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# IDEA Intervention to prevent Depressive symptoms and promote well-being in Early stage dementia: protocol for a randomised controlled feasibility study



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Running head: IDEA INTERVENTION TO PREVENT DEPRESSIVE SYMPTOMS

# IDEA Intervention to prevent Depressive symptoms and promote well-being in Early stage dementia: protocol for a randomised controlled feasibility study

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## ABSTRACT

Depressive symptoms are common among people with dementia, impacting quality of life and cognitive and functional decline. Currently little is known about the acceptability and feasibility of psychological interventions for people with mild dementia, with recent reviews identifying the need for further evidence. Developing and evaluating psychological interventions to prevent and treat these symptoms is therefore an important clinical and research priority. This protocol describes a study testing the acceptability and feasibility of a manual-based Behavioural Activation (BA) intervention for preventing and treating depressive symptoms in people with mild dementia. The aim of this study is to explore the feasibility of conducting a pragmatic multicentre randomised controlled trial of clinical and cost-effectiveness of an 8-session intervention. The IDEA intervention supports people with dementia and their family carers in identifying and scheduling enjoyable and meaningful activities.

**Methods and analysis**: Sixty people who have received a diagnosis of dementia of any type in the last six months will be recruited via memory clinics. Further criteria are a Mini Mental State Examination (MMSE) score of ≥ 20, and a family carer who can assist with the intervention. Consenting participants will be randomised in a ratio of 2:1 to BA or to treatment as usual. Analyses will estimate parameters such as rates of recruitment, retention and number of sessions completed. Questionnaires measuring depressive symptoms and quality of life for both the person with dementia and their carer will be completed at baseline, 3, and 6 months. Qualitative interviews will explore acceptability of the intervention, study procedures and experiences of the sessions.




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**Ethics and dissemination**: This study received a favourable ethical opinion from the London Camberwell St Giles Research Ethics Committee (16/LO/0540). We will disseminate findings at key conferences, the Alzheimer's Society and University College London websites, and local stakeholder events.

**Trial registration number**: ISRCTN75503960

**Key words**: Dementia < Neurology; MENTAL HEALTH; Depression & mood disorders < Psychiatry; Old age psychiatry < Psychiatry; Clinical Trials < Therapeutics

**Strengths and limitations**:

- This will be the first study to provide acceptability and feasibility data for a psychological intervention based on BA for preventing and treating depressive symptoms in people with mild dementia.
- Explores feasibility parameters such as rates of recruitment, follow-up retention and number of sessions completed, with several proposed outcome measures tested for suitability for a full scale trial.
- By using both quantitative and qualitative data, the results will inform a future large scale randomised controlled trial (RCT) of clinical effectiveness.
- Limited to follow-ups at 3 and 6 months.
- People with dementia and their carers will be recruited from two London National Health Service (NHS) sites which may be associated with sample selection bias.



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## INTRODUCTION

Dementia is a leading cause of disability in late life [1], with economic costs to society expected to double from £26bn per year to £55bn in 2040 in the UK alone [2]. There are currently over 50 million people living with dementia, with numbers of people affected expected to increase to 66 million by 2030 [3, 4]. People with dementia are at increased risk of experiencing psychological distress such as depression [5, 6], which is not only distressing but persistent and associated with increasing cognitive and functional decline [7, 8], a risk of earlier care home admission [9], and reduced life expectancy [10]. In line with current NHS policies and the National Dementia Strategy [11], accessing emotional, social and practical support after diagnosis is an important and timely objective for people with dementia [12, 13], and it is reasonable to assume that people with dementia who additionally experience symptoms of depression will require more resources and support. In a review of experiences of post-diagnostic treatment, psychological care for people with dementia was described as least developed [14], indicating that access to psychological support remains poor despite an increasing emphasis on supporting people to maintain a sense of well-being.

Current estimates show that up to 50% of people living with dementia experience depression at least once during the course of the disease [15]. Major depressive disorder affects approximately 20 to 30% of people with dementia [7, 15], with personal or family history of depression [16] and a younger age at onset of dementia increasing risk of depression [17]. Sub-clinical or sub-threshold symptoms of depression occur at a higher rate than clinical depression [18], tend to be highly persistent [7], and are often experienced during the early stages of the disease [19]. Both depression and less severe



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depressive symptoms are sources of excess disability for people with dementia, therefore both major and subthreshold symptoms of depression are considered clinically important [18, 20].

Although depression is associated with high burden for people with dementia and their carers, there are currently no interventions available to prevent depressive symptoms occurring or becoming worse, which is key given poor efficacy of antidepressants [21]. Despite limited efficacy of pharmacological interventions and increased risk of side-effects, about a third of people with Alzheimer's disease living in the community are prescribed antidepressants [22, 23], and up to 40% in care homes [24] indicating a high need to manage these symptoms [19].

A Cochrane Review [25] of the effects of psychological treatments for people with dementia found that these treatments may contribute to a reduction in depressive symptoms, however evidence comes mostly from small-scale studies, with heterogeneous treatments [25]. A recent systematic review of Behavioural Activation (BA) interventions for older people found that these are associated with a reduction in depressive symptoms in older people without dementia living in the community [26]. The review also highlighted that most studies so far including people with dementia do not use well-defined interventions. The long-term aim of this research is to test effectiveness and cost-effectiveness of behavioural activation for people with dementia living in the community.

This study aims to establish the acceptability and feasibility of an 8-week intervention using BA principles [27, 28] developed after extensive consultations and field testing with people with mild dementia and their family carers. The study design is a feasibility randomised controlled trial (RCT), with two treatment arms (BA vs treatment as usual)



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following participants over 8 months. A secondary objective is to test the feasibility of procedures for conducting and planning a multicentre randomised controlled trial by exploring trial processes, and acceptability and feasibility of the intervention.

## METHODS AND ANALYSIS

### Participant recruitment

Inclusion criteria

Participants will be people who have received a diagnosis of dementia of any type in the last 6 months and: 1) are living in the community, 2) have a family carer who is available to participate and support the person in the intervention, and 3) have mild dementia (determined by a MMSE score of ≥ 20).

Exclusion criteria

Participants will be excluded if 1) they are deemed by their clinical team to be at risk of self-harm (excluding neglect) or a risk to others, 2) have difficulties communicating in English, or 3) are already taking part in another intervention study. People with previous depression, or previous or current treatment of antidepressants or experience of psychological treatments will not be excluded. The study will recruit a total of 60 people with dementia and their carers from Memory Clinics and Community Mental Health Teams of older people in London. Potential participants will be recruited by clinicians in relevant Trusts, by invitation letter or by a 'consent to contact' approach.

### Sample size considerations and randomisation

A total of 60 people will be recruited [29, 30] and randomised in a ratio of 2:1 to either the BA intervention or treatment as usual. Among the 40 participants in the BA



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arm, we will be able to estimate 75% acceptability of the IDEA intervention with a 95% confidence interval (CI) of 59 to 87%.

Participant randomisation will be undertaken at University College London (UCL) using a randomisation system stratified by site provided by internet-based sealed envelope codes, based on random permuted blocks of sizes three and six to allow an 2:1 allocation to intervention and treatment as usual. Randomisation allocation will be sent by automated email, to the unblind researcher performing the randomisation using their unique username and password.

**Treatment as usual**

This study is designed to be a pragmatic feasibility study, and no participants will be denied access to any treatment that they would have had access to. Both groups will receive regular treatment as usual, which is expected to be in line with NICE guidelines for treatment of dementia, details of which will be recorded for each participant using the Client Service Receipt Inventory (CSRI) [31].

**Blinding**

All follow-up assessments will be conducted by a researcher who is blind to treatment allocation. In trials of psychological interventions, it is difficult to blind therapists and participants to which intervention they are delivering or receiving. Any incidents of un-blinding will be recorded to inform the future trial.

**Intervention**

The proposed intervention will follow theory and models of BA [27, 28], and key components identified to be associated with effectiveness in trials of older people [26]. BA is defined as a brief structured therapeutic approach aimed at increasing engagement



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in adaptive activities often associated with pleasure and mastery, through structured activity scheduling and monitoring of mood, supplemented by additional behavioural strategies such as relaxation techniques, and hierarchical construction of goals [26].

The IDEA intervention will include:

(a) identifying pleasant activities for the person and developing and agreeing a plan of which activities to implement

(b) setting goals about implementing these activities

(c) monitoring and reviewing activities on a weekly basis

(d) teaching of specific relaxation skills [32]

(e) discussing accessing help

(f) making a plan for the future

The intervention will be an individual home-based manualised programme, comprised of a total of 8 weekly 1-hour sessions, delivered by a psychology graduate who will be trained in the intervention, and supervised monthly by one of the co-investigators. Based on suggestions and observations when developing the intervention, session frequency will depend on participants, with sessions completed over 8-12 weeks.

**Adherence to treatment protocol**

A manual guiding therapists in delivering the intervention will be developed, describing its key components. The feasibility of the treatment adherence measures and competency assessment will be assessed by developing a checklist for use in the main trial.

**Subsequent assessments of outcomes**



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All participants receiving the intervention will be asked to complete a follow-up qualitative interview at their home administered by a researcher not providing the intervention. These interviews will examine experiences and expectations of the intervention, and suitability of intervention materials in order to inform their further refinement in the main trial. Participants will be recruited until theoretical saturation has been achieved. Data on acceptability, completion rates and attrition will be supplemented by qualitative data.

**Proposed outcome measures for the full scale clinical trial**

The flow diagram of the current trial is presented in Figure 1. In order to inform the future trial, outcome measures will be trialled for suitability. Depressive symptoms is proposed as the outcome for the main study. Carers will complete generic health and quality of life measures, and resource use questionnaires to examine the feasibility of cost-effectiveness analysis. Questionnaires will be completed at baseline, 3 and 6-months after randomisation.

**Outcomes tested for acceptability for the main trial**

1. Depressive symptoms - Cornell Scale for Depression in Dementia *(CSDD)* [33]. The CSDD is a 19-item interviewer-administered measure which uses information provided by interviewing the person with dementia and their carer. Symptoms are described to the carer as they appear on the scale. Where there is a discrepancy between the carer and the researcher's ratings the carer is re-interviewed before making a final judgment.

1. Self-rated and carer-rated dementia-specific quality of life for the person with dementia – *DEMQOL and DEMQOL-proxy* [34]. The DEMQOL measures quality of life,



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[35] in five domains, including daily activities, health and well-being, cognitive functioning, social relationships and self-concept. The scale is used as a self or carer-rated report, administered to the person with dementia and carer, with established validity [36].

2. Self and carer-rated quality of life using the European Quality of Life-5 Dimensions *(EQ-5D)* for the person with dementia, measured using the three-level response version of the EQ-5D, a standardised instrument for use as a measure of health outcome [37].

3. Neuropsychiatric symptoms - Neuropsychiatric Inventory *(NPI)* [38]. The NPI assesses 12 behavioural disturbances occurring in people with dementia as rated by the carer, using a screening strategy to minimise administration time by examining and scoring only those behavioural domains with positive responses to screening questions. Both frequency and severity of each behaviour are also rated with higher scores indicative of more symptoms. Both validity and reliability of the measure has been established [35].

4. Health services utilisation - Client Service Receipt Inventory *(CSRI)* [39]. The CSRI will be used to collect feasibility data on the use of health and social care services provided by public or non-public bodies, and information on carers' costs and participants' use of health and social care services to inform the full trial. The feasibility of collecting service use data will be assessed, which will allow identification of services received in both groups and any changes that may occur.

5. Carers' mental health - Hospital and Anxiety Depression Scale *(HADS)* [40]. Depressive and anxiety symptoms in carers will be measured using the HADS, a self-



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rated measure, generating scores for both generalised anxiety and depressive symptoms, used widely to identify caseness for clinically significant depression and anxiety [41].

6. Carers' quality of life - the EQ-5D [37] and Short Form-12 Health Survey *(SF-12)* [42]. Carer health-related quality of life, will be measured using the EQ-5D. Carers' mental and physical health will be measured by the SF-12, measuring health by standardised responses, expressed in terms of two meta-scores: the physical component summary and the mental component summary.

**Safety monitoring**

Adverse events will be closely monitored. These are events that are likely to affect to a significant degree the safety or physical or mental integrity of the participants in the trial. The sponsor will be notified immediately of any case where the above definition applies during the trial.

**Statistical analysis plan**

Given this is a feasibility study it does not aim to provide a hypothesis test of the effectiveness of the intervention but to estimate feasibility study parameters. The main aims therefore are feasibility of the randomised controlled study, and acceptability of the intervention for people with dementia and their carers. We will therefore test analysis procedures in order to inform the statistical analysis plan of the main trial as opposed to making statistical comparisons of outcomes between the intervention and treatment as usual groups. The analyses will include the following:

- Rates of clinicians' referrals, number of participants recruited and randomised to the study (number of dyads referred and recruited per month, % reaching inclusion criteria, and any barriers or facilitators to recruitment)



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- Percentage of eligible participants that consent to the study
- Percentage of BA sessions completed (percentage in the BA group completing all sessions)
- Follow-up rates and number completing each outcome measure proposed for the main trial

We will produce a CONSORT diagram to represent numbers of people with dementia eligible for inclusion, numbers recruited, randomised and completing the study. Details of participants who meet the inclusion criteria but are not randomised will be recorded in order to inform the future trial. Essential baseline information will be recorded which will include quantitative and qualitative information (i.e. specifics of diagnosis, psychiatric history, use of medications, and demographics). In line with current recommendations of Good Clinical Practice, analyses will be descriptive. We will estimate standard deviations (95% CI) of potential outcome measures at baseline, 3 months, and 6 months and changes in scores from baseline. We will use rates of missing questionnaire data to inform the full trial. For the feasibility economic evaluation component we will collect data on resource use and costs for the future trial including resources required to deliver the intervention.

## ETHICS AND DISSEMINATION

### Ethics

The study is registered as a clinical trial and has been allocated an International Standard Randomised Controlled Trial Number (ISRCTN75503960). As the intervention is a psychological therapy, the trial is not covered by the Medicines for Human Use (Clinical Trials) Regulations 2004. The study has received a favourable ethical opinion from the London Camberwell St Giles Research Ethics Committee (16/LO/0540).



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**Informed consent and withdrawal from the study**

Participants will be in the mild stages of dementia, and therefore would generally be expected to be able to provide informed consent. In instances where the participant's level of impairment increases, so that they are no longer able to provide informed consent, the provisions of the Mental Capacity Act will be followed. Participants will be informed of their right to withdraw at any time without their care being affected in any way.

**Data management**

All participant information will be stored in accordance with the UK Data protection Act 1998 guidance, with all personally identifiable information stored in locked cabinets and stored separately from study data which will be anonymised and saved on password-protected computers at UCL, in line with UCL Data Protection Policy.

**Patient and public involvement**

Local user groups of people with dementia and their carers, and professionals supporting them have been consulted and involved in the design of the study, the development of the intervention and recruitment strategies in line with INVOLVE recommendations [43]. A dissemination strategy will be developed that will identify key stakeholder groups who will be communicated of the study's findings. We will also consult our PPI members for the design of the main trial.

**Oversight Committees**

A Trial Steering Committee has been set-up and will include an independent Chair, two independent members, and the study's co-investigator(s).

**DISCUSSION**



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This study will evaluate the acceptability and feasibility of a psychological intervention using BA principles to prevent and treat depressive symptoms for people with mild dementia informing a clinical and cost-effectiveness trial. In line with Medical Research Council (MRC) guidelines [44], we will use data from this study to further refine the intervention, produce a training package, and inform approaches for recruitment, and analyses for the full scale trial. This feasibility study is necessary preparatory work to inform to inform a full RCT and the psychological care of people with dementia.

## TRIAL SPONSORSHIP

UCL is the nominated sponsor.

## AUTHOR'S CONTRIBUTION

VO and GL developed the original concept of the trial, and VO drafted the original protocol; RG provided guidance on the development of the intervention; RJ provided statistical input; RT adapted the trial proposal as a protocol paper with help from ESV; VO, RT, RG, and GL have contributed to the development of the IDEA intervention; all authors reviewed and commented on drafts of the protocol and paper. All authors read and approved the final manuscript.

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## COMPETING INTERESTS

The authors hereby declare they have no competing interests.



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## LIST OF ABBREVIATIONS

| | |
|---|---|
| BA | Behavioural Activation |
| CI | Confidence Interval |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| MMSE | Mini Mental State Examination |
| NICE | National Institute for Health and Care Excellence |
| NHS | National Health Service |
| RCT | Randomised Controlled Trial |
| UCL | University College London |

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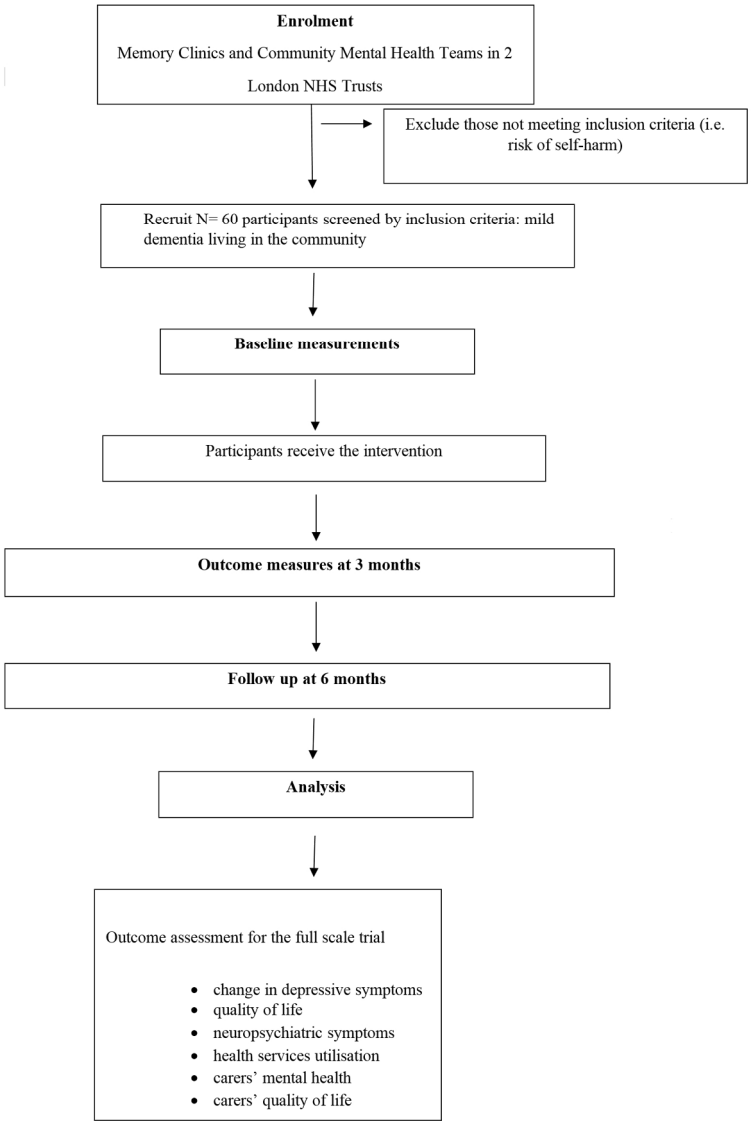


Figure 1

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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 | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 1/2/3/14[1] |
| Protocol version | 3 | Date and version identifier | Full protocol |
| Funding | 4 | Sources and types of financial, material, and other support | 14 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1/14 |
| | 5b | Name and contact information for the trial sponsor | Full protocol |
| | 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 | 13/14 |

[1] Date of Enrolment of first participant included in full protocol



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| | | | |
|---|---|---|---|
| | 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) | 13 |
| **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 | 4-6 |
| | 6b | Explanation for choice of comparators | 5 |
| Objectives | 7 | Specific objectives or hypotheses | 5/6 |
| 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) | 5/6 |
| **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 | 6 |
| 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) | 6 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 7-8 |
| | 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) | 11/13 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 8 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |

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| | | | |
|---|---|---|---|
| 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 | 9/10/11/12 |
| 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) | 8 |
| 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 | 6/7 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **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 | 7 |
| 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 | 7 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 7 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 7 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 7 |
| **Methods: Data collection, management, and analysis** | | | |

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|---|---|---|---|
| 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 | 9-12 |
| | 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 | 11-12 |
| 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 | 13 |
| 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 | 11-12 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 11-12 |
| | 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) | 11-12 |
| **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 | 11 |
| | 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 | Full protocol |
| 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 | 11 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Full protocol |
| **Ethics and dissemination** | | | |

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|---|---|---|---|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 12 |
| 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) | Full protocol |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 13 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 13 |
| 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 | 13 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 14 |
| 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 | 13 |
| 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 | Full protocol |
| 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 | 13 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 14 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | None |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Full protocol |

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| | | | |
|---|---|---|---|
| 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.

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