien
19. Robert Perneckzy
20. James Pickett
21. Charlotte Roberts
22. Justine Schneider
23. Sasha Shepperd
24. Clare Surr
25. Jo Thompson-Coon
26. Lucy Webster
27. Bob Woods.

EME
HS&DR
HTA
PGfAR
PHR

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