Full Study Title: The Cognition and Flow Study: The Effects of Brain Training on Brain Blood Flow

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Signatures:	The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and / or Sponsor.

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(In cases of Multi-centre studies, this must be replicated for each site)

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
	0.1	29/6/18	V.J Haunton R.B Panerai T.G Robinson R. Evley L. Beishon	Revision of the protocol pre-sponsor submission.
	0.2	8/8/18	L. Beishon	Pre-sponsor submission
	0.3	22/8/18	L. Beishon	Post-sponsor review revisions
	1	30/8/18	L. Beishon	Post-sponsor review
	2	30/10/18	L. Beishon	Post-Rec review
	3	14/11/2018	L.Beishon	Substantial amendment: 1. Change to order of study assessments 2. Participants will be asked to take dietary and lifestyle measures prior to assessment 3. Participants will not be withdrawn for low compliance 4. Participants cannot use tablet devices
	5	21/2/19	L. Beishon	Substantial amendment: 1. Addition of a post-stroke sub-group 2. Provision of laptops to participants where necessary

				3. To interview the healthy participant sub-group 4. To remove the upper limit on the MoCA cut-off
	6	5/9/19	L.Beishon	Substantial amendment: To increase the number of cognitive tasks for the post-stroke sub-group To collect data on the type, location, and size of the infarct
	7	19/12/19	L.Beishon	Removal of age limit on stroke sub-group (50 years)

List details of all protocol amendments here whenever a new version of the protocol is produced.

2. SYNOPSIS

Study Title	The Cognition and Flow Study: The Effects of Brain Training on Brain Blood Flow
Internal ref. no.	0677
Trial Design	Feasibility Randomised Controlled Trial
Trial Participants	Healthy older adults, adults with mild cognitive impairment (undifferentiated), adults with mild to moderate Alzheimer's disease, adults 12 months post-ischaemic stroke.
Planned Sample Size	80 participants in total, 20 participants in each of the four sub-groups.
Follow-up duration	Three to six months
Planned Trial Period	12 -18 months
Primary Objective	The primary objective of this study is to determine the ability to carry out (feasibility) of a large scale randomised controlled trial (RCT) of cognitive training (CT) in healthy older adults (HC), and people with Alzheimer's disease (AzD), mild cognitive impairment (MCI), and people post-ischaemic stroke.
Secondary Objectives	Are there any clinical benefits of a CT program in patients with dementia and any difference between groups (MCI/AzD/healthy older adults/post-ischaemic stroke) in ability to carry out everyday activities, memory, mood, and quality of life outcomes?
Primary Endpoints	1) Percentage of participants successfully recruited 2) Percentage of participants able to successfully complete CT program and complete all assessments 3) Percentage of participants with full bilateral data for CBFv 4) Feasibility of randomisation to waiting list control
Secondary Endpoints	1) Change in cognition score as detected by the Addenbrooke's cognitive examination (ACE-III) 2) Change in functional status - Lawton Instrumental Activities of Daily Living (IADL)

	3) Change in mood – Geriatric Depression Scale (GDS-15) 4) Change in quality of life measure – Dementia Quality of Life Measure (DEMQOL) 5) Change in task activation increase in CBFv from baseline
Qualitative objectives	The third element to this study is a qualitative component which will seek to explore any patient or carer benefits or harms not identified by the traditional measures listed above, specifically: • What are the barriers to CT in patients with dementia? • What are the facilitators (benefits) to brain training in patients with dementia? • Could CT programs be adapted further to support the participation of patients with dementia? • Are there any additional benefits to CT programs not measured by traditional methods as perceived by the patients and their carers? • To explore the lived experience of the patient and their carer and the impact CT has on them and their life

3. ABBREVIATIONS

AE	Adverse event
ACE-III	Addenbrooke's Cognitive Examination III
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
AR	Adverse reaction
AzD	Alzheimer's disease
CBFv	Cerebral blood flow velocity
CHIASM	Cerebral Haemodynamics in Ageing and Stroke Medicine
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRN	Clinical Research Network
CRO	Contract Research Organisation
CT	Cognitive Training
DEMQOL	Dementia Quality of Life Measure
EC	Ethics Committee (see REC)
$ETCO_2$	End-tidal CO_2
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HC	Healthy control
HR	Heart Rate
IADL	Instrumental Activity of Daily Living
ICF	Informed Consent Form
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MCI	Mild cognitive impairment
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL/S	Participant/ Patient Information Leaflet/Sheet
QoL	Quality of Life
RCT	Randomised controlled trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCD	Transcranial Doppler ultrasonography

TMF	Trial Master File
TSC	Trial Steering Committee

4. BACKGROUND AND RATIONALE

Disease Characteristics and Population Studied

The incidence of dementia is rising as the population ages, with 850,000 patients currently living in the UK alone (1). By 2026, this is projected to have risen by a further 40% (1). However, there are currently few diagnostic or therapeutic strategies available to offer patients. Dementia is a progressive condition characterised by gradual loss of cognitive or non-cognitive higher functions (i.e. language, visuospatial, attention) (2). Dementia is an umbrella term that encompasses a number of cognitive disorders including; Alzheimer's disease (AzD), vascular dementia, Lewy body dementia, fronto-temporal dementia and Parkinson's dementia (2). Mild cognitive impairment (MCI) is characterised by subjective and objective decline in cognitive function, but with preserved functional independence in daily living (3). It has become increasingly recognised that deranged vascular function is an early contributor to the deposition of amyloid plaques and tau tangles in AzD, and that these pathologies exacerbate one another (two-hit hypothesis) (4). In a recent systematic review and meta-analysis undertaken by this group, we demonstrated clear abnormalities in vascular function across a number of imaging modalities at the MCI stage (5). Thus, treatments that can improve cerebral perfusion or vascular function could represent an early treatment option for dementia (5). In this study, the target populations are; healthy older adults (as controls), adults with AzD, and MCI, to capture the effects of brain training (BT) on vascular physiology at an early stage in the dementia process.

Summary of the Project and Evidence Base

This project is a feasibility randomised controlled trial (RCT) as part of a PhD qualification to examine the use of a brain training (BT) program in adults with MCI, early AzD and healthy older adults (HC). In addition to measuring cognitive and functional outcomes, this study will also use transcranial Doppler ultrasonography (TCD) to measure changes in cerebral blood flow before and after an 8-12-week CT program. A recent systematic review found that longer, more intensive programs appeared to have no benefit over shorter programs, which are more likely to encourage adherence for patients with cognitive impairment (6, 7).

The evidence for CT in MCI, AzD, and vascular dementia (VaD) is heterogeneous, and frequently of low quality (8, 9). Few studies have included neuroimaging outcomes to explore brain plasticity or neural mechanisms underlying changes in cognition after CT (10). Therefore, this study not only addresses the development of a future high quality RCT of CT

in dementia, but also aims to fill the evidence gap on the use of TCD to assess neurovascular plasticity.

The use of TCD is a novel method to investigate for neurovascular training effects and for markers predictive of which patients may benefit from particular CT programs. This would allow the development of a personalised approach to developing CT programs for people with dementia. Given its low cost, portability and acceptability (11, 12), further studies are required to investigate the utility of TCD in older people and those living with dementia.

CT provides an attractive treatment target in dementia given there are few side effects and it is relatively cheap (7). However the evidence base at present is unclear, largely due to the poor quality studies that have been carried out to date (8, 9). Therefore, this study provides the basis for designing a high quality RCT of CT in dementia that can help address this issue.

Furthermore, this study will include a qualitative component to explore any benefits, problems or barriers to engaging with the training program that could be improved upon in future studies, and identify any benefits not measured by traditional outcomes.

TCD

TCD is a non-invasive, ultrasound based imaging modality that allows measurements of cerebral blood flow velocity (CBFv) at rest (13) and following activation by cognitive tasks (14). TCD has a number of advantages over other functional imaging techniques (magnetic resonance imaging (MRI) and positron emission tomography (PET)), including lower cost, portability, relative ease of operator training, and higher acceptability to patients (12, 15). TCD is particularly suited to older people, and those with dementia, as it can be used in patients with pacemakers, metal implants and claustrophobia (12).

Cognitive Training

Cognitive interventions can be considered as three broad categories; CT, cognitive rehabilitation and cognitive stimulation (9, 16). CT describes a structured, guided program of standardised tasks designed to provide practice or training with a specified cognitive domain(s), to translate into functional benefits (9, 16). This is distinguished from cognitive rehabilitation, where patient centered approaches and goals are used to improve everyday function, rather than improve cognition function (8, 9, 16), and cognitive stimulation which aims to generally improve cognition, social function and quality of life (17). CT is attractive in that it offers a cost effective, non-invasive and acceptable intervention to patients, with no reported adverse effects (18). A recent systematic review of 51 RCTs demonstrated improvements with CT in overall cognition, non-verbal memory, working memory, processing

speed, and visuospatial skills in healthy older adults (6). High quality RCT evidence is however lacking in studies of CT in dementia (7-9, 19). Two previous Cochrane reviews (8, 9), demonstrated the evidence was sparse, with many of the studies under-powered, of low-to-moderate quality, and with relatively few for MCI (8, 9). Recent systematic reviews of CT in MCI have demonstrated moderate benefits in verbal learning and memory, global cognition, non-verbal learning, working memory, attention and psychosocial functioning (19, 20). Thus far, studies of CT in dementia have been heterogeneous in study design, participants included, type and definition of training, outcome measures, and duration and intensity of intervention (7-9, 21, 22). This hampers the adequate meta-analysis of data and of conclusions that can be drawn from pooled analyses (7, 10).

Neuroimaging and CT

The use of neuroimaging outcomes has also been limited in CT studies (10, 23), but understanding the training effects occurring at the physiological level would provide important mechanistic information to any potential benefits conferred by CT (24-26). Belleville et al demonstrate increased parietal activation in patients with MCI, following a multi-modal CT program designed to improve episodic memory (24). In a near-infrared spectroscopy study by Vermeij et al, patients with MCI had greater training benefits at high load working memory where participants had greater pre-frontal activation (27), and baseline global and hippocampal atrophy were predictive of poorer training gains in healthy older adults and those with MCI (25). Therefore, imaging biomarkers can potentially be used to predict and tailor interventions to individual patient's needs (25, 26). Whilst a number of studies have demonstrated positive structural and functional effects of CT (26, 28, 29), they have largely focused on healthy older adults (28), the use of structural (28) or functional MRI (24, 25), and PET (30, 31), but there have been no TCD studies examining changes in neurovascular response to CT in patients with cognitive impairment.

5. OBJECTIVES

5.1 Primary Objectives

The primary objective of this study is to determine the ability to carry out (feasibility) a large scale RCT of CT in healthy older adults, and people with AzD and MCI.

5.2 Secondary Objectives

1) Are there any clinical benefits of a brain training program in patients with dementia and any difference between groups (MCI/AzD/healthy older adults/post-ischaemic stroke) in ability to carry out everyday activities, memory, mood, and quality of life outcomes?
2) Are there any changes in blood flow responses to cognitive tasks using TCD before and after brain training?
3) Are there any brain blood flow markers that can be used to predict who will benefit from brain training, and in which memory areas to generate a personalised training plan for individual patients?

5.3 Qualitative Study Objectives

1) What are the barriers to brain training in patients with dementia?
2) What are the facilitators (benefits) to brain training in patients with dementia?
3) Could brain training programs be adapted further to support the participation of patients with dementia?
4) Are there any additional benefits to brain training programs not measured by traditional methods as perceived by the patients and their carers?
5) To explore the lived experience of the patient and their carer and the impact brain training has on them and their life.

6. STUDY DESIGN

6.1 Summary of Trial Design

This is a prospective, feasibility, RCT of CT in healthy older adults, and adults with AzD, MCI, or post-ischaemic stroke. This trial is un-blinded, due to the nature of the intervention. The expected duration of participation per individual is three to six months. Initially, participants will be approached by a member of the clinical care team or research support staff, who will screen and identify eligible participants. Study specific information will then be provided by the researcher. Following this, participants will undergo informed consent. Each participant will have two visits (initial and follow-up assessment). After the first visit, participants will be randomised to control or intervention (CT), and will complete an 8-12 week CT program, if selected for the intervention group. Participants will be randomised using Sealed Envelope ©, an online, commercially available randomisation tool. At the end of the trial, participants will be given the option to participate in a qualitative study by semi-structured interviews or focus group. A flow chart for this process can be seen in Appendix A.

6.2 Primary and Secondary Endpoints/Outcome Measures

Primary end point measures:

1) Number of participants successfully recruited
2) Percentage of participants able to successfully complete the CT program and all assessments
3) Percentage of participants with full bilateral data for CBFv
4) Feasibility of randomisation to waiting list control

Secondary end points:

1) Change in cognition score as detected by the Addenbrooke's cognitive examination (ACE-III)
2) Change in functional status - Lawton IADL
3) Change in mood – GDS-15
4) Change in quality of life measure – DEMQOL
5) Change in task activation increase in CBFv from baseline

7. TRIAL PARTICIPANTS

7.1 Overall Description of Trial Participants

1) Participants with mild-moderate AzD
2) Participants with MCI
3) Healthy older adults
4) Post-ischaemic stroke

7.2 Inclusion Criteria

Study specific inclusion criteria will be as follows:

One of:

1) Healthy controls will be free of any medical co-morbidity or medication that could adversely affect cognition. Volunteers with well-controlled co-morbidities (i.e. hypertension, diabetes, will be considered for inclusion)
2) MCI as defined by NIA/AA 2011 and Petersen criteria
3) AzD as defined by the NIA/AA 2011 criteria
4) Ischaemic stroke within the last 12 months

And:

5) Deficits will be mild to moderate as defined by Montreal Cognitive Assessment (MoCA) score of >/=9 for all participants with MCI or Alzheimer's disease (32-34).
6) Willing to participate
7) Capacity to consent to the study/personal consultee
8) Patients on and off anti-dementia medications will be included (acetylcholinesterase inhibitors, glutamate receptor antagonists)
9) Good understanding of written and spoken English
10) Age >50 years (MCI, AzD, and healthy controls only)
11) Access to the internet and a computer or laptop.

7.3 Exclusion Criteria

Study specific exclusion criteria as follows:

1) Healthy controls with any medical co-morbidity or medication that could adversely affect cognition, or poorly controlled medical co-morbidities (i.e. hypertension, diabetes)
2) Unwilling to take part
3) Unable to consent/no personal consultee
4) Major medical co-morbidity; severe heart failure (ejection fraction <20%), significant carotid artery stenosis >50%), severe respiratory disease, major stroke (MCI and AzD groups only)
5) Pregnancy, planning pregnancy, or lactating
6) Inadequate bilateral TCD windows
7) Participants already enrolled into other interventional studies
8) Insufficient understanding of written and spoken English
9) Age <50 years (MCI, AzD, and healthy controls only)
10) No access to the internet and a computer or laptop.

8. STUDY PROCEDURES

8.1 Participant identification

This study has broad recruitment strategy to ensure that recruitment targets are met. Our previous pilot study, and other dementia studies have demonstrated that this is the most appropriate recruitment strategy. Appendix A outlines the participant recruitment pathway for this study. Appendix B outlines the overall study flow process, and Appendix C outlines the schedule of procedures for each participant.

Healthy volunteer identification

Healthy volunteers will be recruited through poster advertisement at the University of Leicester, University Hospitals of Leicester (UHL), LPT, and GP surgeries, and pharmacies in the East Midlands. In addition, healthy volunteers will be recruited from friends, family, and carers of enrolled patient participants, and through the healthy volunteer section of Join Dementia Research (see below). In addition, the University of Leicester holds a research interested list of healthy volunteers who will be contacted by the researcher to provide study specific information if they are interested in participating. Interested participants will self-refer directly to the researcher who will provide study specific information. Participants will be allowed a minimum of 24 hours to decide if they would like to enrol in the study, and to contact the researcher who will arrange for them to undergo an eligibility assessment (see Section 8.2) and the formal consent (Section 8.3) and study enrolment.

Patient identification

Secondary care services - geriatric and memory service recruitment

Eligible participants will be identified by Consultants and specialist registrars in Geriatric Medicine, or Old Age Psychiatry, or specialist nurses from the memory service, by screening their medical records for the inclusion and exclusion criteria. Eligible participants will be approached by the above members of the direct care team and referred to the researcher or research delivery team for further information. In addition, screening of eligible participants under the geriatric and memory service will be undertaken by research delivery officers from the NIHR CRN, UHL, and LPT, and eligible participants that are interested will be approached by a member of their direct care team, and if interested referred to the researcher or research delivery team and provided with study specific information.

Research interested list

The LPT hold a research interested list of patients whom they may approach if they are eligible for the study. Research delivery staff at the LPT will eligibility screen the list and contact participants who meet the inclusion and exclusion criteria. Interested participants will then be provided with study specific information by the LPT research delivery team.

Primary care recruitment

A database search will be conducted with the support of the NHR CRN for GP surgeries in Leicester and Leicestershire. Eligible participants will be screened from the database by a member of the direct care team at that practice. Participants that meet the inclusion and exclusion criteria will be invited to join the study through letter invitation from their GP surgery. Participants who contact the researcher or research delivery officer after letter invitation will then be provided with study specific information by the research team.

Community group recruitment

Study specific information will be provided to attendees at local community groups (i.e. Alzheimer's society memory café) by volunteers and the members of the research team. In order to eligibility screen the interested participants, a referral will be made to their GP practice or LPT research delivery team (depending on participant location) to check eligibility prior to study recruitment. This will be prior to consent and will be limited to the GP practice or LPT research delivery team confirming to the researcher that the participant meets the inclusion and exclusion criteria to enrol in the study.

Join Dementia Research recruitment

Join Dementia Research is an online platform that patients with dementia can access to register their interest in dementia research studies. Participants upload information to allow researchers to screen their medical history to check for study eligibility prior to contacting them. JDR provides formal training to researchers using JDR to recruit eligible patients. For this study, the researcher or research delivery officers will screen potential participants utilising the information provided on JDR and contact eligible

participants by their preferred contact method or chosen representative to provide study specific information.

Self-referral

Posters advertising the study will be displayed in the GP practices and pharmacies in the East midlands. In addition, posters will be displayed on the University of Leicester campus, and in the University of Leicester newsletter, outpatient clinics in the Geriatric and memory services at University Hospitals of Leicester and LPT. The researcher's contact details will be displayed on the poster's and leaflets. Participants can contact the researcher for further information, and if interested, a referral will be made to their GP practice or LPT research delivery team (depending on participant location) to check eligibility prior to study recruitment. This will be prior to consent and will be limited to the GP practice or LPT research delivery team confirming to the researcher that the participant meets the inclusion and exclusion criteria to enrol in the study.

Participants must be enrolled into the study and randomised to control or intervention within four to six weeks of initial screening.

Post stroke sub-group

Participants in the stroke sub-group will be recruited from ongoing observational studies in the department, stroke and rehabilitation wards, and stroke and TIA clinics at UHL, and stroke community groups and organisations. Potential participants will be screened and approached by a member of the direct care team, or research nurses from the NIHR CRN, in the first instance, and referred to the research team to provide study specific information. Stroke specific posters will be displayed in the stroke and rehabilitation wards, and stroke and TIA clinics at UHL. In the same manner as the main study, any participant who self refers or is identified through a community group, will be screened either by their direct clinical care team, or NIHR CRN research nurse to ensure they meet the study inclusion and exclusion criteria. Participants in the post-stroke sub-group will then undergo identical study procedures as outlined below.

8.2 Eligibility visit (cognitive assessment)

Healthy volunteer eligibility assessment

Eligibility assessment will take place by discussion with the volunteer and researcher to confirm the inclusion and exclusion criteria, prior to provision of study specific information. Medical records will not be screened to eligibility assess healthy volunteers. Volunteers who meet the inclusion and exclusion criteria will be invited to the cerebral haemodynamics in ageing and stroke medicine (CHiASM) research space for formal consent.

Patient eligibility assessment

Medical records will be reviewed by the direct care team referring the participant for study inclusion, or by LPT/UHL research delivery officers to ensure they meet the inclusion and exclusion criteria prior to referral to the researcher or research delivery team and provision of study specific information. Eligibility screening will only be undertaken by the direct clinical care team for potential participants, or by research delivery officers that are authorised to do so. Members of the research team will only screen medical records to confirm medical and medication history after formal consent to the study has taken place.

In all cases, a permission to screen consent form will be undertaken to allow a Montreal Cognitive Assessment (MoCA) to take place, to ensure deficits are classified as mild to moderate to be eligible for study inclusion. Participants will be counselled that this may preclude them from enrolling in the study, and will be detailed on the permission to screen consent form.

8.3 Informed Consent

Healthy volunteer consent procedure

Participants who meet the inclusion and exclusion criteria will then be invited by the researcher to attend the CHiASM research space at UHL to undergo formal consent and the baseline assessments outlined in Section 8.3. All informed consent procedures and healthy volunteer assessments will be undertaken by the researcher.

Patient consent procedure

Informed consent will be undertaken by either Dr Lucy Beishon (researcher) or an appropriately qualified research delivery officer at the LPT research delivery team. This will take place in the most convenient location for the participant including; their home, memory service, dedicated research space at the LPT, or invited to the Cerebral

Haemodynamics in Ageing and Stroke Medicine (CHiASM) research space.

Both participants who have capacity, and those that lack capacity will be suitable for inclusion in this study. In cases where the participant lacks capacity, a friend, relative or carer will act as a personal consultee to consent on behalf of the participant. Please see section 14.1 for more information on the ethical code of practice for the inclusion of adults lacking capacity in this study.

The participant or personal consultee must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

The qualitative arm of the study will be consented alongside the feasibility RCT. All participants will be offered to take part in the qualitative arm of the study. Participants will be consented at enrolment into the RCT to be contacted at later date to discuss the option of the qualitative study. Participants that completed the RCT and all assessments will be suitable for inclusion in the qualitative study, and their carers will also be invited to participate. Qualitative study specific information will be provided by the researcher alongside information for the feasibility RCT at study enrolment.

Written and verbal versions of the participant information and Informed consent will be presented to the participants/personal consultee detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed a minimum of 24 hours to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant or personal consultee dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent will be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within the Trial Master File (TMF) or Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants and a copy retained in the participant medical notes.

8.4 Baseline Assessments

Participants who meet the inclusion criteria, will undergo baseline assessments with a member of the research team, or research delivery officer, either at home, designated LPT research space, or invited to attend the CHiASM research space. The first visit will take place at the CHiASM research space, based at the Leicester Royal Infirmary, for an assessment of cognition (ACE-III) and neurovascular function (outline below). Approximately 20-25% of potential participants will have insufficient bilateral temporal windows for assessment, and this would preclude their study entry. Following successful window insonation, and completion of the neurovascular assessment, the following baseline assessments will be undertaken at the same visit or within two weeks at the participant's home: mood (GDS-15), function/ADLs (Lawton-IADL), quality of life (DEMQOL), handedness (Edinburgh handedness inventory).

An assessment of neurovascular function will take place using a protocol validated by this group previously (35). Participants will be asked to refrain from caffeine, nicotine, alcohol, heavy meals, or strenuous exercise for at least four hours prior to the neurovascular assessment. In summary, participants will under-go continuous beat-to-beat monitoring of cerebral blood flow velocity (CBFv) using transcranial Doppler ultrasound (TCD, DWL Doppler box), blood pressure (Finometer), heart rate (3-lead ECG), and end-tidal CO_2 ($ETCO_2$, capnography, nasal speculum). Participants will undergo a five-minute baseline recording. Participants will be asked five selected tasks from the ACE-III (attention, memory, language, fluency and visuospatial domains) to stimulate changes in CBFv, which can be measured by the above methods.

For the post-stroke sub-group, a further four tasks will be undertaken. The serial sevens will be completed in addition to serial 2s and 17s, and the naming words with "p" will be completed in addition to words beginning with "r" and "v". This is to identify subtler deficits that may be present in the stroke sub-group.

Data collected on baseline demographic information will include the following:

<u>Demographics</u>

The age, sex, ethnicity, smoking status, alcohol intake, height, weight, BMI, years of education, and socioeconomic status (postcode) will be recorded.

<u>Medical History</u>

Details of any history of disease or surgical interventions in the following systems will be recorded; cardiovascular, abdominal, respiratory, neurological, and hearing and visual impairment. Data will be collected on the type, size, and location of the infarct in the post-stroke sub-group, and any complications of the infarct.

Concomitant Medication

All over-the-counter or prescription medication, vitamins, and/or herbal supplements will be recorded on CRFs. Medication, dose, duration, strength and frequency will be recorded.

8.5 Randomisation and Codebreaking (if applicable)

Randomisation will be performed using Sealed Envelope©, by the researcher. This is an online-based randomisation tool which uses random permuted blocks to allocate participants to waiting list control or intervention. Participants will be enrolled and assigned a PIN consecutively, and randomised to a treatment arm corresponding to the PIN. Given the nature of the trial, it is not possible to blind participants to the intervention. The Investigator will be providing weekly telephone support with the intervention, in addition to undertaking baseline and follow-up measurements, and therefore blinding of the investigator is also not possible. However, data analysis will be blinded by generating a batch-anonymised data set. Randomisation will be undertaken at the initial visit. As this is an un-blinded trial, code breaking will not be required.

Once participants have been randomised to the intervention arm, they will be provided with information on how to access and use the CT program.

8.6 Subsequent Assessments

Participants randomised to the intervention will be followed-up on a weekly basis by the investigator with a telephone call to troubleshoot any problems arising with software/cognitive training program, or any changes in circumstance that would preclude ongoing study involvement. Participants will be followed up after 8-12 weeks of cognitive training, and will return to the CHIASM laboratory to repeat the baseline assessments (cognition (ACE-III), mood (GDS-15), function/ADLs (Lawton-IADL), quality of life (DEMQOL), neurovascular function (TCD), blood pressure (Finometer), heart rate (3 lead ECG) and end-tidal CO_2 ($ETCO_2$, capnography, nasal speculum). Adverse events will also be assessed at this time point.

8.7 Qualitative Data Collection

Patient participants will be offered to participate in a qualitative study at the end of the cognitive training RCT. Participants will be invited to take part in either an interview or a focus group. Not all participants will be required to participate in the qualitative arm of the study.

Semi-structured Interviews

At least 1 week after the completion of the CT program, participants will be invited to participate in semi-structured interviews to be held in the CHiASM research space, or the participant's home. All travel expenses will be paid to allow participants to attend the interviews. Participants will need to produce a receipt to claim expenses, and this will be outlined in the PIS.

A digital audio recorder will be used to record all the discussions continuously, and notes of non-verbal and paralinguistic clues will be made.

All digital recordings will be transcribed within 5-7 days of the interviews.

Semi-structured interviews are an iterative process, following the first couple of interviews the transcripts will be analysed and the themes and concepts emerging from this initial data will be further explored at the following interviews.

Focus Group

At the end of the study period participants will be offered the option to take part in a focus group instead of participating in a semi-structured interview; the focus group will be held at the University of Leicester. All travel expenses will be paid to allow participants to attend the focus group. Participants will need to produce a receipt to claim expenses, and this will be outlined in the PIS.

The focus Group will be run by two named investigators, one of them will act as the moderator and the other will take written notes. A digital audio recorder will be used to record all the discussions. The interview schedule will be used to start the focus group discussions. The questions within the schedule will be the same as for the semi-structured interviews. The focus group will be taped continuously.

The digital recordings will be transcribed within 5-7 days of holding the focus group. The typed transcript will be read, and checked against the tape recordings for the completeness and accuracy, and any further comments will be added.

Interview & Focus Group Schedule

An interview guide will be used in the semi-structured interviews and the focus group to provide a prompt for the topics that need to be discussed; these will be changed or modified as appropriate to the context of the conversation. The interview guide is a dynamic tool; it is not there to be prescriptive or ask closed response questions (36).

The interview guide will consist of questions on the following themes, specifically designed to explore the six predictors of health behaviours of the health belief model (risk susceptibility, risk severity, benefits to action, barriers to action, self-efficacy, and cues to action) (37) and to evaluate the cognitive training program and the experience of the participant and their carer:

1. What are the barriers to brain training in patients with dementia?
2. What are the facilitators (benefits) to brain training in patients with dementia?
3. Could brain training programs be adapted further to support the participation of patients with dementia?
4. Are there any additional benefits to brain training programs not measured by traditional methods as perceived by the patients and their carers?
5. To explore the lived experience of the patient and their carer and the impact brain training has on them and their life

8.8 Definition of End of Trial

The end of trial is the date of the last visit of the final participant. The end of the qualitative study will be at the date of the last interview or focus group.

8.9 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

Ineligibility (either arising during the study or retrospective having been overlooked at screening)
Significant protocol deviation
An adverse event which requires discontinuation of the study or results in inability to continue to comply with study procedures

Disease progression which requires discontinuation of the study or results in inability to continue to comply with study procedures
Consent withdrawn
Lost to follow up

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. If a participant has been withdrawn from the study, they will not be required to attend any further assessments or follow-up. Participants who have withdrawn from the study will be included in the data analysis (intention to treat analysis) and will be consented to do so. In the healthy volunteer arm, as this is a feasibility study, withdrawn participants will not be replaced. The reason for withdrawal will be recorded in the CRF.

8.10 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, radiographs/scan reports, and correspondence, interview and focus group recordings and transcripts.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study the CRF will be used as the source document for; cognition (ACE-III), mood (GDS-15), function/ADLs (Lawton-IADL), quality of life (DEMQOL), handedness (Edinburgh Handedness Inventory), and assessments of neurovascular function (TCD), blood pressure, heart rate and $ETCO_2$.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

9. TREATMENT OF TRIAL PARTICIPANTS

9.1 Description of Study Treatment

Participants randomised to the intervention will complete an 8-12 week CT program. Participants will be required to complete five, 30 minute sessions per week for eight to twelve weeks. The CT program will be provided by Lumosity© as part of a collaboration through the Human Cognition Project. Lumosity© is a commercially available software, developed by a group of neuropsychologists, which has been used across several studies of brain training and disciplines (38-40). These studies have also been included in a number of systematic reviews and meta-analysis (6, 19). It is a multi-domain, online based cognitive training tool, which is relatively easy to use and administer. It has been designed to adapt to the individual's cognitive function in order to personalise the training program to their needs. Exercises will be selected with the support of Lumosity© to target the following cognitive domains; attention, memory, visuospatial, verbal fluency, and language.

9.2 Storage of Study Equipment or Related apparatus

Study equipment is stored securely in the CHIASM laboratory and maintained annually by the medical physics department at the University Hospitals of Leicester NHS Trust.

9.3 Compliance with Study Treatment

Compliance will be monitored through Lumosity© online software which will log and track the number of minutes and times per week a participant has spent training, to determine the training dose received by each participant. Participants will not be excluded based on non-adherence, as this is considered an integral component to the feasibility assessment.

10. SAFETY REPORTING

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study.

10.1.2 Adverse Reaction (AR)

All untoward and unintended responses related to the study.
All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions.

10.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,

- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" 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.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.1.5 Expected Serious Adverse Events/Reactions

See Appendix D for a complete list of expected adverse events not subject to immediate reporting.

10.1.6 Suspected Unexpected Serious Adverse Reactions

Not applicable for this type of study.

10.2 Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study, will be recorded on the CRF.
The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.
It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also

voluntarily withdraw from the study due to what he or she perceives as an intolerable AE.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

The relationship of AEs to the study will be assessed by a medically qualified investigator.

10.3 Reporting Procedures for Serious Adverse Events

All SAEs, except those expected ones defined in section 10.1.5 that do not require immediate reporting (see 10.1.5), must be reported to the Sponsor within one working day of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&D Management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form which must be sent to the Sponsor using the appropriate reporting form and the contact details on there.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the CI shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceding 12 months.

11. STATISTICS

11.1 Description of Statistical Methods

All data will be tested for normality prior to statistical testing using Shapiro-Wilks or visual inspection of histograms. Where data are found to be non-parametric, data will be appropriately transformed prior to statistical testing, and parametric tests then applied. Data will be recorded in Microsoft Excel. Statistical analyses will be performed using the latest version of SPSS for Windows, and graphs will be produced using the latest version of GraphPad Prism for Windows.

Feasibility and Baseline Demographics

Data will be reported as mean (standard deviation) for continuous variables, and number (percentage) for nominal data. Differences between the intervention and control groups will be analysed within population group (HC/AzD/MCI) using Chi-Square for nominal data, and independent t-testing for continuous data. Any differences between population groups will also be reported.

Outcome Data

The difference for each participant between baseline and follow-up assessment for each of the continuous outcome measures described in Section 6.2 (secondary outcome measures) will be reported along with the overall mean difference. To assess the impact of the intervention and population group on each of these differences, a two-way ANOVA will be carried out. The interaction between population group and treatment group will also be included to assess if the difference between the treatment groups is different between the population groups.

Power calculation

The results from this study will be used to inform a power calculation to determine the sample size for a larger trial investigating the outcome measures described in Section 6.2. Specific statistical support will be sought within the Department of Cardiovascular Sciences to carry out this power calculation using the outcome data from this study.

11.2 The Number of Participants

60 participants will be required to complete the programme, in three sub-groups of twenty (healthy older adults, AzD and MCI). This does not include participants who did not have adequate bilateral TCD windows, which has been listed in section 7.3 as an exclusion criterion. Authors generally agree that recruiting between 24 and 50 participants for a feasibility study is adequate and therefore the planned target of 60 participants is sufficiently large enough whilst giving a margin for drop-outs and loss to follow-up (41, 42). Given the primary aim of this study is feasibility, a formal power calculation has not been performed.

For the qualitative arm, participants will be recruited as a sub-set of those who were enrolled into the training arm of the trial. Both participants who did and did not complete the training programme will be invited for interview or focus group to better understand any issues that arose during the programme, reasons for non-adherence, or premature withdrawal. The sample size will therefore be determined by the number who were randomised to the treatment arm and are willing to return for interview or focus group. At the point at which responses to interview questions become saturated, no further participants will be recruited to the qualitative arm.

11.3 The Level of Statistical Significance

Statistical significance will be set at $p<0.05$.

11.4 Criteria for the Termination of the Trial.

This is a feasibility trial, therefore trial termination will be after the final participant has completed all assessments or interview.

11.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

Unused data will be reported, with reasons in the final report after study completion, and in any publication. Spurious and missing data will be reported, but not included in final analyses.

11.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Statistical support, including any deviations will be supported by the departmental statistician, Dr Chris Nelson. Any deviations will be reported to the Trial Steering Committee (TSC), and included in any reports to Sponsor or REC.

11.7 Inclusion in Analysis

All randomised participants will be included in the analysis.

11.8 Qualitative data analysis

The findings from the semi-structured interviews and focus groups will be evaluated using framework analysis (41). The digital recordings of the interviews and focus groups will be transcribed verbatim, the transcripts will be read in detail, i.e. line-by-line, and open codes will be formed categorising and conceptualising the responses and identifying the major themes. Two researchers LB & RE will independently code the first few transcripts to ensure consistency in coding.

Following this initial coding the analytical framework will be developed, this is an iterative process and will develop through coding of additional transcripts. Once the final transcript has been coded the analytic framework will be used to generate the framework matrix. The framework matrix will be developed in NVivo 11 (QSR International), and allow for the recognition of patterns and outliers within the data.

Respondent Validation

The technique of showing the transcripts to the research participants and ascertaining their opinions on the accuracy of the transcripts will be used, to establish the degree of correspondence between the researcher's views and those of the research participants (36). Once completed the transcripts of the semi-structured interviews will be sent to the participants for their approval. Any comments by the participant will be added prior to analysis. This technique ensures the researchers accurately portray the experiences and viewpoints of the research participants. It is also hoped that by involving research participants in analysis and interpretation it will increase their engagement with the research.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution, and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

The University of Leicester operate a risk based audit programme to which this study will be subject.

14. CODES OF PRACTICE AND REGULATIONS

14.1 Ethics

Consent and Capacity

This study plans to recruit participants with dementia or cognitive impairment. We anticipate that a number of participants will not have sufficient capacity to consent to the study. Given the nature of dementia, we feel it would be unethical to exclude participants who are unable to consent to the study, particularly where they have expressed prior willingness to be involved in research should they lose capacity. Therefore, for those individuals who do not have capacity, we plan to consent a close relative, friend or carer (personal consultee) who is able to express the views of the participant and consent on their behalf to the study. Any volunteer who has been recruited through this process who appears distressed or unwilling to participate in the study at any point will be withdrawn accordingly. Participants who have capacity will be asked at the point of consent what they would like to happen should they lose capacity, i.e. be withdrawn from the study, or continue in the study. Any participant who then loses capacity, an assessment of this pre-disclosed opinion, any available personal consultee opinion and their ongoing engagement/willingness or lack of distress will be used to decide whether study participation should continue. If there is any doubt about ongoing participation, this can be referred to the trial steering committee and/or research supervisors. Participants who lack capacity at study inclusion who later regain capacity will be re-consented before ongoing study participation.

Waiting list control for intervention

All study participants who are randomised to the control arm will be offered the intervention at the end of the study (waiting list control). This is not a cross over trial, and therefore these participants will not have any further assessments after provision of the CT program. This is to remove any ethical concerns about participants not being able to undertake the CT program through study participation. Some participants may deteriorate over the course of the study and may be unable to utilise the intervention effectively as waiting list control.

Recruitment

A broad recruitment strategy has been developed to ensure this project can recruit to target (total 60 participants, 20 healthy older adults, 20 MCI and 20 AzD). This will encompass memory and geriatric clinics, GP surgeries, and community groups. This recruitment strategy and rate has been based on a recent pilot study undertaken in the department where 55 participants were recruited over a period of 6 months.

Study procedures

All methods in this study have been tested in a recent pilot observational study. The TCD device utilises a head-frame which exerts a slight pressure; but has been used previously in several studies in the department and is well tolerated in patients with stroke and dementia. Participants will wear a finger blood pressure monitor, which exerts intermittent pressure. Again, this has been well tolerated in previous studies of patients with stroke and dementia.

Industry collaboration

This study is being undertaken as a collaboration between Lumosity© and University of Leicester. Lumosity© are providing the CT program free of charge but have not funded this study, and therefore the study is financially independent of Lumosity©. A contract has been checked by the University of Leicester who will retain the rights to publication.

14.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines

14.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

14.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

14.5 Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA), and host institution(s) for written approval.

Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.6 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14.7 Other Ethical Considerations

As outlined above.

15. DATA HANDLING AND RECORD KEEPING

15.1 Data Extraction

As supportive evidence of the diagnosis of MCI or AzD, results and significant findings from Computerised Tomography (CTo) head/Brain Magnetic Resonance Imaging (MRI), if undertaken, will be recorded on the CRF.

Other information which will be extracted from the medical notes and recorded on the CRF include results and details of any previous cognitive testing, and the date of diagnosis of MCI or AzD.

15.2 Data Analysis

All other parameters recorded, including CBFv, heart rate, blood pressure, and $ETCO_2$ will be simultaneously recorded onto a computer system (PHYSIDAS), providing data for subsequent analyses. Off-line analyses will be undertaken using software designed by the University of Leicester's Department of Cardiovascular Sciences.

15.3 Data Management

All parameters (signals) that are collected during the measurement will be saved using a coded filename. The name and other identifying detail will NOT be included in any study data electronic file. All study data will be entered into Microsoft Excel for Windows.

All files will be encrypted and stored on a password secured computer/laptop, which will have restricted access to members who are authorised on the authorisation log.

The participants will be identified by a study specific participant number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

16. STUDY GOVERNANCE

16.1 Trial Steering Committee (TSC)

A TSC consisting of lay members, and independent academics from the host institution, will be convened. The TSC will meet at six monthly intervals, and will assess the progress of the trial, recruitment, compliance with study protocol, ethical and regulatory standards, and safety or adverse outcomes.

16.2 Data Safety Monitoring Committee (DSMC)

As this is a non-pharmacological feasibility RCT, a DSMC is not required, but adverse events will be reviewed at TSC meetings.

17. FINANCING AND INSURANCE

This study is funded as part of Research Training Fellowship by the Dunhill Medical Trust. A full breakdown of the study costs are included in the approved grant application which has been submitted in PDF format with this protocol.

17.1 Research Costs

The research costs have been calculated by the NIHR CRN East Midlands to include time for research support staff, or clinical staff to screen eligible participants for the study in the memory and geriatric services as £3250.80

The NIHR CRN have also calculated the relevant costs for screening General Practice databases and mailing out invitation letters to potential, eligible participants at £328.60.

NHS Treatment Costs
None.

NHS Support Costs
None.

18. PUBLICATION POLICY

On all publications, the funding body and Lumosity© will be acknowledged, and each author will be required to disclose details of their own involvement/contribution in the study (specific publication).

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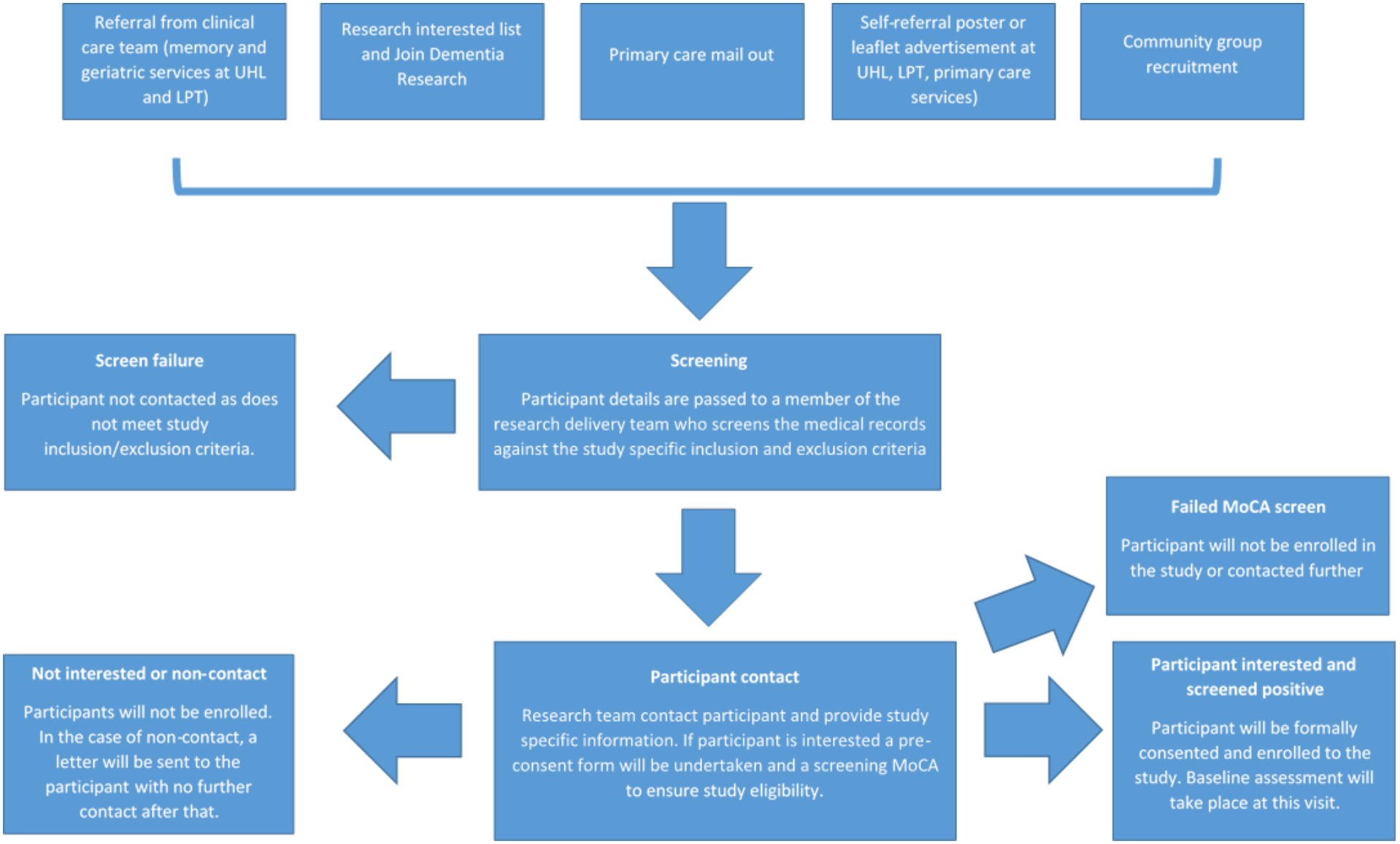
APPENDIX A: PATIENT RECRUITMENT FLOW CHART



20. APPENDIX B: STUDY FLOWCHART

21. APPENDIX C: SCHEDULE OF PROCEDURES

Procedures	Visits				
	Screening	**Baseline**	**Follow-up**	**Qualitative arm**	**Windows**
Informed consent	**x**			**x**	1 month
Screening MoCA	**x**				1 month
Demographics	**x**	**x**		**x (carers)**	1 month
Medical history	**x**	**x**			1 month
Concomitant medications	**x**	**x**			1 month
Eligibility assessment	**x**				N/A
Randomisation		**x**			4-6 weeks
Compliance		**x**	**x**		N/A
Cognition (ACE-III)		**x**	**x**		Baseline: 4-6 weeks, Follow-up: 8-12 weeks from randomisation
Mood (GDS)		**x**	**x**		Baseline: 1 month, Follow-up: 8-12 weeks from randomisation
Edinburgh handedness Inventory		**x**			Baseline: 1 month, Follow-up: 8-12 weeks from randomisation
Function (Lawton-IADL)		**x**	**x**		Baseline: 1 month, Follow-up: 8-12 weeks from randomisation
Quality of Life (DEMQOL)		**x**	**x**		Baseline: 1 month, Follow-up: 8-12 weeks from randomisation
Neurovascular function (TCD, blood pressure, ECG, $ETCO_2$)		**x**	**x**		Baseline: 4-6 weeks, Follow-up: 8-12 weeks from randomisation
Adverse event assessments			**x**		N/A

Telephone Support (intervention arm only)		**x**	**x**		Weekly telephone support to participants in intervention arm.
Qualitative interview/focus group (optional)				**x**	At least 1 week after trial completion

22. APPENDIX D: EXPECTED EVENTS NOT SUBJECT TO EXPEDITED REPORTING

Acute Coronary Syndromes	Malignancy
Agitation	Myocardial infarction
Angina	Nausea
Anorexia	Personality change
Anxiety	Peripheral Vascular Disease
Cognitive decline	Pressure sores
Constipation	Renal impairment
Delirium	Sedation
Depression	Seizure
Disease progression	Sexual dysfunction
Dysphagia	Sleep disturbance
Electrolyte disturbance	Stroke
Fall	Syncope
Fatigue	Transient ischemic attack
Fracture	Urinary retention/catheterisation
Gastrointestinal disturbance	Urinary tract infection
Hallucinations	Ulceration
Heart failure	Violent behaviour
Incontinence, faecal	Visual loss
Incontinence, urinary	Vomiting
Infections	Wandering
Institutionalisation / Admission to care home	Weakness
Intracerebral Haemorrhage	Weight loss
Loss of ability to function or care for self	