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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Scientific summary

Disease modification trials in mind to moderate dementia

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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.

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