BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005623
Article Type:	Protocol
Date Submitted by the Author:	05-May-2014
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Geriatric medicine, Neurology
Keywords:	Dementia < NEUROLOGY, Old age psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY

RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia using cognitive bias modification: RAPID Study Protocol

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Word count: 4854

Date: 9 May 2014

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ABSTRACT

Introduction: Depressive symptoms are common and undermine the quality of life of people with Alzheimer's disease (AD). Cholinesterase inhibitors and antidepressants have all but no effect on the mood of patients, and their use increases adverse events. Cognitive bias modification (CBM) targets attentional and interpretative biases associated with anxiety, dysphoria and depression and may be useful to treat depression in AD (DAD). This trial aims to determine the effect of CBM on depression scores and the quality of life of people with DAD.

Methods and analysis: Randomised, double-blind, parallel, controlled trial of CBM (1:1 allocation ratio). Participants will be 80 adults with probable AD living in the Western Australian community who score 8 or more on the Cornell Scale for Depression in Dementia (CSDD). They will have mild to moderate dementia (Mini-Mental State Examination - MMSE score ≥ 15) and will be free of severe sensory impairment or suicidal intent. The intervention will consist of ten 40-minute sessions of CBM delivered over two weeks using a high resolution monitor using a local computer station at the WA Centre for Health & Ageing. The primary outcomes of interest are the two-week change, from baseline, in the severity of CSDD scores and the Quality of Life AD (QoL-AD) scores. Secondary outcomes include changes in the CSDD, QoL-AD after 12 weeks, and changes in MMSE scores, negative attentional and interpretative bias and the proportion of participants with CSDD<8 after 2 and 12 weeks.

Ethics and dissemination: The study will comply with the principles of the Declaration of Helsinki and participants will provide written informed consent. The Ethics Committee of the Royal Perth Hospital will approve and oversee the study (REG14-036). The results of this trial will provide level 2 evidence of efficacy for CBM as a treatment of DAD.

Trial registration number: Australian and New Zealand Clinical Trials Registry number ACTRN12614000420640, date registered 06/04/2014.

Key-words: depression, quality of life, dementia, Alzheimer's disease, treatment, RCT, cognitive bias modification.

Strengths and limitations

- Strong empirical evidence supports the testing of cognitive bias modification as a treatment for depression in Alzheimer's disease.
- Cognitive bias modification interventions are not associated with clinically significant adverse events.
- The design of this trial follows SPIRIT guidelines and its results will be reported according to CONSORT guidelines.
- The pragmatic definition of depression in this trial will be based on the use of a validated cut-point on the Cornell Scale for Depression in Dementia rather than diagnostic criteria.
- The trial will be limited to people with depression in Alzheimer's disease of mild to moderate severity.
- The intervention will be limited to two weeks.

INTRODUCTION

Dementia is a leading cause of disability, affecting as many as 5% of the population over the age of 65 and 40% of those older than 80 years.[1,2] As the World's population continues to age, the number of people living with dementia is expected to increase exponentially over the next 40 years,[3] and this will lead to growing demands on residential care and health services.[4] In addition, the characteristic cognitive decline that affects people with dementia is commonly accompanied by other mental health changes involving perception, reasoning, behaviour and mood.[5] Most relevant to the current proposal is the fact that about 25% of people with Alzheimer's disease (AD), which is the most frequent cause of dementia in Western societies, show evidence of clinically significant depressive symptoms at assessment independent of the level of severity of the disease.[5,6] Currently available data also show that symptoms of anxiety and depression tend to co-occur in AD and may affect as many as 1 in every 2 people during the course of the illness.[7,8] Worryingly, the presence of mood disturbances in AD increases disability and burden of care,[8] impairs quality of life,[9] and has been associated with accelerated cognitive decline in longitudinal studies.[10] As currently available treatments for AD do not affect disease progression,[11] it is important that we develop interventions that improve the quality of life of these patients.

Treatments for AD do not ameliorate psychological comorbidity

Medications commonly used to treat people with AD have no obvious effect on mood. The cholinesterase inhibitors donepezil, galantamine and rivastigmine improve the cognitive scores of patients with AD compared with placebo,[12] but have no consistent impact on comorbid psychological and behavioural symptoms, including depression.[13] Similarly, data from randomised controlled trials suggest that memantine does not possess antidepressant properties.[14]

Treatments for depression associated with AD do not work and cause more side-effects

A large multicentre trial of the antidepressants sertraline and mirtazapine for the treatment of depression associated with dementia failed to show any benefit of treatment.[15] The investigators randomly assigned 326 people with AD and depression to treatment with sertraline (n=107, up to 150 mg daily), mirtazapine (n=108, up to 45 mg daily) or placebo (n=111). Thirty-nine weeks of follow up data were available. Treatment with antidepressants did not reduce depression scores relative to placebo after 13 or 39 weeks of treatment, but both sertraline and mirtazapine were associated with greater frequency of adverse reactions than placebo (43%, 41% and 26% respectively). Moreover, a systematic review of randomised placebo-controlled trials for the treatment of depression in dementia showed that the efficacy of antidepressants is equivalent to that of placebo over a period of 6 to 12 weeks.[16] These negative results are alarming, as depression is commonly associated with AD, hinders quality of life and is a significant source of stress for carers.[8,9] Novel and effective approaches to manage these patients are needed.

The contribution of cognitive bias to depression

Various psychological interventions have been tested for the treatment of depression to date, with the most robust empirical evidence for efficacy arising from trials of cognitive-behavioural therapy (CBT).[17] CBT uses a systematic approach to cognitive restructuring, change of biased negative beliefs and behavioural activation to mitigate the intensity and presence of depression.[18] Meta-analysis of pooled data of published trials indicates that CBT may also contribute to decreasing the risk of relapse over 12 to 24 months, suggesting that its benefits might extend beyond the acute phase of treatment.[19] The theoretical framework underpinning CBT recognises that depressed mood becomes apparent when a set of biased beliefs and thinking processes predominate, commonly involving preferential attention to negative aspects of experience and an inflated tendency to impose negative interpretations to ambiguous events. Such biases in the processing of information initiate the cycle of negative thinking and behavioural changes that are characteristic of depression. CBT challenges negative thoughts about the self, others and the future with the aim of modifying biased

ways of thinking and, consequently, leading to improved mood and behaviour. Effective shifts of dysfunctional biased beliefs have been associated with robust response to treatment and decreased risk of relapse of symptoms in cognitively intact people able to engage with the demands and requirements of the therapy.[20] However, a substantial gap persists in treatment options for depressed adults with cognitive impairment.

Cognitive models of depression ascribe the development of symptoms to systematic biases in low-level mechanisms not readily accessible to conscious introspection that operate before thoughts are formed in ways that shape their nature.[21] Selective biases in attention and interpretation that favour the processing of emotionally negative information are believed to represent the psychological basis of disordered mood, and emerging empirical and clinical findings support this hypothesis.[22] People with depression have more difficulty keeping their attention away from negative stimuli than non-depressed people. For example, adults with depression shown a series of faces on a computer screen selectively direct attention to sad faces, but show no such bias when presented with angry or happy faces.[23] In addition, when faced with ambiguity, people with depressed mood favour negative interpretations of stimuli. For example, when presented with the ambiguous cue word 'GROWTH' (which can be interpreted negatively to mean tumour or non-negatively to mean increased size or wealth), people with low mood are significantly faster to then complete fragments of semantically related words associated with the negative rather than the non-negative meanings of the ambiguous cue: C_NC_ER and GR_AT_R (cancer and greater).[24] These findings invite the question: are these biases amenable to change, and could they be a target for the treatment of dysphoria and depression in people with dementia?

What is cognitive bias modification (CBM)?

MacLeod and colleagues introduced the most widely used approach worldwide to modify attentional bias.[25] The procedure exposes participants to pairs of words or images on a computer

screen for 500 ms, with each pair including one emotionally negative and one neutral item. Immediately after the words/images disappear, a single small visual probe is presented in the same spatial position where one of the original stimuli had been displayed. Participants are required to indicate, as quickly as possible, the orientation of this probe (horizontal or vertical), and their speed to accurately do so is recorded over dozens of trials. People who display an attentional bias to the more negative information are significantly faster to make this discrimination judgment for probes that appear in the same area as the negative stimuli compared with probes in the region of the neutral stimuli. Cognitive bias modification for attention (CBM-A) delivers hundreds of trials in which all probes are presented where the neutral rather than the negative stimuli had just appeared (promoting attentional avoidance of negative information). A control condition presents probes with equal frequency to each of these two areas. In cognitive bias modification to reduce negative interpretative bias (CBM-I), participants are exposed to ambiguous information, followed by a word fragment that must be completed in a semantically consistent manner. CBM-I delivers hundreds of trials in which fragments yield only words consistent with non-negative interpretations of the ambiguity (discouraging negative interpretation). Thus, the ambiguous text "When you chat to people at a party they are soon chuckling, because you are so", will be followed by the fragment W_T_Y (yielding WITTY as opposed to 'silly'). A control condition employs fragments that equally often yield words consistent with negative or non-negative interpretation of the ambiguity. Single sessions of CBM can reduce negative attentional and interpretive bias, although multiple sessions may be associated with more lasting change.[25]

CBM improves mood: previous trial evidence

Recent trial data show that CBM-A attenuates anxiety reactions to stressful life events,[26] reduces recurrent negative thought intrusions in chronic worriers,[27] decreases avoidant behaviours[28] and mitigates the intensity of depressive and dysphoric symptoms over a 2-week period.[29] CBM is also effective at mitigating depressive symptoms in people with major depressive disorder. Williams and

colleagues randomised adults to CBM (n=38) or to a wait-list (n=31). CBM sessions were delivered daily over the internet for one week, and were associated with greater reduction in the severity of depressive symptoms.[30]

Rationale for the proposed trial

Depression commonly affects people with AD during the course of their illness. Data from randomised controlled trials show that treatment with cholinesterase inhibitors, memantine and antidepressants is ineffective at reducing the severity of depressive symptoms, while the use of traditional forms of psychotherapy is hindered by the cognitive deficits that characterise AD. As the pronounced impairment of explicit declarative learning (i.e., episodic memory) associated with AD does not compromise the implicit learning that occurs when patients acquire cue-outcome associations,[31] CBM may be a particularly suitable for use in this population.

Objectives

This trial aims to determine the effect of CBM on depressive symptoms and the quality of life of adults with depression in AD after two weeks of treatment. We hypothesise that participants treated with active compared with control CBM will experience greater improvement of depressive symptoms and quality of life scores after two weeks of treatment. We also anticipate that the improvements in depression and quality of life scores will be maintained for 12 weeks and that these changes will be associated with a relative reduction in negative attentional and interpretative biases.

METHODS

Study setting

This study has been designed as a single centre trial based at the Western Australian Centre for Health & Ageing at the Royal Perth Hospital in Australia. Participants will be community-dwelling older adults with Alzheimer's disease in contact with the metropolitan health services.

Trial design

The RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia (RAPID) is a parallel, double-blind, controlled randomised trial of cognitive bias modification with a 1:1 allocation ratio.

Eligibility criteria

We will recruit 80 people with depression in mild to moderate severity Alzheimer's disease according to the following inclusion criteria:

1. Diagnosis of probable AD according to NINCDS-ADRDA criteria,[32] which is largely consistent with DSM-5 diagnosis of major neurocognitive disorder due to probable AD,
2. Mini-Mental State Examination (**MMSE**) score ≥ 15,[33]
3. Cornell Scale for Depression in Dementia (CSDD) ≥ 8,[34]
4. Fluent in written and spoken English (preferred language for at least 10 years),

We will exclude from participation people who have:

1. One or more diseases likely to compromise ongoing participation in the trial (for example, severe visual impairment),
2. A weekly alcohol consumption greater than 28 standard drinks (> 4 drinks per day) or 6 or more standard drinks on any one day of the week,
3. Active suicidal intent,
4. No health practitioner who is able to provide ongoing clinical care,
5. Changed antidepressants during the preceding four weeks,

6. Not been able or willing to provide informed consent to participate.

Participants will be recruited from metropolitan Memory Clinics and through advertisement via local health services, carer groups and the media.

Interventions

Participants randomly assigned to the active and control CBM interventions will be exposed to the same study procedures and daily activities. They will be asked to attend the Western Australian Centre for Health and Ageing, Royal Perth Hospital, on a daily basis for a total of 10 CBM sessions (2 weeks – excluding weekends). Each session will be delivered on a 24'' high-resolution screen using a local PC station, and will last approximately 30 minutes: 15 minutes each for CBM-A and for CBM-I.

In the CBM-A session, participants will be shown pairs of emotionally discrepant photos for 500 ms (sad or neutral/happy faces). Each pair will then be replaced by a small probe (square or circle) appearing in the screen position previously occupied by one of the photos. Participants will be instructed to use a response box to indicate the shape of the small probe (by pressing the circle or square buttons of the response box). The probe will then disappear and will be replaced, after 1 second, by another pair that of photos to initiate the next trial. The time to discriminate probe identity will be recorded automatically. In the active CBM condition, designed to reduce attention to negative information, probes will always appear in the position of neutral/happy faces. In the control condition, probes will appear 50% of the time in the position of neutral/happy faces and 50% of the time in the position of the sad faces.

In the interpretative CBM sessions (CBM-I), single ambiguous cue-words that permit a negative and benign interpretation (e.g., HIT) will first appear in the top half of the screen for 1s. Then two

words will appear on the bottom half of the screen: one on the left and the other on the right hand side. This word-pair will consist of one target word that is semantically related either to the negative or benign meaning of the ambiguous cue-word (e.g., SUCCESS or PUNISH), and one foil word that is unrelated to either meaning of the ambiguous cue-word (e.g., CLOUD). Participants will be asked to identify which is the target word and use the response box to indicate whether the semantically-related word appeared on the left or right-hand side of the screen (by pressing the left or the right hand side button of the response box, respectively). The time required to accurately identify the target word will be recorded automatically. In the active CBM condition, designed to reduce negative interpretations of ambiguity, target words always will be associated with the benign meanings of the cue-words, discouraging their negative interpretation. In the control condition, 50% of the target words will be associated with the benign meaning and 50% with the negative meanings of the cue-words.

A trained graduate research officer will supervise all CBM sessions, and participants will be randomly assigned to the active or control CBM groups. Previous studies (reviewed in the Introduction) have shown that both attentional and interpretative biases can be modified successfully using these procedures. In addition, there is evidence that exposure to daily CBM leads to extinction of negative bias within two weeks,[35,36] thereby guiding the duration of our trial for efficacy whilst minimising treatment burden.

Outcomes

This trial has two primary outcomes of interest: depression and quality of life. We will use the Cornell Scale for Depression in Dementia (CSDD) to establish the presence of clinically significant symptoms of depression (CSDD ≥ 8), measure changes in the severity of symptoms over 2 and 12 weeks, and to ascertain the remission of symptoms after 2 and 12 weeks (CSDD < 8). The primary outcome of interest is the change, from baseline, in the severity of symptoms after 2 weeks of

treatment. The CSDD is the most widely used instrument worldwide to assess depression in dementia. The 19-item scale is rated on a 3-point score that ranges from absent to severe. The scale has robust psychometric properties, with good inter-rater reliability and internal consistency.[34] The CSDD is a rater-based assessment that takes about 10 minutes to complete.[34]

The Quality of Life AD (QoL-AD) scale will be this study's measure of quality of life.[37] It consists of 13 items that assess behavioural competence, psychological status, physical functioning and interpersonal environment that is of relevance to older adults. Each item offers four answers that range from poor (1) to excellent (4), with the total possible score ranging from 13 to 52. Higher scores indicate better quality of life. The QoL-AD has the added advantage of offering patient and carer versions. The QoL-AD has robust psychometric properties.[37] Changes in QoL-AD scores from baseline represent another outcome of interest of this trial, and will be measured 2 (primary endpoint) and 12 weeks (secondary endpoint) after the baseline assessment.

Before the intervention starts, all participants will complete a baseline assessment of attentional and interpretative biases, using assessment variants of the procedures described for the intervention. In the attentional assessment, probes will appear 50% of the time in the position of neutral/happy faces and 50% of the time in the position of sad faces. Negative attentional bias will be indexed by degree of relative speeding to discriminate probes in the latter condition compared to the former. In the interpretative assessment, target words will be related to the benign meaning of the ambiguous cue word 50% of the time and to its negative meaning 50% of the time. Negative interpretative bias will be indexed by degree of relative speeding to identify target words in the latter condition compared to the former. This assessment will be repeated 2 and 12 weeks after the start of the intervention, so that change in attentional and interpretative biases can be ascertained (secondary outcomes).

We will also collect data on acceptability of the intervention, adherence to treatment and reasons for withdrawal from the study. We will measure acceptability by asking participants after two weeks: (1) Please rate your experience with the CBM program: very unpleasant / unpleasant / unsure / pleasant / very pleasant. (2) If your doctor recommends CBM treatment for you in the future, would you: refuse it / be unsure whether to do it / be happy to do it again. Adherence will be measured automatically by the number of scheduled CBM session completed. We will consider that participants adhered to treatment if they completed at least 8 of 10 sessions. Partial and poor adherence will be defined by completion of 5 to 7 and less than 5 sessions, respectively. We will also ask participants who withdraw from the study to list the factors that might have contributed to their decision. Supportive collateral information will be sought from carers and treating physicians.

Other study measures

We will use a number of validated measures and procedures to collect demographic, lifestyle and clinical information from participants, including age, place of birth, time living in Australia, marital status, education, current and past occupations, living arrangements, religion and religion practices, weight and height, hobbies and financial concerns, smoking (never, past and current, amount and time), physical activity and alcohol consumption (standard units per day in a usual week), social support, prevalent medical conditions (diabetes, hypertension, dyslipidaemia, coronary heart disease, cerebrovascular disease, chronic respiratory diseases, arthritis and other rheumatic disorders, chronic pain, sensory impairment, cancer, and others), as well as prescribed and over the counter medications (including antidepressants). The approach to data gathering will follow the same procedures that we have used successfully in other trials.[38-40]

The Mini-Mental State Examination (MMSE) is the most widely used screening instrument for the assessment of cognitive function worldwide.[33] Scores can range from 0 to 30, with lower scores indicating increasing cognitive impairment. The MMSE requires about 10 minutes to complete, and

will be carried out at screening and 12 weeks. Changes of MMSE scores over 2 and 12 weeks will be additional secondary outcomes of interest of this trial. Table 1 summarises the timeline for the collection of the outcomes of the study.

TABLE 1

Sample size

Data from the placebo-controlled trial of mirtazapine and sertraline indicate that people with DAD treated with placebo improved, on average, 6 points (standard deviation, SD = 4) after 13 weeks.[15] We estimate that people treated with CBM should improve an additional 3 points (9 in total, standard deviation = 4). A sample size of 76 people with DAD (38 per group) would give the study 90% power to declare this difference as significant (alpha < 5%, two-tailed). We plan to recruit 80 participants with DAD (40 randomly assigned to each treatment group) and, pessimistically, anticipate that 15% of them will be lost during the study (our retention of people with AD in our trials is higher over a period of 6 months).[41] In this case, the trial would be completed by 68 participants and would still have 87% power. We further anticipate that loss to follow up will be minimal during the initial two weeks of treatment, although changes in scores may also be smaller at that point in time (3 points for controls and 6 for intervention participants). If we lose 10% of our sample during the initial two weeks, primary outcome data would be available for 72 participants (36 per group) and the study would have 89% power to declare as significant such a difference between the groups. Furthermore, a sample of this size would give the study 84% power to declare as significant changes in QoL-AD scores of 1 point for controls and 4.5 points for active CBM participants over three months (SD=5 for both groups; positive changes indicate expected improvement). The changes in response bias (measured in milliseconds) are expected to be associated with a minimum effect size of 0.4 (Cohen's d),[26] which would require about 50 trials per participant (within group comparison). As each CBM session includes 96 trials for attention (faces)

and 96 trials for interpretative bias (words), the study will have ample power to investigate this outcome.

Randomisation and allocation concealment

Participants will be randomly assigned to control and active CBM according to a list of random numbers generated by computer in blocks of ten. The allocation ratio will be 1:1. An independent biostatistician working at the WA Centre for Health and Ageing will generate the random allocation sequence. The sequence code will then be used to automatically select the appropriate intervention for the participant (control or active CBM) from our server (i.e., the id number will be linked to the randomisation code and the relevant intervention will be activated when the user id is entered on the computer). Neither the participant nor research staff will be aware of the independently controlled randomisation code. Participants will be advised about the study's aims and procedures (which will be exactly the same for all participants), but not about the details characterising the control and the active intervention. In addition, the staff member supervising the CBM sessions will not be involved in the collection of outcome data. This professional will be directed not to discuss any aspects of the intervention with other research staff. Previous trials have shown this approach is sufficient to ensure masking.[42] Group assignment codes will only be opened after the last endpoint of interest of the last participant in the trial is collected.

Data collection and management

Attentional and interpretative bias data will be collected automatically by the study computer during the assessment. In order to optimise the validity of the data collected, participants will be offered three breaks during each assessment once 25%, 50% and 75% of each session is completed. They may elect to take or override such offers of rest by asking the research officer to press the space bar, which once pressed will re-start the task. If response to a trial (faces or words) takes longer than

five seconds, that trial will be disregarded in the calculation of attentional and interpretative bias (long response latencies indicate distraction rather than bias).

The collection of endpoints will occur regardless the intervention adherence of participants. If participants become unable, or unwilling, to present to the research site for assessment, a home assessment will be offered. OPA will train research staff in the use of the CSDD and QoL-AD – agreement of 0.8 or greater on weighted Kappa will be required before the research officer is allowed to collect endpoints independently (minimum of five assessments).

Statistical methods

We will use means and standard deviations to describe continuous variables with normal distribution, medians and inter-quartile ranges for ordinal variables, and frequency tables for categorical variables. We will use t-tests to compare the change in CSDD and QoL-AD scores between baseline and week 2. If statistical adjustments are required because of imbalance in other study measures (e.g., gender distribution), we will use analysis of co-variance. We will use multilevel mixed models to analyse changes in CSDD, QoL and attentional and interpretative biases from baseline to week 2 and 12. We will investigate the interaction between group and time effects (statistical adjustments will be made, if necessary). This analysis is intention to treat. Multiple imputation (imputed chain equations) will be employed for the analysis of week 2 data, if necessary.

Data monitoring

No interim analyses are planned for this trial.

Harms

We do not anticipate that the procedures associated with the intervention have potential to causing clinically significant harm. Participants will be offered the opportunity of having breaks in order to minimize fatigue, although each intervention session is expected to last no more than 10 minutes. There will also be an opportunity for coffee and toilet breaks between intervention sessions and throughout the assessment procedures.

Auditing

Once a participant is randomised, the study computer will set up the study agenda for that person automatically – adherence will be recorded, analysed and reported. A quarterly internal audit will evaluate possible violations of protocol and research schedule, as well as integrity of the study's database (including accuracy of the data recorded). Electronic records will be backed up and maintained in a secure server at the University of Western Australia. Paper records of assessments will be kept for a minimum period of 5 years following the collection of the last endpoint of the trial. No external auditing is planned.

DISCUSSION

Alzheimer's disease is a leading cause of disability worldwide and the course of the illness is often complicated by the presence of depressive symptoms. Currently available antidepressant medications are not effective to treating depression in AD, so that efficacious alternatives are needed. There is strong empirical support for testing the efficacy of cognitive bias modification in this population, and the design of our study has followed SPIRIT and CONSORT guidelines in order to ensure that the trial generates high quality data that address its objectives appropriately.[43,44]

We have designed a CBM intervention that does not require the use of a keyboard or mouse (i.e., response entails the pressing of one of two buttons of the response box) and imposes only minimal

demands on the cognitive function of participants. We expect that this will increase the acceptability of and adherence to the intervention in this group of older participants.

Study limitations

The definition of depression in this study will be guided by the use of a validated cut-point on the Cornell Scale for Depression in Dementia rather than DSM-IV, DSM-5 or ICD-10 criteria for the diagnosis of a depressive episode.[34] We chose this approach for two reasons: (1) both the DSM and ICD criteria for the diagnosis of a major depressive episode associated with AD have uncertain validity, even though provisional alternate criteria have been proposed;[45,46] (2) pragmatic trials for the treatment of depression in AD have used CSDD scores of 8 or more to define clinically significant depression, with the use of the scale offering the additional advantage of measuring change in the severity of symptoms over time[15] and of allowing direct comparisons between the results of previous studies and ours.

This trial will be limited to people with depression in AD of mild to moderate severity. Consequently, its findings will not be generalisable to older adults with severe AD. This criterion for inclusion took into account the ability of participants to offer informed consent, and the relative integrity of brain systems involved in implicit learning during the early stages of illness. CBM works through implicit learning, which might be undermined late in the course of AD.[47]

The duration of the intervention in RAPID will be limited to two weeks, which is the time required to modify cognitive biases in adults free of cognitive impairment.[35,36] We anticipate that a similar timeline will be required to treat older adults with depression in AD, but cannot be certain, at this stage, that this will be the case. We will monitor attentional and interpretative biases throughout the study, and this will enable us to measure the association between extinction of bias and decline in

the severity of depressive symptoms. Moreover, we have included a 12-week follow up assessment to investigate the medium term sustainability of the changes in bias and mood of participants.

Funding

RAPID is currently funded by an unrestricted start-up grant from the Theodore and Isabella Wearne Charitable Trust.

Declaration of interests

The authors declare they have no conflicts of interest.

Roles and responsibilities

OPA and CM conceived and designed the study. LF, AF, BG and CEB contributed to the development of the protocol. OPA, LF, AF and CEB obtained the start-up funding for the trial. BG retrieved and organised the material for the CBM tasks. OPA drafted the manuscript, which all authors reviewed critically and approved for submission to BMJ Open.

Patient consent

This will be a requirement for participation in the study.

Ethics approval

The Human Research Ethics Committee of the Royal Perth Hospital approved the research protocol and procedures of the study (protocol number 14-036, 26 March 2014), which follow the principles of the Declaration of Helsinki. All participants will be required to provide written informed consent, which will be obtained by a member of the research team during the time of screening for eligibility.

Confidentiality

All participants will be identified by a number in the study database, which will not contain any identifiable data. Consent forms, screening questionnaires and contact details will be kept in a locked filing cabinet at the WA Centre for Health & Ageing. Publications arising from this trial will not contain any identifiable data.

Access to data

Only study investigators and project staff will have access to the study's database.

Ancillary and post-trial care

All participants will be required to have an active health practitioner, who will provide ongoing care during, and following completion of, the trial.

Dissemination

The results of RAPID will be published in a scientific journal. We also intend to disseminate the findings of the study through presentations to community groups and at scientific meetings, as well as press releases.

Provenance and peer review

This is an investigator initiated trial; not commissioned. The study protocol underwent independent external review for ethical and funding approval.

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Table 1. Timeline for the collection of outcomes for RAPID.

	Screening	Baseline	Week 2	Week 12
Sociodemographic data	YES			
Lifestyle	YES			
Medical conditions and medications	YES			
Daily alcohol consumption	YES			
Confirming diagnosis of AD	YES			
Mini-Mental State Examination	YES		YES	YES
Cornell Scale for Depression in Dementia	YES	YES	YES	YES
Quality of Life AD		YES	YES	YES
Attentional and interpretative biases		YES	YES	YES

RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia using cognitive bias modification: RAPID study protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	18-19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-8
	6b	Explanation for choice of comparators	18
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9 / 19
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	24

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15-16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia using cognitive bias modification: RAPID Study Protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005623.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Jun-2014
Complete List of Authors:	Almeida, Osvaldo; University of Western Australia, Psychiatry & Clinical Neurosciences MacLeod, Colin; University of Western Australia, Psychology Flicker, Leon; University of Western Australia, WA Centre for Health & Ageing Ford, Andrew; University of Western Australia, Psychiatry & Clinical Neurosciences Grafton, Ben; University of Western Australia, Psychology Etherton-Beer, Christopher; University of Western Australia, WA Centre for Health & Ageing
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Geriatric medicine, Neurology
Keywords:	Dementia < NEUROLOGY, Old age psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY

RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia using cognitive bias modification: RAPID Study Protocol

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Word count: 4854

Date: 9 May 2014

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ABSTRACT

Introduction: Depressive symptoms are common and undermine the quality of life of people with Alzheimer's disease (AD). Cholinesterase inhibitors and antidepressants have all but no effect on the mood of patients, and their use increases adverse events. Cognitive bias modification (CBM) targets attentional and interpretative biases associated with anxiety, dysphoria and depression and may be useful to treat depression in AD (DAD). This trial aims to determine the effect of CBM on depression scores and the quality of life of people with DAD.

Methods and analysis: Randomised, double-blind, parallel, controlled trial of CBM (1:1 allocation ratio). Participants will be 80 adults with probable AD living in the Western Australian community who score 8 or more on the Cornell Scale for Depression in Dementia (CSDD). They will have mild to moderate dementia (Mini-Mental State Examination - MMSE score ≥ 15) and will be free of severe sensory impairment or suicidal intent. The intervention will consist of ten 40-minute sessions of CBM delivered over two weeks using a high resolution monitor using a local computer station at the WA Centre for Health & Ageing. The primary outcomes of interest are the two-week change, from baseline, in the severity of CSDD scores and the Quality of Life AD (QoL-AD) scores. Secondary outcomes include changes in the CSDD, QoL-AD after 12 weeks, and changes in MMSE scores, negative attentional and interpretative bias and the proportion of participants with CSDD<8 after 2 and 12 weeks.

Ethics and dissemination: The study will comply with the principles of the Declaration of Helsinki and participants will provide written informed consent. The Ethics Committee of the Royal Perth Hospital will approve and oversee the study (REG14-036). The results of this trial will provide level 2 evidence of efficacy for CBM as a treatment of DAD.

Trial registration number: Australian and New Zealand Clinical Trials Registry number ACTRN12614000420640, date registered 06/04/2014.

Key-words: depression, quality of life, dementia, Alzheimer's disease, treatment, RCT, cognitive bias modification.

Strengths and limitations

- Strong empirical evidence supports the testing of cognitive bias modification as a treatment for depression in Alzheimer's disease.
- Cognitive bias modification interventions are not associated with clinically significant adverse events.
- The design of this trial follows SPIRIT guidelines and its results will be reported according to CONSORT guidelines.
- The pragmatic definition of depression in this trial will be based on the use of a validated cut-point on the Cornell Scale for Depression in Dementia rather than diagnostic criteria.
- The trial will be limited to people with depression in Alzheimer's disease of mild to moderate severity.
- The intervention will be limited to two weeks.

INTRODUCTION

Dementia is a leading cause of disability, affecting as many as 5% of the population over the age of 65 and 40% of those older than 80 years.[1,2] As the World's population continues to age, the number of people living with dementia is expected to increase exponentially over the next 40 years,[3] and this will lead to growing demands on residential care and health services.[4] In addition, the characteristic cognitive decline that affects people with dementia is commonly accompanied by other mental health changes involving perception, reasoning, behaviour and mood.[5] Most relevant to the current proposal is the fact that about 25% of people with Alzheimer's disease (AD), which is the most frequent cause of dementia in Western societies, show evidence of clinically significant depressive symptoms at assessment independent of the level of severity of the disease.[5,6] Currently available data also show that symptoms of anxiety and depression tend to co-occur in AD and may affect as many as 1 in every 2 people during the course of the illness.[7,8] Worryingly, the presence of mood disturbances in AD increases disability and burden of care,[8] impairs quality of life,[9] and has been associated with accelerated cognitive decline in longitudinal studies.[10] As currently available treatments for AD do not affect disease progression,[11] it is important that we develop interventions that improve the quality of life of these patients.

Treatments for AD do not ameliorate psychological comorbidity

Medications commonly used to treat people with AD have no obvious effect on mood. The cholinesterase inhibitors donepezil, galantamine and rivastigmine improve the cognitive scores of patients with AD compared with placebo,[12] but have no consistent impact on comorbid psychological and behavioural symptoms, including depression.[13] Similarly, data from randomised controlled trials suggest that memantine does not possess antidepressant properties.[14]

Treatments for depression associated with AD do not work and cause more side-effects

A large multicentre trial of the antidepressants sertraline and mirtazapine for the treatment of depression associated with dementia failed to show any benefit of treatment.[15] The investigators randomly assigned 326 people with AD and depression to treatment with sertraline (n=107, up to 150 mg daily), mirtazapine (n=108, up to 45 mg daily) or placebo (n=111). Thirty-nine weeks of follow up data were available. Treatment with antidepressants did not reduce depression scores relative to placebo after 13 or 39 weeks of treatment, but both sertraline and mirtazapine were associated with greater frequency of adverse reactions than placebo (43%, 41% and 26% respectively). Moreover, a systematic review of randomised placebo-controlled trials for the treatment of depression in dementia showed that the efficacy of antidepressants is equivalent to that of placebo over a period of 6 to 12 weeks.[16] These negative results are alarming, as depression is commonly associated with AD, hinders quality of life and is a significant source of stress for carers.[8,9] Novel and effective approaches to manage these patients are needed.

The contribution of cognitive bias to depression

Various psychological interventions have been tested for the treatment of depression to date, with the most robust empirical evidence for efficacy arising from trials of cognitive-behavioural therapy (CBT).[17] CBT uses a systematic approach to cognitive restructuring, change of biased negative beliefs and behavioural activation to mitigate the intensity and presence of depression.[18] Meta-analysis of pooled data of published trials indicates that CBT may also contribute to decreasing the risk of relapse over 12 to 24 months, suggesting that its benefits might extend beyond the acute phase of treatment.[19] The theoretical framework underpinning CBT recognises that depressed mood becomes apparent when a set of biased beliefs and thinking processes predominate, commonly involving preferential attention to negative aspects of experience and an inflated tendency to impose negative interpretations to ambiguous events. Such biases in the processing of information initiate the cycle of negative thinking and behavioural changes that are characteristic of depression. CBT challenges negative thoughts about the self, others and the future with the aim of modifying biased

ways of thinking and, consequently, leading to improved mood and behaviour. Effective shifts of dysfunctional biased beliefs have been associated with robust response to treatment and decreased risk of relapse of symptoms in cognitively intact people able to engage with the demands and requirements of the therapy.[20] However, a substantial gap persists in treatment options for depressed adults with cognitive impairment.

Cognitive models of depression ascribe the development of symptoms to systematic biases in low-level mechanisms not readily accessible to conscious introspection that operate before thoughts are formed in ways that shape their nature.[21] Selective biases in attention and interpretation that favour the processing of emotionally negative information are believed to represent the psychological basis of disordered mood, and emerging empirical and clinical findings support this hypothesis.[22] People with depression have more difficulty keeping their attention away from negative stimuli than non-depressed people. For example, adults with depression shown a series of faces on a computer screen selectively direct attention to sad faces, but show no such bias when presented with angry or happy faces.[23] In addition, when faced with ambiguity, people with depressed mood favour negative interpretations of stimuli. For example, when presented with the ambiguous cue word 'GROWTH' (which can be interpreted negatively to mean tumour or non-negatively to mean increased size or wealth), people with low mood are significantly faster to then complete fragments of semantically related words associated with the negative rather than the non-negative meanings of the ambiguous cue: C_NC_ER and GR_AT_R (cancer and greater).[24] These findings invite the question: are these biases amenable to change, and could they be a target for the treatment of dysphoria and depression in people with dementia?

What is cognitive bias modification (CBM)?

MacLeod and colleagues introduced the most widely used approach worldwide to modify attentional bias.[25] The procedure exposes participants to pairs of words or images on a computer

screen for 500 ms, with each pair including one emotionally negative and one neutral item. Immediately after the words/images disappear, a single small visual probe is presented in the same spatial position where one of the original stimuli had been displayed. Participants are required to indicate, as quickly as possible, the orientation of this probe (horizontal or vertical), and their speed to accurately do so is recorded over dozens of trials. People who display an attentional bias to the more negative information are significantly faster to make this discrimination judgment for probes that appear in the same area as the negative stimuli compared with probes in the region of the neutral stimuli. Cognitive bias modification for attention (CBM-A) delivers hundreds of trials in which all probes are presented where the neutral rather than the negative stimuli had just appeared (promoting attentional avoidance of negative information). A control condition presents probes with equal frequency to each of these two areas. In cognitive bias modification to reduce negative interpretative bias (CBM-I), participants are exposed to ambiguous information, followed by a word fragment that must be completed in a semantically consistent manner. CBM-I delivers hundreds of trials in which fragments yield only words consistent with non-negative interpretations of the ambiguity (discouraging negative interpretation). Thus, the ambiguous text "When you chat to people at a party they are soon chuckling, because you are so", will be followed by the fragment W_T_Y (yielding WITTY as opposed to 'silly'). A control condition employs fragments that equally often yield words consistent with negative or non-negative interpretation of the ambiguity. Single sessions of CBM can reduce negative attentional and interpretive bias, although multiple sessions may be associated with more lasting change.[25]

CBM improves mood: previous trial evidence

Recent trial data show that CBM-A attenuates anxiety reactions to stressful life events,[26] reduces recurrent negative thought intrusions in chronic worriers,[27] decreases avoidant behaviours[28] and mitigates the intensity of depressive and dysphoric symptoms over a 2-week period.[29] CBM is also effective at mitigating depressive symptoms in people with major depressive disorder. Williams and

colleagues randomised adults to CBM (n=38) or to a wait-list (n=31). CBM sessions were delivered daily over the internet for one week, and were associated with greater reduction in the severity of depressive symptoms.[30]

Rationale for the proposed trial

Depression commonly affects people with AD during the course of their illness. Data from randomised controlled trials show that treatment with cholinesterase inhibitors, memantine and antidepressants is ineffective at reducing the severity of depressive symptoms, while the use of traditional forms of psychotherapy is hindered by the cognitive deficits that characterise AD. As the pronounced impairment of explicit declarative learning (i.e., episodic memory) associated with AD does not compromise the implicit learning that occurs when patients acquire cue-outcome associations,[31] CBM may be a particularly suitable for use in this population.

Objectives

This trial aims to determine the effect of CBM on depressive symptoms and the quality of life of adults with depression in AD after two weeks of treatment. We hypothesise that participants treated with active compared with control CBM will experience greater improvement of depressive symptoms and quality of life scores after two weeks of treatment. We also anticipate that the improvements in depression and quality of life scores will be maintained for 12 weeks and that these changes will be associated with a relative reduction in negative attentional and interpretative biases.

METHODS

Study setting

This study has been designed as a single centre trial based at the Western Australian Centre for Health & Ageing at the Royal Perth Hospital in Australia. Participants will be community-dwelling older adults with Alzheimer's disease in contact with the metropolitan health services.

Trial design

The RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia (RAPID) is a parallel, double-blind, controlled randomised trial of cognitive bias modification with a 1:1 allocation ratio.

Eligibility criteria

We will recruit 80 people with depression in mild to moderate severity Alzheimer's disease according to the following inclusion criteria:

1. Diagnosis of probable AD according to NINCDS-ADRDA criteria,[32] which is largely consistent with DSM-5 diagnosis of major neurocognitive disorder due to probable AD,
2. Mini-Mental State Examination (**MMSE**) score ≥ 15,[33]
3. Cornell Scale for Depression in Dementia (CSDD) ≥ 8,[34]
4. Fluent in written and spoken English (preferred language for at least 10 years),

We will exclude from participation people who have:

1. One or more diseases likely to compromise ongoing participation in the trial (for example, severe visual impairment),
2. A weekly alcohol consumption greater than 28 standard drinks (> 4 drinks per day) or 6 or more standard drinks on any one day of the week,
3. Active suicidal intent,
4. No health practitioner who is able to provide ongoing clinical care,
5. Changed antidepressants during the preceding four weeks,

6. Not been able or willing to provide informed consent to participate.

Participants will be recruited from metropolitan Memory Clinics and through advertisement via local health services, carer groups and the media.

Interventions

Participants randomly assigned to the active and control CBM interventions will be exposed to the same study procedures and daily activities. They will be asked to attend the Western Australian Centre for Health and Ageing, Royal Perth Hospital, on a daily basis for a total of 10 CBM sessions (2 weeks – excluding weekends). Each session will be delivered on a 24'' high-resolution screen using a local PC station, and will last approximately 30 minutes: 15 minutes each for CBM-A and for CBM-I.

In the CBM-A session, participants will be shown pairs of emotionally discrepant photos for 500 ms (sad or neutral/happy faces). Each pair will then be replaced by a small probe (square or circle) appearing in the screen position previously occupied by one of the photos. Participants will be instructed to use a response box to indicate the shape of the small probe (by pressing the circle or square buttons of the response box). The probe will then disappear and will be replaced, after 1 second, by another pair that of photos to initiate the next trial. The time to discriminate probe identity will be recorded automatically. In the active CBM condition, designed to reduce attention to negative information, probes will always appear in the position of neutral/happy faces. In the control condition, probes will appear 50% of the time in the position of neutral/happy faces and 50% of the time in the position of the sad faces.

In the interpretative CBM sessions (CBM-I), single ambiguous cue-words that permit a negative and benign interpretation (e.g., HIT) will first appear in the top half of the screen for 1s. Then two

words will appear on the bottom half of the screen: one on the left and the other on the right hand side. This word-pair will consist of one target word that is semantically related either to the negative or benign meaning of the ambiguous cue-word (e.g., SUCCESS or PUNISH), and one foil word that is unrelated to either meaning of the ambiguous cue-word (e.g., CLOUD). Participants will be asked to identify which is the target word and use the response box to indicate whether the semantically-related word appeared on the left or right-hand side of the screen (by pressing the left or the right hand side button of the response box, respectively). The time required to accurately identify the target word will be recorded automatically. In the active CBM condition, designed to reduce negative interpretations of ambiguity, target words always will be associated with the benign meanings of the cue-words, discouraging their negative interpretation. In the control condition, 50% of the target words will be associated with the benign meaning and 50% with the negative meanings of the cue-words.

A trained graduate research officer will supervise all CBM sessions, and participants will be randomly assigned to the active or control CBM groups. Previous studies (reviewed in the Introduction) have shown that both attentional and interpretative biases can be modified successfully using these procedures. In addition, there is evidence that exposure to daily CBM leads to extinction of negative bias within two weeks,[35,36] thereby guiding the duration of our trial for efficacy whilst minimising treatment burden.

Outcomes

This trial has two primary outcomes of interest: depression and quality of life. We will use the Cornell Scale for Depression in Dementia (CSDD) to establish the presence of clinically significant symptoms of depression (CSDD ≥ 8), measure changes in the severity of symptoms over 2 and 12 weeks, and to ascertain the remission of symptoms after 2 and 12 weeks (CSDD < 8). The primary outcome of interest is the change, from baseline, in the severity of symptoms after 2 weeks of

treatment. The CSDD is the most widely used instrument worldwide to assess depression in dementia. The 19-item scale is rated on a 3-point score that ranges from absent to severe. The scale has robust psychometric properties, with good inter-rater reliability and internal consistency.[34] We are not aware of data describing minimal clinical important differences or minimal detectable changes for this scale. The CSDD is a rater-based assessment that takes about 10 minutes to complete.[34]

The Quality of Life AD (QoL-AD) scale will be this study's measure of quality of life.[37] It consists of 13 items that assess behavioural competence, psychological status, physical functioning and interpersonal environment that is of relevance to older adults. Each item offers four answers that range from poor (1) to excellent (4), with the total possible score ranging from 13 to 52. Higher scores indicate better quality of life. The QoL-AD has the added advantage of offering patient and carer versions. The QoL-AD has robust psychometric properties.[37] Changes in QoL-AD scores from baseline represent another outcome of interest of this trial, and will be measured 2 (primary endpoint) and 12 weeks (secondary endpoint) after the baseline assessment.

Before the intervention starts, all participants will complete a baseline assessment of attentional and interpretative biases, using assessment variants of the procedures described for the intervention. In the attentional assessment, probes will appear 50% of the time in the position of neutral/happy faces and 50% of the time in the position of sad faces. Negative attentional bias will be indexed by degree of relative speeding to discriminate probes in the latter condition compared to the former. In the interpretative assessment, target words will be related to the benign meaning of the ambiguous cue word 50% of the time and to its negative meaning 50% of the time. Negative interpretative bias will be indexed by degree of relative speeding to identify target words in the latter condition compared to the former. This assessment will be repeated 2 and 12 weeks after the start of the intervention, so that change in attentional and interpretative biases can be ascertained (secondary outcomes).

We will also collect data on acceptability of the intervention, adherence to treatment and reasons for withdrawal from the study. We will measure acceptability by asking participants after two weeks: (1) Please rate your experience with the CBM program: very unpleasant / unpleasant / unsure / pleasant / very pleasant. (2) If your doctor recommends CBM treatment for you in the future, would you: refuse it / be unsure whether to do it / be happy to do it again. Adherence will be measured automatically by the number of scheduled CBM session completed. We will consider that participants adhered to treatment if they completed at least 8 of 10 sessions. Partial and poor adherence will be defined by completion of 5 to 7 and less than 5 sessions, respectively. We will also ask participants who withdraw from the study to list the factors that might have contributed to their decision. Supportive collateral information will be sought from carers and treating physicians.

Other study measures

We will use a number of validated measures and procedures to collect demographic, lifestyle and clinical information from participants, including age, place of birth, time living in Australia, marital status, education, current and past occupations, living arrangements, religion and religion practices, weight and height, hobbies and financial concerns, smoking (never, past and current, amount and time), physical activity and alcohol consumption (standard units per day in a usual week), social support, prevalent medical conditions (diabetes, hypertension, dyslipidaemia, coronary heart disease, cerebrovascular disease, chronic respiratory diseases, arthritis and other rheumatic disorders, chronic pain, sensory impairment, cancer, and others), as well as prescribed and over the counter medications (including antidepressants). The approach to data gathering will follow the same procedures that we have used successfully in other trials.[38-40]

The Mini-Mental State Examination (MMSE) is the most widely used screening instrument for the assessment of cognitive function worldwide.[33] Scores can range from 0 to 30, with lower scores

indicating increasing cognitive impairment. The MMSE requires about 10 minutes to complete, and will be carried out at screening and 12 weeks. Changes of MMSE scores over 2 and 12 weeks will be additional secondary outcomes of interest of this trial. Table 1 summarises the timeline for the collection of the outcomes of the study.

TABLE 1

Sample size

Data from the placebo-controlled trial of mirtazapine and sertraline indicate that people with DAD treated with placebo improved, on average, 6 points (standard deviation, SD = 4) on the CSDD after 13 weeks.[15] We estimate that people treated with CBM should improve an additional 3 points (9 in total, standard deviation = 4). A sample size of 76 people with DAD (38 per group) would give the study 90% power to declare this difference as significant (alpha < 5%, two-tailed). We plan to recruit 80 participants with DAD (40 randomly assigned to each treatment group) and, pessimistically, anticipate that 15% of them will be lost during the study (our retention of people with AD in our trials is higher over a period of 6 months).[41] In this case, the trial would be completed by 68 participants and would still have 87% power. We further anticipate that loss to follow up will be minimal during the initial two weeks of treatment, although changes in scores may also be smaller at that point in time (3 points for controls and 6 for intervention participants). If we lose 10% of our sample during the initial two weeks, primary outcome data would be available for 72 participants (36 per group) and the study would have 89% power to declare as significant such a difference between the groups. Furthermore, a sample of this size would give the study 84% power to declare as significant changes in QoL-AD scores of 1 point for controls and 4.5 points for active CBM participants over three months (SD=5 for both groups; positive changes indicate expected improvement). The changes in response bias (measured in milliseconds) are expected to be associated with a minimum effect size of 0.4 (Cohen's d),[26] which would require about 50 trials

per participant (within group comparison). As each CBM session includes 96 trials for attention (faces) and 96 trials for interpretative bias (words), the study will have ample power to investigate this outcome.

Randomisation and allocation concealment

Participants will be randomly assigned to control and active CBM according to a list of random numbers generated by computer in blocks of ten. The allocation ratio will be 1:1. An independent biostatistician working at the WA Centre for Health and Ageing will generate the random allocation sequence. The sequence code will then be used to automatically select the appropriate intervention for the participant (control or active CBM) from our server (i.e., the id number will be linked to the randomisation code and the relevant intervention will be activated when the user id is entered on the computer). Neither the participant nor research staff will be aware of the independently controlled randomisation code. Participants will be advised about the study's aims and procedures (which will be exactly the same for all participants), but not about the details characterising the control and the active intervention. In addition, the staff member supervising the CBM sessions will not be involved in the collection of outcome data. This professional will be directed not to discuss any aspects of the intervention with other research staff. Previous trials have shown this approach is sufficient to ensure masking.[42] Group assignment codes will only be opened after the last endpoint of interest of the last participant in the trial is collected.

Data collection and management

Attentional and interpretative bias data will be collected automatically by the study computer during the assessment. In order to optimise the validity of the data collected, participants will be offered three breaks during each assessment once 25%, 50% and 75% of each session is completed. They may elect to take or override such offers of rest by asking the research officer to press the space bar, which once pressed will re-start the task. If response to a trial (faces or words) takes longer than

five seconds, that trial will be disregarded in the calculation of attentional and interpretative bias (long response latencies indicate distraction rather than bias).

The collection of endpoints will occur regardless the intervention adherence of participants. If participants become unable, or unwilling, to present to the research site for assessment, a home assessment will be offered. OPA will train research staff in the use of the CSDD and QoL-AD – agreement of 0.8 or greater on weighted Kappa will be required before the research officer is allowed to collect endpoints independently (minimum of five assessments).

Statistical methods

We will use means and standard deviations to describe continuous variables with normal distribution, medians and inter-quartile ranges for ordinal variables, and frequency tables for categorical variables. We will use t-tests to compare the change in CSDD and QoL-AD scores between baseline and week 2. If statistical adjustments are required because of imbalance in other study measures (e.g., gender distribution), we will use analysis of co-variance. We will use multilevel mixed models to analyse changes in CSDD, QoL and attentional and interpretative biases from baseline to week 2 and 12. We will investigate the interaction between group and time effects (statistical adjustments will be made, if necessary). This analysis is intention to treat. Multiple imputation (imputed chain equations) will be employed for the analysis of week 2 data, if necessary.

Data monitoring

No interim analyses are planned for this trial.

Harms

We do not anticipate that the procedures associated with the intervention have potential to causing clinically significant harm. Participants will be offered the opportunity of having breaks in order to minimize fatigue, although each intervention session is expected to last no more than 10 minutes. There will also be an opportunity for coffee and toilet breaks between intervention sessions and throughout the assessment procedures.

Auditing

Once a participant is randomised, the study computer will set up the study agenda for that person automatically – adherence will be recorded, analysed and reported. A quarterly internal audit will evaluate possible violations of protocol and research schedule, as well as integrity of the study's database (including accuracy of the data recorded). Electronic records will be backed up and maintained in a secure server at the University of Western Australia. Paper records of assessments will be kept for a minimum period of 5 years following the collection of the last endpoint of the trial. No external auditing is planned.

DISCUSSION

Alzheimer's disease is a leading cause of disability worldwide and the course of the illness is often complicated by the presence of depressive symptoms. Currently available antidepressant medications are not effective to treating depression in AD, so that efficacious alternatives are needed. There is strong empirical support for testing the efficacy of cognitive bias modification in this population, and the design of our study has followed SPIRIT and CONSORT guidelines in order to ensure that the trial generates high quality data that address its objectives appropriately.[43,44]

We have designed a CBM intervention that does not require the use of a keyboard or mouse (i.e., response entails the pressing of one of two buttons of the response box) and imposes only minimal

demands on the cognitive function of participants. We expect that this will increase the acceptability of and adherence to the intervention in this group of older participants.

Study limitations

The definition of depression in this study will be guided by the use of a validated cut-point on the Cornell Scale for Depression in Dementia rather than DSM-IV, DSM-5 or ICD-10 criteria for the diagnosis of a depressive episode.[34] We chose this approach for two reasons: (1) both the DSM and ICD criteria for the diagnosis of a major depressive episode associated with AD have uncertain validity, even though provisional alternate criteria have been proposed;[45,46] (2) pragmatic trials for the treatment of depression in AD have used CSDD scores of 8 or more to define clinically significant depression, with the use of the scale offering the additional advantage of measuring change in the severity of symptoms over time[15] and of allowing direct comparisons between the results of previous studies and ours.

This trial will be limited to people with depression in AD of mild to moderate severity. Consequently, its findings will not be generalisable to older adults with severe AD. This criterion for inclusion took into account the ability of participants to offer informed consent, and the relative integrity of brain systems involved in implicit learning during the early stages of illness. CBM works through implicit learning, which might be undermined late in the course of AD.[47]

The duration of the intervention in RAPID will be limited to two weeks, which is the time required to modify cognitive biases in adults free of cognitive impairment.[35,36] We anticipate that a similar timeline will be required to treat older adults with depression in AD, but cannot be certain, at this stage, that this will be the case. In addition, at this point in time, there is no direct evidence that the CBM paradigm will work as well in people with AD as it does in younger adults free of cognitive impairment. Our trial will yield such evidence, and this will allow us to ascertain if the effect (or

lack of effect) of the intervention was due to the expected shifting of attentional and interpretative biases. We will monitor attentional and interpretative biases throughout the study, and this will enable us to measure the association between extinction of bias and decline in the severity of depressive symptoms. Moreover, we have included a 12-week follow up assessment to investigate the medium term sustainability of the changes in bias and mood of participants.

Finally, we acknowledge that our power calculations are based on an expectation of clinically significant improvement rather than existing preliminary data. Our predictions assume that the intervention will be associated with a relative reduction of an additional 3 out of a possible 38 points compared with controls. Consequently, this trial will be underpowered to declare as statistically significant smaller differences between the groups.

Funding

RAPID is currently funded by an unrestricted start-up grant from the Theodore and Isabella Wearne Charitable Trust.

Declaration of interests

The authors declare they have no conflicts of interest.

Roles and responsibilities

OPA and CM conceived and designed the study. LF, AF, BG and CEB contributed to the development of the protocol. OPA, LF, AF and CEB obtained the start-up funding for the trial. BG retrieved and organised the material for the CBM tasks. OPA drafted the manuscript, which all authors reviewed critically and approved for submission to BMJ Open.

Patient consent

This will be a requirement for participation in the study.

Ethics approval

The Human Research Ethics Committee of the Royal Perth Hospital approved the research protocol and procedures of the study (protocol number 14-036, 26 March 2014), which follow the principles of the Declaration of Helsinki. All participants will be required to provide written informed consent, which will be obtained by a member of the research team during the time of screening for eligibility.

Confidentiality

All participants will be identified by a number in the study database, which will not contain any identifiable data. Consent forms, screening questionnaires and contact details will be kept in a locked filing cabinet at the WA Centre for Health & Ageing. Publications arising from this trial will not contain any identifiable data.

Access to data

Only study investigators and project staff will have access to the study's database.

Ancillary and post-trial care

All participants will be required to have an active health practitioner, who will provide ongoing care during, and following completion of, the trial.

Dissemination

The results of RAPID will be published in a scientific journal. We also intend to disseminate the findings of the study through presentations to community groups and at scientific meetings, as well as press releases.

Provenance and peer review

This is an investigator initiated trial; not commissioned. The study protocol underwent independent external review for ethical and funding approval.

Trial status

RAPID will start recruitment on the 7th July 2014. We anticipate that the collection of endpoints of the study will be completed by the 31st December 2017.

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Table 1. Timeline for the collection of outcomes for RAPID.

	Screening	Baseline	Week 2	Week 12
Sociodemographic data	YES			
Lifestyle	YES			
Medical conditions and medications	YES			
Daily alcohol consumption	YES			
Confirming diagnosis of AD	YES			
Mini-Mental State Examination	YES		YES	YES
Cornell Scale for Depression in Dementia	YES	YES	YES	YES
Quality of Life AD		YES	YES	YES
Attentional and interpretative biases		YES	YES	YES

RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia using cognitive bias modification: RAPID Study Protocol

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Word count: 4854

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ABSTRACT

Introduction: Depressive symptoms are common and undermine the quality of life of people with Alzheimer's disease (AD). Cholinesterase inhibitors and antidepressants have all but no effect on the mood of patients, and their use increases adverse events. Cognitive bias modification (CBM) targets attentional and interpretative biases associated with anxiety, dysphoria and depression and may be useful to treat depression in AD (DAD). This trial aims to determine the effect of CBM on depression scores and the quality of life of people with DAD.

Methods and analysis: Randomised, double-blind, parallel, controlled trial of CBM (1:1 allocation ratio). Participants will be 80 adults with probable AD living in the Western Australian community who score 8 or more on the Cornell Scale for Depression in Dementia (CSDD). They will have mild to moderate dementia (Mini-Mental State Examination - MMSE score ≥ 15) and will be free of severe sensory impairment or suicidal intent. The intervention will consist of ten 40-minute sessions of CBM delivered over two weeks using a high resolution monitor using a local computer station at the WA Centre for Health & Ageing. The primary outcomes of interest are the two-week change, from baseline, in the severity of CSDD scores and the Quality of Life AD (QoL-AD) scores. Secondary outcomes include changes in the CSDD, QoL-AD after 12 weeks, and changes in MMSE scores, negative attentional and interpretative bias and the proportion of participants with CSDD<8 after 2 and 12 weeks.

Ethics and dissemination: The study will comply with the principles of the Declaration of Helsinki and participants will provide written informed consent. The Ethics Committee of the Royal Perth Hospital will approve and oversee the study (REG14-036). The results of this trial will provide level 2 evidence of efficacy for CBM as a treatment of DAD.

Trial registration number: Australian and New Zealand Clinical Trials Registry number ACTRN12614000420640, date registered 06/04/2014.

Key-words: depression, quality of life, dementia, Alzheimer's disease, treatment, RCT, cognitive bias modification.

Strengths and limitations

- Strong empirical evidence supports the testing of cognitive bias modification as a treatment for depression in Alzheimer's disease.
- Cognitive bias modification interventions are not associated with clinically significant adverse events.
- The design of this trial follows SPIRIT guidelines and its results will be reported according to CONSORT guidelines.
- The pragmatic definition of depression in this trial will be based on the use of a validated cut-point on the Cornell Scale for Depression in Dementia rather than diagnostic criteria.
- The trial will be limited to people with depression in Alzheimer's disease of mild to moderate severity.
- The intervention will be limited to two weeks.

INTRODUCTION

Dementia is a leading cause of disability, affecting as many as 5% of the population over the age of 65 and 40% of those older than 80 years.[1,2] As the World's population continues to age, the number of people living with dementia is expected to increase exponentially over the next 40 years,[3] and this will lead to growing demands on residential care and health services.[4] In addition, the characteristic cognitive decline that affects people with dementia is commonly accompanied by other mental health changes involving perception, reasoning, behaviour and mood.[5] Most relevant to the current proposal is the fact that about 25% of people with Alzheimer's disease (AD), which is the most frequent cause of dementia in Western societies, show evidence of clinically significant depressive symptoms at assessment independent of the level of severity of the disease.[5,6] Currently available data also show that symptoms of anxiety and depression tend to co-occur in AD and may affect as many as 1 in every 2 people during the course of the illness.[7,8] Worryingly, the presence of mood disturbances in AD increases disability and burden of care,[8] impairs quality of life,[9] and has been associated with accelerated cognitive decline in longitudinal studies.[10] As currently available treatments for AD do not affect disease progression,[11] it is important that we develop interventions that improve the quality of life of these patients.

Treatments for AD do not ameliorate psychological comorbidity

Medications commonly used to treat people with AD have no obvious effect on mood. The cholinesterase inhibitors donepezil, galantamine and rivastigmine improve the cognitive scores of patients with AD compared with placebo,[12] but have no consistent impact on comorbid psychological and behavioural symptoms, including depression.[13] Similarly, data from randomised controlled trials suggest that memantine does not possess antidepressant properties.[14]

Treatments for depression associated with AD do not work and cause more side-effects

A large multicentre trial of the antidepressants sertraline and mirtazapine for the treatment of depression associated with dementia failed to show any benefit of treatment.[15] The investigators randomly assigned 326 people with AD and depression to treatment with sertraline (n=107, up to 150 mg daily), mirtazapine (n=108, up to 45 mg daily) or placebo (n=111). Thirty-nine weeks of follow up data were available. Treatment with antidepressants did not reduce depression scores relative to placebo after 13 or 39 weeks of treatment, but both sertraline and mirtazapine were associated with greater frequency of adverse reactions than placebo (43%, 41% and 26% respectively). Moreover, a systematic review of randomised placebo-controlled trials for the treatment of depression in dementia showed that the efficacy of antidepressants is equivalent to that of placebo over a period of 6 to 12 weeks.[16] These negative results are alarming, as depression is commonly associated with AD, hinders quality of life and is a significant source of stress for carers.[8,9] Novel and effective approaches to manage these patients are needed.

The contribution of cognitive bias to depression

Various psychological interventions have been tested for the treatment of depression to date, with the most robust empirical evidence for efficacy arising from trials of cognitive-behavioural therapy (CBT).[17] CBT uses a systematic approach to cognitive restructuring, change of biased negative beliefs and behavioural activation to mitigate the intensity and presence of depression.[18] Meta-analysis of pooled data of published trials indicates that CBT may also contribute to decreasing the risk of relapse over 12 to 24 months, suggesting that its benefits might extend beyond the acute phase of treatment.[19] The theoretical framework underpinning CBT recognises that depressed mood becomes apparent when a set of biased beliefs and thinking processes predominate, commonly involving preferential attention to negative aspects of experience and an inflated tendency to impose negative interpretations to ambiguous events. Such biases in the processing of information initiate the cycle of negative thinking and behavioural changes that are characteristic of depression. CBT challenges negative thoughts about the self, others and the future with the aim of modifying biased

ways of thinking and, consequently, leading to improved mood and behaviour. Effective shifts of dysfunctional biased beliefs have been associated with robust response to treatment and decreased risk of relapse of symptoms in cognitively intact people able to engage with the demands and requirements of the therapy.[20] However, a substantial gap persists in treatment options for depressed adults with cognitive impairment.

Cognitive models of depression ascribe the development of symptoms to systematic biases in low-level mechanisms not readily accessible to conscious introspection that operate before thoughts are formed in ways that shape their nature.[21] Selective biases in attention and interpretation that favour the processing of emotionally negative information are believed to represent the psychological basis of disordered mood, and emerging empirical and clinical findings support this hypothesis.[22] People with depression have more difficulty keeping their attention away from negative stimuli than non-depressed people. For example, adults with depression shown a series of faces on a computer screen selectively direct attention to sad faces, but show no such bias when presented with angry or happy faces.[23] In addition, when faced with ambiguity, people with depressed mood favour negative interpretations of stimuli. For example, when presented with the ambiguous cue word 'GROWTH' (which can be interpreted negatively to mean tumour or non-negatively to mean increased size or wealth), people with low mood are significantly faster to then complete fragments of semantically related words associated with the negative rather than the non-negative meanings of the ambiguous cue: C_NC_ER and GR_AT_R (cancer and greater).[24] These findings invite the question: are these biases amenable to change, and could they be a target for the treatment of dysphoria and depression in people with dementia?

What is cognitive bias modification (CBM)?

MacLeod and colleagues introduced the most widely used approach worldwide to modify attentional bias.[25] The procedure exposes participants to pairs of words or images on a computer

screen for 500 ms, with each pair including one emotionally negative and one neutral item. Immediately after the words/images disappear, a single small visual probe is presented in the same spatial position where one of the original stimuli had been displayed. Participants are required to indicate, as quickly as possible, the orientation of this probe (horizontal or vertical), and their speed to accurately do so is recorded over dozens of trials. People who display an attentional bias to the more negative information are significantly faster to make this discrimination judgment for probes that appear in the same area as the negative stimuli compared with probes in the region of the neutral stimuli. Cognitive bias modification for attention (CBM-A) delivers hundreds of trials in which all probes are presented where the neutral rather than the negative stimuli had just appeared (promoting attentional avoidance of negative information). A control condition presents probes with equal frequency to each of these two areas. In cognitive bias modification to reduce negative interpretative bias (CBM-I), participants are exposed to ambiguous information, followed by a word fragment that must be completed in a semantically consistent manner. CBM-I delivers hundreds of trials in which fragments yield only words consistent with non-negative interpretations of the ambiguity (discouraging negative interpretation). Thus, the ambiguous text "When you chat to people at a party they are soon chuckling, because you are so", will be followed by the fragment W_T_Y (yielding WITTY as opposed to 'silly'). A control condition employs fragments that equally often yield words consistent with negative or non-negative interpretation of the ambiguity. Single sessions of CBM can reduce negative attentional and interpretive bias, although multiple sessions may be associated with more lasting change.[25]

CBM improves mood: previous trial evidence

Recent trial data show that CBM-A attenuates anxiety reactions to stressful life events,[26] reduces recurrent negative thought intrusions in chronic worriers,[27] decreases avoidant behaviours[28] and mitigates the intensity of depressive and dysphoric symptoms over a 2-week period.[29] CBM is also effective at mitigating depressive symptoms in people with major depressive disorder. Williams and

colleagues randomised adults to CBM (n=38) or to a wait-list (n=31). CBM sessions were delivered daily over the internet for one week, and were associated with greater reduction in the severity of depressive symptoms.[30]

Rationale for the proposed trial

Depression commonly affects people with AD during the course of their illness. Data from randomised controlled trials show that treatment with cholinesterase inhibitors, memantine and antidepressants is ineffective at reducing the severity of depressive symptoms, while the use of traditional forms of psychotherapy is hindered by the cognitive deficits that characterise AD. As the pronounced impairment of explicit declarative learning (i.e., episodic memory) associated with AD does not compromise the implicit learning that occurs when patients acquire cue-outcome associations,[31] CBM may be a particularly suitable for use in this population.

Objectives

This trial aims to determine the effect of CBM on depressive symptoms and the quality of life of adults with depression in AD after two weeks of treatment. We hypothesise that participants treated with active compared with control CBM will experience greater improvement of depressive symptoms and quality of life scores after two weeks of treatment. We also anticipate that the improvements in depression and quality of life scores will be maintained for 12 weeks and that these changes will be associated with a relative reduction in negative attentional and interpretative biases.

METHODS

Study setting

This study has been designed as a single centre trial based at the Western Australian Centre for Health & Ageing at the Royal Perth Hospital in Australia. Participants will be community-dwelling older adults with Alzheimer's disease in contact with the metropolitan health services.

Trial design

The RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia (RAPID) is a parallel, double-blind, controlled randomised trial of cognitive bias modification with a 1:1 allocation ratio.

Eligibility criteria

We will recruit 80 people with depression in mild to moderate severity Alzheimer's disease according to the following inclusion criteria:

1. Diagnosis of probable AD according to NINCDS-ADRDA criteria,[32] which is largely consistent with DSM-5 diagnosis of major neurocognitive disorder due to probable AD,
2. Mini-Mental State Examination (**MMSE**) score ≥ 15,[33]
3. Cornell Scale for Depression in Dementia (CSDD) ≥ 8,[34]
4. Fluent in written and spoken English (preferred language for at least 10 years),

We will exclude from participation people who have:

1. One or more diseases likely to compromise ongoing participation in the trial (for example, severe visual impairment),
2. A weekly alcohol consumption greater than 28 standard drinks (> 4 drinks per day) or 6 or more standard drinks on any one day of the week,
3. Active suicidal intent,
4. No health practitioner who is able to provide ongoing clinical care,
5. Changed antidepressants during the preceding four weeks,

6. Not been able or willing to provide informed consent to participate.

Participants will be recruited from metropolitan Memory Clinics and through advertisement via local health services, carer groups and the media.

Interventions

Participants randomly assigned to the active and control CBM interventions will be exposed to the same study procedures and daily activities. They will be asked to attend the Western Australian Centre for Health and Ageing, Royal Perth Hospital, on a daily basis for a total of 10 CBM sessions (2 weeks – excluding weekends). Each session will be delivered on a 24'' high-resolution screen using a local PC station, and will last approximately 30 minutes: 15 minutes each for CBM-A and for CBM-I.

In the CBM-A session, participants will be shown pairs of emotionally discrepant photos for 500 ms (sad or neutral/happy faces). Each pair will then be replaced by a small probe (square or circle) appearing in the screen position previously occupied by one of the photos. Participants will be instructed to use a response box to indicate the shape of the small probe (by pressing the circle or square buttons of the response box). The probe will then disappear and will be replaced, after 1 second, by another pair that of photos to initiate the next trial. The time to discriminate probe identity will be recorded automatically. In the active CBM condition, designed to reduce attention to negative information, probes will always appear in the position of neutral/happy faces. In the control condition, probes will appear 50% of the time in the position of neutral/happy faces and 50% of the time in the position of the sad faces.

In the interpretative CBM sessions (CBM-I), single ambiguous cue-words that permit a negative and benign interpretation (e.g., HIT) will first appear in the top half of the screen for 1s. Then two

words will appear on the bottom half of the screen: one on the left and the other on the right hand side. This word-pair will consist of one target word that is semantically related either to the negative or benign meaning of the ambiguous cue-word (e.g., SUCCESS or PUNISH), and one foil word that is unrelated to either meaning of the ambiguous cue-word (e.g., CLOUD). Participants will be asked to identify which is the target word and use the response box to indicate whether the semantically-related word appeared on the left or right-hand side of the screen (by pressing the left or the right hand side button of the response box, respectively). The time required to accurately identify the target word will be recorded automatically. In the active CBM condition, designed to reduce negative interpretations of ambiguity, target words always will be associated with the benign meanings of the cue-words, discouraging their negative interpretation. In the control condition, 50% of the target words will be associated with the benign meaning and 50% with the negative meanings of the cue-words.

A trained graduate research officer will supervise all CBM sessions, and participants will be randomly assigned to the active or control CBM groups. Previous studies (reviewed in the Introduction) have shown that both attentional and interpretative biases can be modified successfully using these procedures. In addition, there is evidence that exposure to daily CBM leads to extinction of negative bias within two weeks,[35,36] thereby guiding the duration of our trial for efficacy whilst minimising treatment burden.

Outcomes

This trial has two primary outcomes of interest: depression and quality of life. We will use the Cornell Scale for Depression in Dementia (CSDD) to establish the presence of clinically significant symptoms of depression (CSDD ≥ 8), measure changes in the severity of symptoms over 2 and 12 weeks, and to ascertain the remission of symptoms after 2 and 12 weeks (CSDD < 8). The primary outcome of interest is the change, from baseline, in the severity of symptoms after 2 weeks of

treatment. The CSDD is the most widely used instrument worldwide to assess depression in dementia. The 19-item scale is rated on a 3-point score that ranges from absent to severe. The scale has robust psychometric properties, with good inter-rater reliability and internal consistency.[34] We are not aware of data describing minimal clinical important differences or minimal detectable changes for this scale. The CSDD is a rater-based assessment that takes about 10 minutes to complete.[34]

The Quality of Life AD (QoL-AD) scale will be this study's measure of quality of life.[37] It consists of 13 items that assess behavioural competence, psychological status, physical functioning and interpersonal environment that is of relevance to older adults. Each item offers four answers that range from poor (1) to excellent (4), with the total possible score ranging from 13 to 52. Higher scores indicate better quality of life. The QoL-AD has the added advantage of offering patient and carer versions. The QoL-AD has robust psychometric properties.[37] Changes in QoL-AD scores from baseline represent another outcome of interest of this trial, and will be measured 2 (primary endpoint) and 12 weeks (secondary endpoint) after the baseline assessment.

Before the intervention starts, all participants will complete a baseline assessment of attentional and interpretative biases, using assessment variants of the procedures described for the intervention. In the attentional assessment, probes will appear 50% of the time in the position of neutral/happy faces and 50% of the time in the position of sad faces. Negative attentional bias will be indexed by degree of relative speeding to discriminate probes in the latter condition compared to the former. In the interpretative assessment, target words will be related to the benign meaning of the ambiguous cue word 50% of the time and to its negative meaning 50% of the time. Negative interpretative bias will be indexed by degree of relative speeding to identify target words in the latter condition compared to the former. This assessment will be repeated 2 and 12 weeks after the start of the intervention, so that change in attentional and interpretative biases can be ascertained (secondary outcomes).

We will also collect data on acceptability of the intervention, adherence to treatment and reasons for withdrawal from the study. We will measure acceptability by asking participants after two weeks: (1) Please rate your experience with the CBM program: very unpleasant / unpleasant / unsure / pleasant / very pleasant. (2) If your doctor recommends CBM treatment for you in the future, would you: refuse it / be unsure whether to do it / be happy to do it again. Adherence will be measured automatically by the number of scheduled CBM session completed. We will consider that participants adhered to treatment if they completed at least 8 of 10 sessions. Partial and poor adherence will be defined by completion of 5 to 7 and less than 5 sessions, respectively. We will also ask participants who withdraw from the study to list the factors that might have contributed to their decision. Supportive collateral information will be sought from carers and treating physicians.

Other study measures

We will use a number of validated measures and procedures to collect demographic, lifestyle and clinical information from participants, including age, place of birth, time living in Australia, marital status, education, current and past occupations, living arrangements, religion and religion practices, weight and height, hobbies and financial concerns, smoking (never, past and current, amount and time), physical activity and alcohol consumption (standard units per day in a usual week), social support, prevalent medical conditions (diabetes, hypertension, dyslipidaemia, coronary heart disease, cerebrovascular disease, chronic respiratory diseases, arthritis and other rheumatic disorders, chronic pain, sensory impairment, cancer, and others), as well as prescribed and over the counter medications (including antidepressants). The approach to data gathering will follow the same procedures that we have used successfully in other trials.[38-40]

The Mini-Mental State Examination (MMSE) is the most widely used screening instrument for the assessment of cognitive function worldwide.[33] Scores can range from 0 to 30, with lower scores

indicating increasing cognitive impairment. The MMSE requires about 10 minutes to complete, and will be carried out at screening and 12 weeks. Changes of MMSE scores over 2 and 12 weeks will be additional secondary outcomes of interest of this trial. Table 1 summarises the timeline for the collection of the outcomes of the study.

TABLE 1

Sample size

Data from the placebo-controlled trial of mirtazapine and sertraline indicate that people with DAD treated with placebo improved, on average, 6 points (standard deviation, SD = 4) on the CSDD after 13 weeks.[15] We estimate that people treated with CBM should improve an additional 3 points (9 in total, standard deviation = 4). A sample size of 76 people with DAD (38 per group) would give the study 90% power to declare this difference as significant (alpha < 5%, two-tailed). We plan to recruit 80 participants with DAD (40 randomly assigned to each treatment group) and, pessimistically, anticipate that 15% of them will be lost during the study (our retention of people with AD in our trials is higher over a period of 6 months).[41] In this case, the trial would be completed by 68 participants and would still have 87% power. We further anticipate that loss to follow up will be minimal during the initial two weeks of treatment, although changes in scores may also be smaller at that point in time (3 points for controls and 6 for intervention participants). If we lose 10% of our sample during the initial two weeks, primary outcome data would be available for 72 participants (36 per group) and the study would have 89% power to declare as significant such a difference between the groups. Furthermore, a sample of this size would give the study 84% power to declare as significant changes in QoL-AD scores of 1 point for controls and 4.5 points for active CBM participants over three months (SD=5 for both groups; positive changes indicate expected improvement). The changes in response bias (measured in milliseconds) are expected to be associated with a minimum effect size of 0.4 (Cohen's d),[26] which would require about 50 trials

per participant (within group comparison). As each CBM session includes 96 trials for attention (faces) and 96 trials for interpretative bias (words), the study will have ample power to investigate this outcome.

Randomisation and allocation concealment

Participants will be randomly assigned to control and active CBM according to a list of random numbers generated by computer in blocks of ten. The allocation ratio will be 1:1. An independent biostatistician working at the WA Centre for Health and Ageing will generate the random allocation sequence. The sequence code will then be used to automatically select the appropriate intervention for the participant (control or active CBM) from our server (i.e., the id number will be linked to the randomisation code and the relevant intervention will be activated when the user id is entered on the computer). Neither the participant nor research staff will be aware of the independently controlled randomisation code. Participants will be advised about the study's aims and procedures (which will be exactly the same for all participants), but not about the details characterising the control and the active intervention. In addition, the staff member supervising the CBM sessions will not be involved in the collection of outcome data. This professional will be directed not to discuss any aspects of the intervention with other research staff. Previous trials have shown this approach is sufficient to ensure masking.[42] Group assignment codes will only be opened after the last endpoint of interest of the last participant in the trial is collected.

Data collection and management

Attentional and interpretative bias data will be collected automatically by the study computer during the assessment. In order to optimise the validity of the data collected, participants will be offered three breaks during each assessment once 25%, 50% and 75% of each session is completed. They may elect to take or override such offers of rest by asking the research officer to press the space bar, which once pressed will re-start the task. If response to a trial (faces or words) takes longer than

five seconds, that trial will be disregarded in the calculation of attentional and interpretative bias (long response latencies indicate distraction rather than bias).

The collection of endpoints will occur regardless the intervention adherence of participants. If participants become unable, or unwilling, to present to the research site for assessment, a home assessment will be offered. OPA will train research staff in the use of the CSDD and QoL-AD – agreement of 0.8 or greater on weighted Kappa will be required before the research officer is allowed to collect endpoints independently (minimum of five assessments).

Statistical methods

We will use means and standard deviations to describe continuous variables with normal distribution, medians and inter-quartile ranges for ordinal variables, and frequency tables for categorical variables. We will use t-tests to compare the change in CSDD and QoL-AD scores between baseline and week 2. If statistical adjustments are required because of imbalance in other study measures (e.g., gender distribution), we will use analysis of co-variance. We will use multilevel mixed models to analyse changes in CSDD, QoL and attentional and interpretative biases from baseline to week 2 and 12. We will investigate the interaction between group and time effects (statistical adjustments will be made, if necessary). This analysis is intention to treat. Multiple imputation (imputed chain equations) will be employed for the analysis of week 2 data, if necessary.

Data monitoring

No interim analyses are planned for this trial.

Harms

We do not anticipate that the procedures associated with the intervention have potential to causing clinically significant harm. Participants will be offered the opportunity of having breaks in order to minimize fatigue, although each intervention session is expected to last no more than 10 minutes. There will also be an opportunity for coffee and toilet breaks between intervention sessions and throughout the assessment procedures.

Auditing

Once a participant is randomised, the study computer will set up the study agenda for that person automatically – adherence will be recorded, analysed and reported. A quarterly internal audit will evaluate possible violations of protocol and research schedule, as well as integrity of the study's database (including accuracy of the data recorded). Electronic records will be backed up and maintained in a secure server at the University of Western Australia. Paper records of assessments will be kept for a minimum period of 5 years following the collection of the last endpoint of the trial. No external auditing is planned.

DISCUSSION

Alzheimer's disease is a leading cause of disability worldwide and the course of the illness is often complicated by the presence of depressive symptoms. Currently available antidepressant medications are not effective to treating depression in AD, so that efficacious alternatives are needed. There is strong empirical support for testing the efficacy of cognitive bias modification in this population, and the design of our study has followed SPIRIT and CONSORT guidelines in order to ensure that the trial generates high quality data that address its objectives appropriately.[43,44]

We have designed a CBM intervention that does not require the use of a keyboard or mouse (i.e., response entails the pressing of one of two buttons of the response box) and imposes only minimal

demands on the cognitive function of participants. We expect that this will increase the acceptability of and adherence to the intervention in this group of older participants.

Study limitations

The definition of depression in this study will be guided by the use of a validated cut-point on the Cornell Scale for Depression in Dementia rather than DSM-IV, DSM-5 or ICD-10 criteria for the diagnosis of a depressive episode.[34] We chose this approach for two reasons: (1) both the DSM and ICD criteria for the diagnosis of a major depressive episode associated with AD have uncertain validity, even though provisional alternate criteria have been proposed;[45,46] (2) pragmatic trials for the treatment of depression in AD have used CSDD scores of 8 or more to define clinically significant depression, with the use of the scale offering the additional advantage of measuring change in the severity of symptoms over time[15] and of allowing direct comparisons between the results of previous studies and ours.

This trial will be limited to people with depression in AD of mild to moderate severity. Consequently, its findings will not be generalisable to older adults with severe AD. This criterion for inclusion took into account the ability of participants to offer informed consent, and the relative integrity of brain systems involved in implicit learning during the early stages of illness. CBM works through implicit learning, which might be undermined late in the course of AD.[47]

The duration of the intervention in RAPID will be limited to two weeks, which is the time required to modify cognitive biases in adults free of cognitive impairment.[35,36] We anticipate that a similar timeline will be required to treat older adults with depression in AD, but cannot be certain, at this stage, that this will be the case. In addition, at this point in time, there is no direct evidence that the CBM paradigm will work as well in people with AD as it does in younger adults free of cognitive impairment. Our trial will yield such evidence, and this will allow us to ascertain if the effect (or

lack of effect) of the intervention was due to the expected shifting of attentional and interpretative biases. We will monitor attentional and interpretative biases throughout the study, and this will enable us to measure the association between extinction of bias and decline in the severity of depressive symptoms. Moreover, we have included a 12-week follow up assessment to investigate the medium term sustainability of the changes in bias and mood of participants.

Finally, we acknowledge that our power calculations are based on an expectation of clinically significant improvement rather than existing preliminary data. Our predictions assume that the intervention will be associated with a relative reduction of an additional 3 out of a possible 38 points compared with controls. Consequently, this trial will be underpowered to declare as statistically significant smaller differences between the groups.

Funding

RAPID is currently funded by an unrestricted start-up grant from the Theodore and Isabella Wearne Charitable Trust.

Declaration of interests

The authors declare they have no conflicts of interest.

Roles and responsibilities

OPA and CM conceived and designed the study. LF, AF, BG and CEB contributed to the development of the protocol. OPA, LF, AF and CEB obtained the start-up funding for the trial. BG retrieved and organised the material for the CBM tasks. OPA drafted the manuscript, which all authors reviewed critically and approved for submission to BMJ Open.

Patient consent

This will be a requirement for participation in the study.

Ethics approval

The Human Research Ethics Committee of the Royal Perth Hospital approved the research protocol and procedures of the study (protocol number 14-036, 26 March 2014), which follow the principles of the Declaration of Helsinki. All participants will be required to provide written informed consent, which will be obtained by a member of the research team during the time of screening for eligibility.

Confidentiality

All participants will be identified by a number in the study database, which will not contain any identifiable data. Consent forms, screening questionnaires and contact details will be kept in a locked filing cabinet at the WA Centre for Health & Ageing. Publications arising from this trial will not contain any identifiable data.

Access to data

Only study investigators and project staff will have access to the study's database.

Ancillary and post-trial care

All participants will be required to have an active health practitioner, who will provide ongoing care during, and following completion of, the trial.

Dissemination

The results of RAPID will be published in a scientific journal. We also intend to disseminate the findings of the study through presentations to community groups and at scientific meetings, as well as press releases.

Provenance and peer review

This is an investigator initiated trial; not commissioned. The study protocol underwent independent external review for ethical and funding approval.

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Table 1. Timeline for the collection of outcomes for RAPID.

	Screening	Baseline	Week 2	Week 12
Sociodemographic data	YES			
Lifestyle	YES			
Medical conditions and medications	YES			
Daily alcohol consumption	YES			
Confirming diagnosis of AD	YES			
Mini-Mental State Examination	YES		YES	YES
Cornell Scale for Depression in Dementia	YES	YES	YES	YES
Quality of Life AD		YES	YES	YES
Attentional and interpretative biases		YES	YES	YES

RAndomised controlled trial to imProve depressIon and the quality of life of people with Dementia using cognitive bias modification: RAPID study protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	18-19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-8
	6b	Explanation for choice of comparators	18
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9 / 19
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	24

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15-16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.