Interventional trial (non-CTIMP, non-device trial)
Protocol

Full title of trial	Feasibility randomised controlled trial of individual Cognitive Stimulation Therapy (iCST) for dementia in people with intellectual disabilities
Short title	CST in people with Intellectual disabilities and dementia
Version and date of protocol	Version 1 (21/10/2016)
Sponsor:	University College London (UCL)
Sponsor protocol number	
Funder (s):	Baily Thomas charitable Fund
ISRCTN / Clinicaltrials.gov no:	To be obtained once study is registered as a NIHR portfolio study
Intervention:	Individual Cognitive Stimulation Therapy
Single site/multi-site:	Multi-site

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Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
Version 1	21/10/2016	Afia Ali	Updated following recommendations from ethical commitee
Version 2	01/02/2017	Afia Ali	Updated following recommendations from ethical committee
Version 3	10/03/2017	Afia Ali	Updated following recommendations from ethical committee
Version 4	08/12/2017	Afia Ali	Minor changes to methodology- substantial amendment submitted to ethics
Version 5	14/02/2018	Afia Ali	Updated following ethics committee review of substantial amendment.

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator		**08/12/2017**
Afia Ali UCL	Signature	Date
Sponsor		
Suzanne Emerton UCL	Signature	Date

Contents

List of abbreviations

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CST	Cognitive Stimulation Therapy
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
ID	Intellectual Disability
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TMG	Trial Management Group

1 Trial personnel

See protocol cover page for Chief Investigator and Sponsor contact details.

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2 Summary

Objectives:	1.To adapt and modify a manualised individual Cognitive Stimulation Therapy (iCST) intervention for people with ID that can be delivered by carers 2. To carry out a feasibility randomised controlled trial of iCST, administered by carers, compared to treatment as usual, and to determine the tolerability and acceptability of the intervention
Type of trial:	A feasibility randomised multi-site trial of individual cognitive stimulation therapy compared to "Treatment as usual" in participants with dementia and intellectual disabilities.
Trial design and methods:	Forty dyads (carers and individuals with ID) will be randomised to either the intervention group or control group (treatment as usual). Randomisation will occur after baseline assessments are completed. Each arm will have 20 participants. Outcome assessments will include an assessment of cognitive functioning, adaptive functioning and quality of life in individuals with dementia. In carers we will assess care giving burden and the presence of anxiety and depression.
Trial duration per participant:	45 weeks
Estimated total trial duration:	15 months
Planned trial sites:	North East London NHS Foundation Trust, East London NHS Foundation Trust, Camden & Islington NHS Foundation Trust and Central and North West London NHS Foundation Trust and Barnet, Enfield & Haringey Mental Health Trust, Dorset Healthcare University NHS Foundation Trust, Northumberland, Tyne and wear NHS foundation Trust, Humber NHS Foundation Trust, Leicestershire Partnership NHS Trust.
Total number of participants planned:	40
Main inclusion/exclusion criteria:	Inclusion criteria 1. Mild or moderate intellectual disabilities 2. ICD-10 diagnosis of mild or moderate dementia 3. A carer available and willing to deliver intervention Exclusion criteria 1. Severe intellectual disabilities 2. Severe dementia 3. Visual or hearing impairment that prevents participation
Statistical methodology	As this is a feasibility study, we do not anticipate that there will be

and analysis:	statistically significant differences in the outcome measures between the intervention and control groups. However, we will examine differences in the mean and standard deviation for the primary outcome (cognitive functioning) in order to calculate a sample size for a larger study.

3 Background and Rationale

The prevalence of dementia in people with intellectual disabilities (ID) is almost five times higher when compared to the general population (1) and in people with Down syndrome, the prevalence is almost 90% (2) and is a significant cause of morbidity and mortality (3). Cognitive Stimulation Therapy (CST) has the strongest evidence for cognitive benefits in dementia (4). In the UK, the NICE guidelines (5) recommend that all people with mild/moderate dementia should be given the opportunity to participate in a structured group cognitive stimulation programme. Currently, people with ID and dementia are not offered CST, as no studies have examined its effectiveness in this group. CST significantly improves cognition and quality of life in people with dementia in the general population (6). It has comparable efficacy to anti-dementia drugs and is cost effective (7). Most of the evidence is based on group CST, typically two sessions a week lasting 45 minutes, over a seven week period (6). The intervention involves activities that include naming people and objects, word association, reminiscence, singing, creative activities, number and word games and discussion of current affairs. A range of evidence-based methods such as errorless learning, reality orientation and multi-sensory stimulation are used (8,9). The benefits of CST may arise from activation of neuronal networks associated with cognition such as memory and language (10).

To our knowledge, there has been only one pilot randomised controlled study of 25 participants with Down syndrome (without dementia) investigating the effectiveness of group CST in improving cognition, adaptive functioning and quality of life, compared to treatment as usual (11). The study found that the treatment significantly improved cognitive functioning in the group receiving CST pre and post treatment, and there was an improvement on quality of life scores at three months compared to pre-treatment. However, when the treatment and control groups were compared there were no differences in any of the outcomes post intervention and at three months. This finding is perhaps not surprising given that the participants did not have dementia and the sample size was also relatively small. However, the study did demonstrate that CST could be adapted for use in people with ID.

From our preliminary enquiries into the feasibility of group CST, several care providers have expressed concerns over the practicalities of running CST groups for people with dementia and ID. In order for group CST to be successful, individuals with a similar degree of cognitive impairment need to be grouped together in order to ensure that appropriate stimulating activities are selected. Differences in baseline cognition in individuals with ID, coupled with possible sensory impairment, poses a challenge for recruitment and effective group work. Individual CST may therefore be a more acceptable option for people with ID and dementia. Participating in one to one activities with someone the person with ID knows well could ensure that the activities are individually targeted and based on the interests of the individual, and may lead to positive interactions between the carer and individual. There is some evidence for the effectiveness of individual CST, delivered by carers, for people with dementia in the general population. Onder et al (12) conducted a randomised controlled trial of individual reality orientation therapy administered by home carers, versus no treatment, in

people receiving anticholinesterase inhibitors. They found significant Improvements in cognition but not for behavioural or functional outcomes.

A group at UCL, led by Professor Martin Orrell, have developed a manualised individual CST (iCST) intervention for people with dementia (without ID (13, 14). They have recently completed a multicentre randomised controlled trial of iCST delivered by family carers, compared to "treatment as usual" in 356 carers and individuals with dementia (15). The intervention comprises 75 sessions (each session was 30 minutes, given 3 times a week, over 25 weeks). This study found that iCST did not improve cognition or quality of life for people with dementia and it did not improve carers' physical or mental health. However, there was some improvement in the caregiving relationship and in carers' health related quality of life. Possible reasons for the lack of differences in the treatment and control groups in relation to cognition and quality of life could be attributed to the poor compliance rate. Only 51% of the dyads completed more than 30 sessions out of 75 and 22% did not complete any sessions. Adherence analyses found that people with dementia who completed more sessions showed improved quality in the caregiving relationship and carers reported lower depressive symptoms at 26 weeks. Qualitative data suggested that people with dementia and their carers experienced better communication as a result of iCST.

No studies have examined the feasibility of individual CST in people with ID with or without dementia. We aim to work closely with our UCL colleagues in developing individual CST for people with ID and dementia.

3.1 Assessment and Management of Risk

There will be no invasive tests or procedures that will be included above standard care. All the assessments will be based on standardised questionnaires. The intervention is not invasive.

The table below summarise the risks and mitigations of all test above standard care that are being performed in a table:

Intervention	Potential risk	Risk Management
Individual Cognitive Stimulation Therapy	Distress to participants	If participants are distressed by activities, the session should be terminated.
Administration of cognitive tests	Distress to participants	If participants are distressed, the session should be terminated.

4 Objectives

Primary:

To adapt and modify a manualised individual Cognitive stimulation (iCST) intervention for people with intellectual disabilities.

Secondary:

1. To carry out a feasibility randomised controlled trial to determine the tolerability and acceptability of the intervention (iCST) by examining the number of eligible participants, willingness of clinicians to recruit participants, willingness of participants to be randomised, appropriateness of outcome measures, drop-out rates, adherence to the intervention and acceptability of the intervention.

2. To determine the standard deviation and mean for the primary outcome measure (improvement in cognition in individuals with dementia and intellectual disability), which will be used to determine the sample size for a larger trial.

5 Trial design

The initial phase will involve the adaptation of the intervention and development of the iCST manual for people with intellectual disabilities and dementia.

1. Adaptation of the intervention (6 months in total)
The intervention will be modified according to the Medical Research Council guidelines on developing complex interventions (17). We will follow a similar procedure to that employed by the UCL group in developing the intervention and manual for iCST (18) and also their guidelines for adapting CST in other cultures (19).

Stage 1: focus groups and interviews (month 0-3)
We plan to hold three focus/consultation groups with carers of people with ID and dementia; professionals who work with people with ID such as psychologists, speech and language therapists, occupational therapists, physiotherapists, psychiatrists and social workers; and individuals with ID, with and without dementia. Each group will be facilitated by two members of the research team. The aim of the focus groups will be to discuss the acceptability of the current intervention, to review the suitability of materials within the existing iCST manual and the group CST manual developed by Shanahan (11) and to discuss suggestions for alternative/more appropriate activities. We will also discuss potential barriers that may affect recruitment or adherence to the intervention and strategies to overcome these barriers. The focus groups and interviews will be audiotaped and transcribed.

Stage 2: field testing the manual (month 4-6)
We will modify the iCST manual based on the focus group discussions, in order to ensure that the content is suitable for people with ID and dementia and that it can be used easily by carers. The existing iCST manual was designed to be delivered by family carers who were elderly and therefore it is already in a user friendly format. A draft manual will be produced with the input of a speech and language therapist and accessible information worker. The manual will then be field tested with five dyads comprising individuals with ID and dementia and their carer (paid and informal/family carers). Training for the carers will be provided by the research assistant. Carers will administer selected activities in five 30 minute sessions with the individual, and both the carer and individual will be asked to rate the activities on a questionnaire according to interest and enjoyment of the activity and ease of completing the activity. Suggested changes will be incorporated into a second version of the manual, which will be used in the feasibility study.

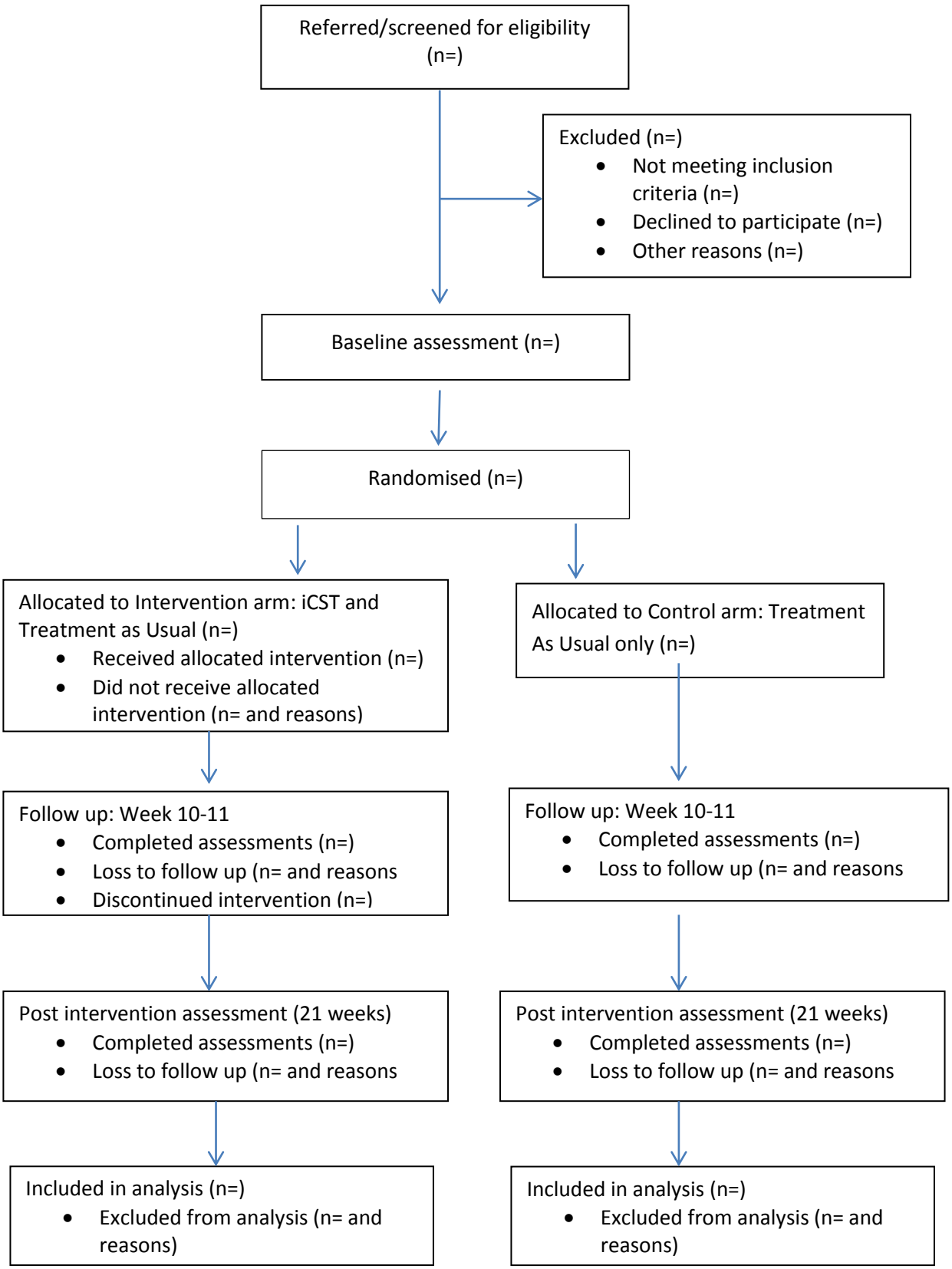
2. Feasibility Randomised Controlled Trial (18 months in total)

This will be a single blind, pilot randomised controlled trial of iCST delivered by carers versus treatment as usual. Forty dyads (carers and individuals with ID) will be randomised to either the intervention group or control group (treatment as usual). Randomisation will occur after baseline assessments are completed. Each arm will have 20 participants.

The duration of the intervention will be 20 weeks. There will be assessments at baseline prior to randomisation, at 11 weeks and at the end of the intervention at 21 weeks.

Please refer to figure 1 which shows the overall trial design.

Figure 1: Trial schematic diagram



6 Selection of Participants

6.1 Inclusion criteria

1. Aged 40 or over
2. Premorbid mild or moderate Intellectual disabilities (based on clinical notes)
3. ICD-10 diagnosis of mild or moderate dementia (assessed using the diagnostic tool from the CAMDEX-DS)
4. Has a carer (paid or informal) who knows the person with dementia well and is willing to deliver the intervention
5. Is able to provide informed consent or where the participant lacks capacity, he/she has a personal consultee who has agreed to the participant taking part in the study.

Participants receiving anticholinesterase inhibitors as part of their usual treatment, will not be excluded.

6.2 Exclusion criteria

1. Severe intellectual disabilities
2. Severe or late stage dementia
3. Has a visual impairment or hearing impairment that may interfere with the participant taking part
4. Has significant physical illness or disability preventing their participation
5. Has significant behavioural problems that could affect participation (e.g. aggressive behaviour)

6.3 Recruitment

Participants will be recruited from community learning (intellectual) disability teams **based in England** They will have been diagnosed (or will be strongly suspected of having dementia) by a clinical psychologist and/or psychiatrist. Psychiatrists/psychologists will be asked to screen their case load for possible participants. Participants will then be approached by members of the multidisciplinary team who work closely with the participant and will discuss the study with the participant and their carer. If they are both interested in taking part, they will be provided with an information sheet and their details will be passed on to the trial research assistant or CI. The research assistant will then contact the participant and their carer by phone and will arrange a face to face meeting to answer questions and to assess eligibility. If the participant and their carer agree to taking part then informed consent will be obtained from both the carer and the participant with dementia. If the participant with dementia lacks the capacity to consent, a personal consultee (a relative or friend) will be consulted, and the participant will only be included if the personal consultee agrees to the participant taking part.

Participant recruitment at a site will only commence when the trial has:

1. Been confirmed by the Sponsor (or it's delegated representative), and

2. Has received Rec Favourable opinion and HRA Approval

6.4 Informed consent

It will be responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The person taking consent will be suitably qualified and experienced, and will have been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks.

"Adequate time" will be given for consideration by the participant before taking part. Consent will be sought at least 24 hours after being given the study documentation. It must be recorded in the medical notes when the participant information sheet (PIS) has been given to the participant.

The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No trial procedures will be conducted prior to the participant giving consent by signing the Consent form. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the trial file at site and a copy placed in the medical notes.

The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

Participants lacking capacity

The intervention will be taking place with participants who may lack capacity to consent to taking part in the study because of their pre-existing intellectual disabilities or because of the development of dementia. We believe it is paramount that individuals who lack capacity are not excluded from the study otherwise the study would have limited applicability and generalisability to the majority of people with intellectual disabilities and dementia.

Capacity to take part in the research will be assessed by the research assistant who will receive training on assessing capacity. He/she will determine whether the participant broadly understands the nature and purpose of the research and the risks and benefits of taking part and not taking part; whether the participant is able to retain the information; whether they can weigh up the pros and cons of taking part in the research and whether they can communicate the decision (verbally or non verbally).

We will follow the guidelines stipulated in the Mental Capacity Act (2005) in relation to including participants lacking capacity in research. A personal consultee will be consulted to consider the participant's beliefs and wishes about taking part in the study and will need to sign the declaration form before the participant is included in the study. If a personal consultee is not available, then we will consider approaching a nominated consultee (a member of the clinical team not directly involved in the research) to provide written agreement.

7 Product/Interventions

7.1 Name and description of intervention(s) under investigation

Intervention group

The intervention will comprise of 40 sessions of individual Cognitive Stimulation Therapy based on a treatment manual. Each session will begin with discussion of the day, date, weather and location (5 mins) followed by discussion of events in the news or current issues (5 mins) and then the main activity (20 mins). The activities are based around a themed activity (e.g. life story, discussion of current affairs, being creative), which are designed to be mentally stimulating.

Each carer will administer the activities within the manual two times a week for 30 minutes, over a period of 20 weeks. The activities will be tailored to the ability and interests of the individual with ID. Carers will be asked to keep a record of their session (e.g. how long, type of activities and reasons for not competing the session) in a diary.

Carers will attend a training session either in a group setting (1 day training) or individual training at home (half a day), depending on their preference, which will be provided by the research team. They will receive training on how to use the adapted manual and will receive a copy of the adapted manual, a workbook and additional materials (e.g. deck cards and dominoes).

The intervention group will continue to have access to their usual care, which includes input from health and social care professionals, anti-dementia medication and their usual day activities.

Control group

The control group will have access to their usual care only for the duration of the trial. At the end of the study, the carers will be offered the manual and will receive the same training as the intervention group (1 day group training or half a day individual training) on how to use the manual to deliver individual CST to the person with dementia that they care for. They will receive monthly telephone calls offering support and will continue to have access to support and care from thei community learning disability service.

7.2 Storage and handling of drug at site (if applicable)

Not applicable

7.3 Accountability of drug (if applicable)

Not applicable

7.4 Concomitant medication (if applicable)

The participants will be permitted to take any medication that they usually take, including medication that may enhance cognition (e.g. acetyl cholinesterase inhibitors). These will be recorded carefully at baseline and follow up and considered in the analysis and interpretation of the data.

Concomitant medications will be recorded in the Participant's medical records/CRF.

7.5 Dosages, modifications and method of administration (if applicable)

Not applicable as the research team will not be administering any drugs.

8 Trial procedures

8.1 Pre-intervention assessments

All the participants with dementia and intellectual disability will be screened for the presence of dementia based on ICD-10 criteria. This will be assessed using the criteria from the CAMDEX-DS. If the participants meet the criteria, they will complete the following baseline assessments (at home) prior to randomisation:

1. Cambridge Cognitive Examination (CAMCOG-DS). This is an assessment of cognitive functioning from the CAMDEX-DS (20), which will be administered directly with the individual with dementia. It includes an assessment of orientation, language, attention, praxis, and abstract thinking. It provides individual subscale scores as well as total scores. Higher scores indicate better ability.

2. Modified Memory for Objects test from the Neuropsychological Assessment of Dementia in Intellectual Disabilities Battery. This will be administered with the individual (21). This assessment will involve presenting 7 every day items to the individual and testing his/her ability to recall an item that has been covered up. The maximum score is 7. Higher scores indicate better ability.

3. The Cognitive Scale for Down Syndrome (CS-DS) (22). This will be administered with the carer. This measure has 61 items that have been validated in adults with Down syndrome but the items are relevant to people with intellectual disability in general. The scale comprises items testing executive functioning, memory and language. Higher scores indicate better cognitive functioning.

4. Activities of Daily Living Inventory (ADCS-ADL) (23). This will be administered with the carer. This is a measure of the ability of the individual with dementia to carry out a range of daily activities. There are 23 items covering a range of areas such as feeding, bathing, grooming, preparing meals, use of household appliances and hobbies. The maximum score is 78. Higher scores indicate better ability.

5. Quality of life will be assessed using the QOL-AD (24). This will be administered with the carer. This is a 13 item scale with items covering physical health, mood, family life and functioning. The maximum score is 52, with higher scores indicating a better quality of life.

All the carers will also be asked to complete the following measures:

1. Care giving burden in both paid and informal carers will be assessed using the Care Giving Burden Scale (25). Carers are asked if the individual requires assistance in a range of areas, whether they have provided assistance in the last month and whether providing assistance has been stressful. There are three domains and each has a maximum score of 15.

2. The competence to look after someone with dementia will be assessed using the Sense of Competence in Dementia Care Staff (SCIDS) Scale. This is a 17 item scale with four subscales (professionalism, Building relationships, Care challenges and sustaining Personhood. The maximum score is 68, with higher scores indicating more competence (26). Although this questionnaire was developed for care staff, the questions may also be relevant for family members. Minor modifications to the questions will need to be made to ensure that it is appropriate for use in both groups.

3. The presence of an anxiety or depressive disorder will be assessed using the Hospital Anxiety and Depression Scale (HADS) (27).

The baseline and subsequent assessments will take up to 90 minutes to complete with the individual with dementia and up to two hours to complete with the carer.

All pre-treatment procedures will be carried out as specified in the schedule of assessments (appendix 1).

8.2 Randomisation Procedures

Participant randomisation will be undertaken centrally by the coordinating trial team using a web based system called Sealed Envelope

Following participant consent, and confirmation of eligibility (see section 8.1 for pre-treatment assessments), the randomisation procedure described below will be carried out.

A research assistant who is not involved in the study will enter the patient's trial ID into the web based randomization system ("sealed Envelope"). This system will randomly allocate the participant to either the intervention or control arm. He/she will inform the participants (carers/ individuals with dementia) of their allocation and will inform a relevant member of the research team. The randomisation list will be kept online.

In order to ensure that randomization is concealed, the professionals referring the participant, the participants at the time of enrollment and the research team will have no knowledge of the allocation prior to the start of the intervention. It will not be possible to blind the participants to the allocation group. However, the research assistant administering the questionnaires will be blind to the allocation group. At the end of the study we will assess researcher blindness by asking them to guess the allocated group.

Participants are considered to be enrolled into the trial following: consent, pre-treatment assessments (see section 8.1), confirmation of eligibility, completion of the randomisation process, allocation of the participant trial number and intervention by the central coordinating team.

8.3 Intervention procedures

The intervention will be delivered by the carer of the individual with dementia and will take place at home. Carers will attend a one day training session either in a group setting or individual training at home, depending on their preference, which will be provided by the research team. They will receive training on how to use the adapted manual and will receive a copy of the adapted manual, a workbook and additional materials (e.g. deck cards and dominoes).

The intervention will comprise of 40 sessions of individual Cognitive Stimulation Therapy (CST). Each carer will administer the activities within the manual two times a week for 30 minutes, over a period of 20 weeks. The activities will be tailored to the ability and interests of the individual with ID. Carers will be asked to keep a record of their session (e.g. how long, type of activities and reasons for not competing the session) in a diary.

If a carer is unable to continue the intervention (e.g. due to poor health) then another carer can be substituted. In order to support the carers and to ensure continued momentum, a member of the research team (clinical psychology trainee) will provide ongoing support to carers during the trial, and will address difficulties that carers may have in implementing the intervention. He/she will visit each dyad at least once a month and will telephone and email in between visits. The intervention group will also have access to "usual care" and therefore the intervention arm will be examining the additional effects of individual CST.

8.4 Subsequent assessments and procedures

The following measures will be administered at 10 weeks and 21 weeks at the participants' homes. See section on pre-intervention assessments for further information about the measures.

1. Cambridge Cognitive Examination (CAMCOG-DS)

2. Memory for Objects test from the Neuropsychological Assessment of Dementia in Intellectual Disabilities Battery.

3. The Cognitive Scale for Down Syndrome (CS-DS).

4. Activities of Daily Living Inventory (ADCS-ADL).

5. QOL-AD

All the carers will also be asked to complete the following measures:

1. Care Giving Burden Scale

2. Sense of competence in Dementia Care Staff (CSIDS) Scale

3. Hospital Anxiety and Depression Scale (HADS).

In order to assess adherence to the manual, for each dyad, two sessions will be audio-recorded (40 sessions in total). A brief adherence measure will be developed for the study.

At the end of intervention all the participants will be given a short questionnaire to complete about their experience of participating in the study, including feedback about whether they thought the intervention was practical and acceptable, such as whether the number of sessions were appropriate.

Ten carers and ten individuals with ID will be invited (5 carers and 5 individuals from each group) to participate in a semi-structured interview where more detailed feedback will be obtained about the study in general, including the study procedures. For those in the intervention arm, we will obtain feedback about the different components of the intervention such as the training given to carers and views about the iCST manual. We will ask about what aspects of the intervention worked or did not work well and what improvements could be made.

A schedule of all trial assessments and procedures is set-out in Appendix 1.

Payment

Gift vouchers will be given to all participants in the study to thank them for their time and for the inconvenience caused by taking part in the study. In the control arm, the carers and participants with dementia will receive a £10 gift voucher for completing each follow up assessment (at 11 weeks and 21 weeks).

The carers (both paid and informal) in the intervention arm will receive a £10 gift voucher after completing each follow up assessment, and a further £10 for completing each audio-taped session (total of £40). The participants with dementia will receive a £10 gift voucher after completing each assessment.

The carers and individuals with ID that volunteer to participate in the semi-structured interview at the end of the trial will receive a £10 gift voucher.

8.5 Samples (if applicable)

Not applicable

8.6 Discontinuation/withdrawal of participants

A participant may be withdrawn from trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing the trial may include:

- disease progression whilst on therapy

- intercurrent illness
- patients withdrawing consent or Personal/Nominated Consultees withdrawing assent for participants lacking capacity
- persistent non-compliance to protocol requirements.

The decision to withdraw a participant from treatment will be recorded in the CRF and medical notes. If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the CRF and medical notes.

8.7 Definition of End of Trial

The expected duration of the trial is 18 months from recruitment of the first participant.
The end of trial is the date of the last home visit of the last participant taking part in the qualitative interviews.

9 Recording and reporting of adverse events

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or trial participant, which does not necessarily have a causal relationship with the intervention involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect.
* A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

9.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

9.2.1 Severity

The generic categories below are given for use as a guide.

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

9.2.2 Causality

The assessment of relationship of adverse events to the intervention is a clinical decision based on all available information at the time of the completion of the case report form.

If a differentiated causality assessment which includes other factors in the trial is deemed appropriate, please add/amend the following wording to specify:

It is of particular importance in this trial to capture events related to the procedure (Cognitive Stimulation Therapy) (refer to section 9.17 for reporting requirements). The assessment of relationship of an adverse event to this/these additional safety issue(s) will also be carried out as part of the trial.

The differentiated causality assessments will be captured in the trial specific CRF or SAE form (amend as required).

The following categories will be used to define the causality of the adverse event:

Category	**Definition**
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

9.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the intervention listed in the SPC, manual of Operation (amend as appropriate) **or clearly defined in this protocol.**
Unexpected	An adverse event which is not consistent with the information about the intervention listed in the SPC, manual of Operation (amend as appropriate)* **or clearly defined in this protocol.**

* This includes listed events that are more frequently reported or more severe than previously reported.

There are no known adverse effects of Cognitive Stimulation Therapy. However, taking part may possibly cause distress/ inconvenience for some participants with dementia

9.3 Recording adverse events

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be recorded in the CRF until the participant completes the trial.

9.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor's AE log. The AE log of SAEs will be reported to the sponsor at least once or twice per year.

All SAEs (except those specified in section 9.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the sponsor's SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Where the event is unexpected and thought to be related to the intervention, this must be reported by the Investigator to the Health Research Authority within 15 days.

Completed SAE forms must be sent within 5 working days of becoming aware of the event to the Sponsor
Email forms to randd@uclh.nhs.uk

Managing serious adverse events in a multi-site trial (if applicable)

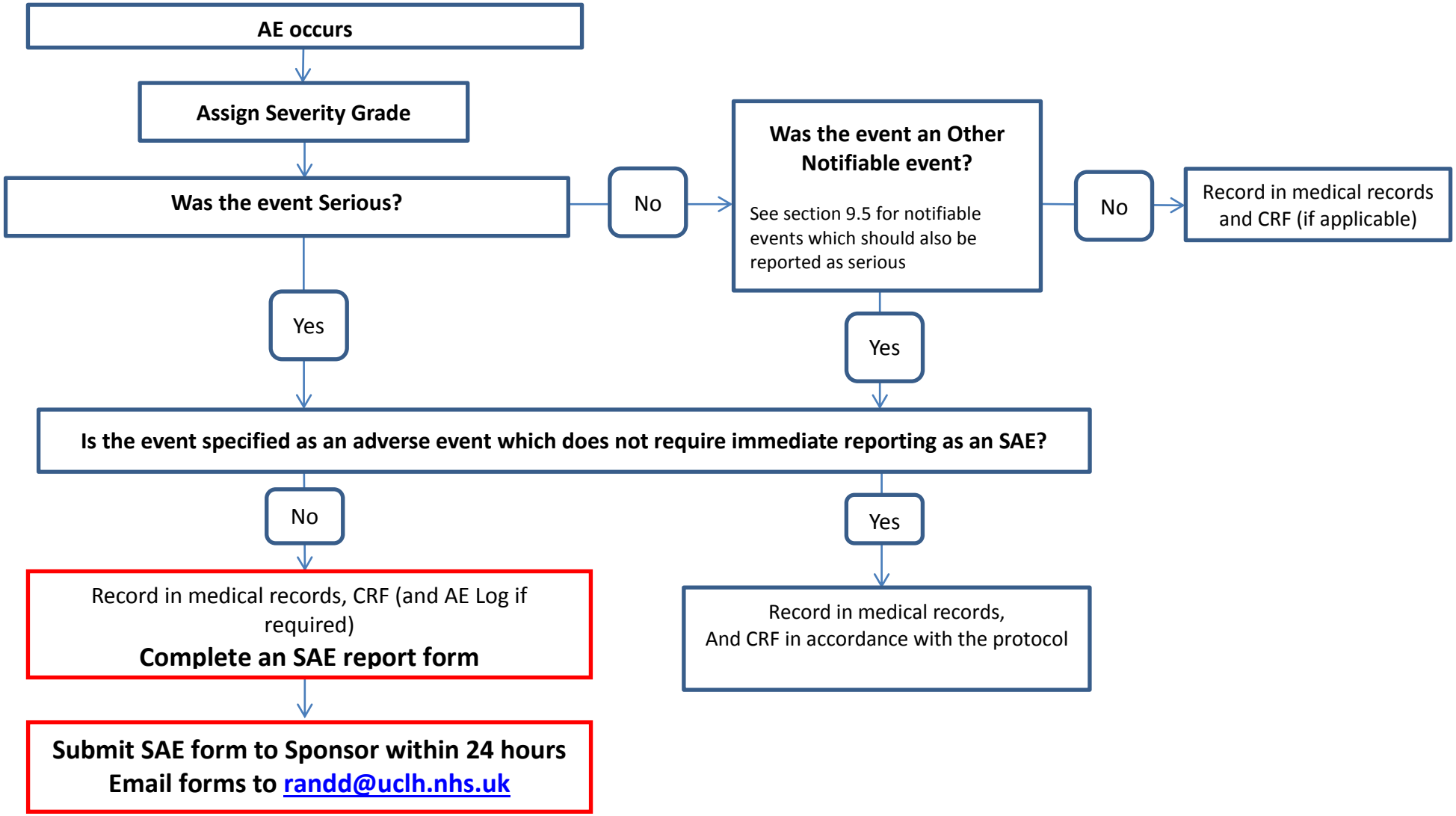
Serious Adverse Events will need to be reported by the PI to the CI within 48 hours. The CI will review the report first before submitting it to the sponsors within 24 hours. Safety information will be disseminated to all the PIs at the participating sites by the CI.

SAEs will be reported to the sponsor until the end of the trial.

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment.

Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to the JRO as further information becomes available.

Flow Chart for SAE reporting (this simple flow chart is for single site trial, please amend in line with trial specific requirements)



9.5 Serious Adverse Events that do not require reporting (if applicable)

Not applicable

9.6 Unblinding (if applicable)

This is not relevant as the participants will be aware of the whether they are receiving the intervention. The research assistant administering the questionnaires will be blind to the treatment group.

9.7 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

9.8 Notification of reportable protocol violations

A reportable protocol violation is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

9.9 Reporting incidents involving a medical device(s) (if applicable)

Not applicable

9.10 Trust Incidents and Near Misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

10 Data management

10.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the participant's name or other personal identifiable data. The participant's initials, date of birth and trial identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.

10.2 Data collection tools and source document identification

Data will be collected from sites on trial specific case report forms (CRFs) or data collection tools such as electronic CRFs.

Source data are contained in source documents and must be accurately transcribed on to the CRF. Examples of source documents are medical records which include laboratory and other clinical reports etc.

A source document list will be implemented prior to the start of the trial to identify:

- which data is to be recorded directly onto the CRF;
- which data is recorded firstly into source documents, such as medical notes, and then transcribed into the CRF; and
- which data is not to be recorded in the CRF but only recorded in source documents, e.g. participant questionnaires.

It is the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

10.3 Completing Case Report Forms

All CRFs must be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI/ PI to perform this duty. The CI/PI is responsible for the accuracy of all data reported in the CRF.

Once completed the original CRFs must be sent to the research team at UCL (Division of Psychiatry) and a copy kept at site. The CRFs must be returned within two weeks of the participant visit. Source data verification of a CRF page should be completed and all data queries answered prior to submission where possible.

10.4 Data handling

In the study, questionnaires (see section on pre-assessment and assessment measures) will be collected from patients in accordance with the patient consent form, patient information sheet and section 8 of this protocol.

The questionnaires will be appropriately sent to Dr Afia Ali (Division of Psychiatry, 6th floor Maple House, 149 Tottenham Court Road) for statistical analysis and Dr Afia Ali will act as the data controller of such data for the study

Afia Ali (Division of Psychiatry, 6th floor Maple House, 149 Tottenham Court Road) will process, store and dispose of questionnaires in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto. Patient data will be stored centrally at in a locked filing cabinet controlled by the Chief Investigator.

The questionnaires will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients' consent.

11 Statistical Considerations

11.1 Primary Outcome

The primary outcome will be changes in cognitive functioning, measured by the CAMCOG-DS. This will be measured before the intervention, midway (10 weeks) and after the intervention (20 weeks). Both are continuous measures. Pre and post intervention scores in each group will be calculated as well as the mean difference in scores in the intervention arm and the control group.

11.2 Secondary outcome(s)

For all the secondary outcomes, we will explore changes in the mean scores and standard deviation pre and post intervention in each group, as well as between group differences.

1. Cognitive functioning measured using the memory for Objects test. This is a continuous measure.

2. Cognitive functioning measured using the CS-DS. This is a continuous measure.

3. Adaptive functioning will be measured using the ADCS-ADL. This is a continuous measure.

4. Quality of Life will be measured using the QOL-AD. This is a continuous measure.

5. Care giving burden will be assessed using the care Giving Burden Scale. This is a continuous measure.

6. The competence of dementia staff will be measured using the SCIDS. This is a continuous measure.

7. Anxiety and depression in carers will be measured using the Hospital Anxiety and Depression Scale. This is a continuous measure.

11.3 Sample size calculation

This is a feasibility study with no formal power calculation. There is no available data on the use of individual Cognitive Stimulation Therapy in the treatment of dementia in people with intellectual disability. This study may provide cautious estimates of changes in cognition as result of the intervention, which could then be used to power a larger randomised controlled trial. For a feasibility study, including 20 participants in each arm is considered to be an acceptable number.

11.4 Planned recruitment rate

We will be recruiting for ten months. We estimate that we will recruit four eligible participants each month from at least seven learning disability services in London. If recruitment is anticipated to be slow, we will recruit other centres if necessary.

11.5 Randomisation methods

We will be randomising participants (dyads comprising individuals with dementia and carers) to either the treatment or control arm. Randomisation will be based on varying block sizes and will be balanced to ensure an even distribution of participants taking cholinesterase inhibitors. There will be 20 participants in each arm. This will be carried out by a web-based package (Sealed Envelope).

11.6 Statistical analysis

11.6.1 Summary of baseline data and flow of participants

Following randomisation we will compare baseline characteristics in both groups to assess comparability. These will be gender, age, type of accommodation (family home, supported housing, residential or nursing home) carer status (informal or paid carer), mean scores on the primary outcome (Cognitive functioning, as measured by the CAMCOG-DS) and the mean number of people on anticholinesterase inhibitors.

We will produce a Consort Flow diagram to record the flow of participants in the trial, e.g. number of people who were screened and were eligible; the number of people who were randomised to each arm; the number of people who completed the first assessment (week 10-11); the number of people who completed the intervention or dropped out and the number of people who completed the final assessment (post intervention, 20-21 weeks).

11.6.2 Primary outcome analysis

This is a feasibility study and therefore we are interested in examining the data in relation to recruitment. This will include information on how many participants were approached and agreed to be screened; how many met the eligibility criteria and agreed to take part and how many completed the study, or dropped out.

We do not anticipate that there will be any differences in between the intervention group and control with respect to the primary outcome as this is a feasibility study. We will calculate the changes in the mean and standard deviation between the two groups using Analysis of Covariance (ANCOVA), adjusting for the baseline score on the primary cognitive measure.

11.6.3 Secondary outcome analysis

As this is a feasibility study, we do not anticipate that there will be a statistically significant difference between the two groups in relation to the secondary outcomes. For each of the secondary outcomes, changes in the mean and standard deviation between the two groups will be calculated using Analysis of Covariance (ANCOVA), adjusting for the baseline score on the secondary outcome measure.

Other analyses:

The 40 recorded iCST sessions will be independently assessed by two raters for adherence to the manual. We will examine the carers' diaries to calculate the mean number of sessions that were completed by the carers and reasons for non-completion.

The qualitative interviews will be transcribed and analysed using thematic analysis to identify recurrent themes concerning participants' perceptions of the intervention. The findings will be used to further modify the intervention and to revise the manual.

11.6.4 Sensitivity and other planned analyses

No sensitivity analysis will be conducted.

12 Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

13 Oversight Committees

There will be a Trial Management Group.

13.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly (four times a year) and will send updates to PIs.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

14 Ethical requirements and patient and public involvement

Ethics

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and HRA approval. Amendments will not be implemented prior to receipt of the required approval(s).

Before any NHS site may be opened to recruit participants, the Chief Investigator/Principal Investigator must obtain HRA approval and all subsequent amendments must be submitted for HRA approval. This does not affect the individual clinician's responsibility to take immediate action if

thought necessary to protect the health and interest of individual participants (see section 9.6 for reporting urgent safety measures).

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the trial, which will then be submitted to the REC within 1 year after the end of the trial.

Patient and public involvement (PPI)

Service users/patients with intellectual disability and their carers will be involved in adapting the activities within the Individual Cognitive Stimulation manual, in order to produce an adapted version that will be suitable for individuals with intellectual disability and dementia.

15 Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

The degree of monitoring will be proportionate to the risks associated with the trial.

A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

16 Finance

The study is being funded by the Baily Thomas Charitable Fund. They have agreed to provide a funding of £94,463.00 subject to obtaining ethical approval.

There are no conflicts of interest to declare.

17 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this trial without the need to prove negligence on the part of University College London or another party.

Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this trial shall provide negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

18 Publication policy

All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings.

19 Intellectual property

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCLH. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL.

Each participating site agrees to, at the request and expense of UCL execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section X.Y shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

20 Appendices

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Appendix 1 - Schedule of assessments

	Screening (pre-treatment assessment)	Intervention phase				Final visit	Optional
Visit No:	1	2	3	4	5	6	7
		Week 1	Week 5	Week 11	Week 15	Week 20	
Window of flexibility for timing of visits:			e.g.+/- 7 days	E.g..+/- 7 days		e.g.+/- 7 days	
Informed Consent	X						
Medical History	X						
Eligibility confirmation (ICD-10 criteria)	X						
CAMCOG-DS	x			x		x	
Memory for Objects Test	x			X		x	
CSDS	x			X		x	
ADCS-ADL	x			X		x	
QOL-AD	x			X		x	
Care giver burden scale	x			x		x	
HADS	x			x		x	
SCIDS Scale	x						
Training for carers		x					
Treatment adherence/monitoring visit			x		x		
Trial evaluation questionnaire						x	
Semi-structured interview							x
Randomisation	X						
Adverse Events review	X	X		X		X	
Concomitant Medication review	X	X		X		X	