RECALL – REducing Cognitive decline and dementiA by Lowering bLood pressure- PILOT

Study Protocol

A pilot study to determine the feasibility of a prospective, randomised, double-blind clinical trial of reducing systolic blood pressure to prevent dementia and cognitive decline

Date: 26 April 2021

Version: 5

Trial/Study Acronym	**RECALL Pilot**
Sponsor	UoD-NHS Tayside
Sponsor Ref Number	1-020-18
Chief Investigator	Prof T MacDonald
REC Number	19/NE/0172
Version Number and Date	V5 dated 26 April 2021

PROTOCOL APPROVAL

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial/study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Prof T MacDonald

Chief Investigator	Signature	28 April 2021 Date

LIST OF ABBREVIATIONS

AE	Adverse Event
API	Application Programming Interface
BP	Blood Pressure
CBS	Cambridge Brain Science
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMS	Data Management System
eGFR	Estimated Glomerular Filtration Rate
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practice
HBPM	Home Blood Pressure Monitor
ICF	Informed Consent Form
HTTPS	Hypertext Transfer Protocol Secure
HRA	Health Research Authority
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISF	Investigator Site File
IMP	Investigational Medicinal Product
MEMO	Medicines Monitoring Unit
NCTIMP	Non-Clinical Trial of an Investigational Medicinal Product
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PDF	Portable Document Format
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Patient Information Sheet

R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SC	Steering Committee
SMG	Study Management Group
SOP	Standard Operating Procedures
SSL	Secure Sockets Layer
TASC	Tayside Medical Science Centre
TMF	Trial Master File

SUMMARY/SYNOPSIS

Study Title	RECALL Pilot - A pilot study to determine the feasibility of a prospective, randomised, double-blind clinical trial of reducing systolic blood pressure to prevent dementia and cognitive decline	
Study Design	Feasibility study	
Study Population	Adults aged 60 or over	
Sample Size	At least 100	
Planned Trial/study Period	approximately 17 months	
Clinical phase duration	n/a	
Follow up phase duration	n/a	
Primary	**Objective** Determine the feasibility of carrying out a larger trial by testing the recruitment and screening processes in primary care	**Outcome Measures** Recruitment Protocol adherence
Secondary	**Objectives** Assess suitability of online cognitive testing for study cohort Assess baseline cognitive function Assess feasibility of requiring each participant to identify two individuals who agree to act as alternative contacts Assess feasibility of home blood pressure monitoring using study supplied HBPM machine Assess baseline blood pressure suitability of study cohort Assess feasibility of using portable i-STAT Alinity device for providing blood results	**Outcome Measures** Proportion of participants who complete a baseline test Proportion of study population completing online screening cognitive function test and scores obtained Proportion of participants who have two consenting alternative contacts Proportion of participants submitting a complete set of home BP measurements Proportion of participants with a home BP submission averaging 140mmHg or below systolic Proportion of blood results obtained using portable system

	Assess the likely number of eligible patients signing up	Proportion of those invited who meet proposed formal study entry criteria
Inclusion Criteria	Aged 60 years or over Email address (per participant) and internet access	
Exclusion Criteria	Patients considered unsuitable for invitation (GP opinion) Patients with a medical history of dementia or on treatment for dementia	

1 INTRODUCTION

This protocol describes the methods of a feasibility study to test several aspects of trial methodology (including recruitment, eligibility testing and baseline data collection) as part of the planning for a large-scale online trial of blood pressure lowering to prevent dementia.

2 BACKGROUND & RATIONALE

Dementia is the leading cause of death in the UK and the biggest health and social care challenge of the 21st century. There is no effective treatment available or imminent for the commonest causes, which are Alzheimer's disease and vascular dementia. About half of cases have a significant vascular component. There is evidence that other end-organ damage driven by vascular disease is preventable (for example, cardiac, renal and stroke disease). Primary prevention is therefore also a realistic possibility for dementia.

Complex interventions aiming to slow cognitive decline have been disappointing, are time consuming and labour intensive and require extensive commitment on behalf of the health services, individual therapist, and participant. Mounting evidence supports the beneficial effects of reducing blood pressure to ameliorate cognitive decline and to prevent dementia. We intend to conduct a large online study of blood pressure lowering medication to lower blood pressure and prevent dementia. Although elements of the proposed study methodology have been used in other studies, they have not yet been tested in the target population. We therefore plan a pilot study to assess the feasibility of several aspects of the proposed method.

3 STUDY OBJECTIVES & OUTCOMES

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
Determine the feasibility of carrying out a larger trial by testing the recruitment and screening processes in primary care.	Recruitment numbers Protocol adherence	End of pilot

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	Outcome Measure:	Timepoint of outcome measured
Assess suitability of online cognitive testing for study cohort	Proportion of participants who complete a baseline test	n/a
Assess baseline cognitive function	Proportion of study population completing online screening cognitive function test, and scores obtained	n/a
Assess feasibility of requiring each participant to identify two individuals who agree to act as alternative contacts	Proportion of participants who have two consenting alternative contacts	n/a
Assess feasibility of home blood pressure monitoring using study supplied HBPM machine	Proportion of participants submitting a complete set of home BP measurements	n/a
Assess baseline blood pressure suitability of study cohort	Proportion of participants with a home BP submission averaging 140mmHg or below systolic	n/a
Assess feasibility of using portable i-STAT Alinity device for providing blood results	Proportion of blood results obtained using portable system	n/a
Assess the likely number of eligible patients signing up	Proportion of those invited who meet proposed formal study entry criteria	n/a

4 STUDY DESIGN

Cohort feasibility study.

4.1 INTERVENTION

Components of the proposed formal study methodology for recruitment and baseline data collection will be tested including:

- Online registration and consent procedures
- Online cognitive function testing
- Home blood pressure submission
- Bloods results obtained using portable i-STAT Alinity device
- Participant feedback questionnaires

4.1.1 Online registration and Consent

See section 5.2

4.1.2 Online Cognitive Testing

Cognitive testing will be performed by Cambridge Brain Sciences (CANADA), a well-established provider of online cognitive testing with a custom-built research platform (http://www.cambridgebrainsciences.com/).
All transaction between MEMO Research and CBS will be end-to-end encrypted via the use of HTTPS and SSL certificates. The only data sent from MEMO Research to CBS will be an anonymous locally generated patient identifier. CBS will return the results of the tests via an encrypted API to MEMO Research along with the anonymous patient identifier. Only MEMO Research will be able to map results to the study participants.

4.1.3 Home Blood Pressure Submission

Consenting participants will be provided with a home blood pressure monitor and instructions for use. They will be invited to submit a baseline set of home readings (modified version of NICE guidance on HBPM for diagnosis of hypertension) [1] via a unique emailed link or by logging in to their study homepage.

4.1.4 Blood Tests

Participants will be asked to have a blood test carried out using the i-STAT Alinity portable system developed by Abbott. This sample will be obtained at either the GP practice, MEMO Research at Ninewells Hospital, a Community hub or other suitable facility (investigator opinion) as necessary. The blood test will involve one draw of venous blood and will provide results for: Sodium, Potassium, Chloride, TCO2, Anion Group, Ionized Calcium, Glucose, Urea Nitrogen (BUN), Creatinine, calculated eGFR, Haematocrit and Haemoglobin

Full working instructions and training will be provided to the Health Care Professional using the i-STAT system.

4.1.5 Alternative Contacts

Consented participants will be asked to provide the email addresses of two alternative contacts (relative, family friend or carer) who can be contacted if the study team are unable to contact the participant. The participant will be asked to seek agreement from their alternative contacts prior to them entering their details into the RECALL secure website. Alternative contacts will be asked by email to confirm that they are willing to act in this capacity and to verify their email address. If any alternative contacts select not to agree to this provision on the website, the participant will be asked to provide a further contact. Although participants will be requested to provide two alternative contacts, if they cannot provide this, they can still proceed into the study. Alternative contacts will only be emailed should contact with the participant be lost during the study.

4.1.6 Participant Feedback Questionnaires

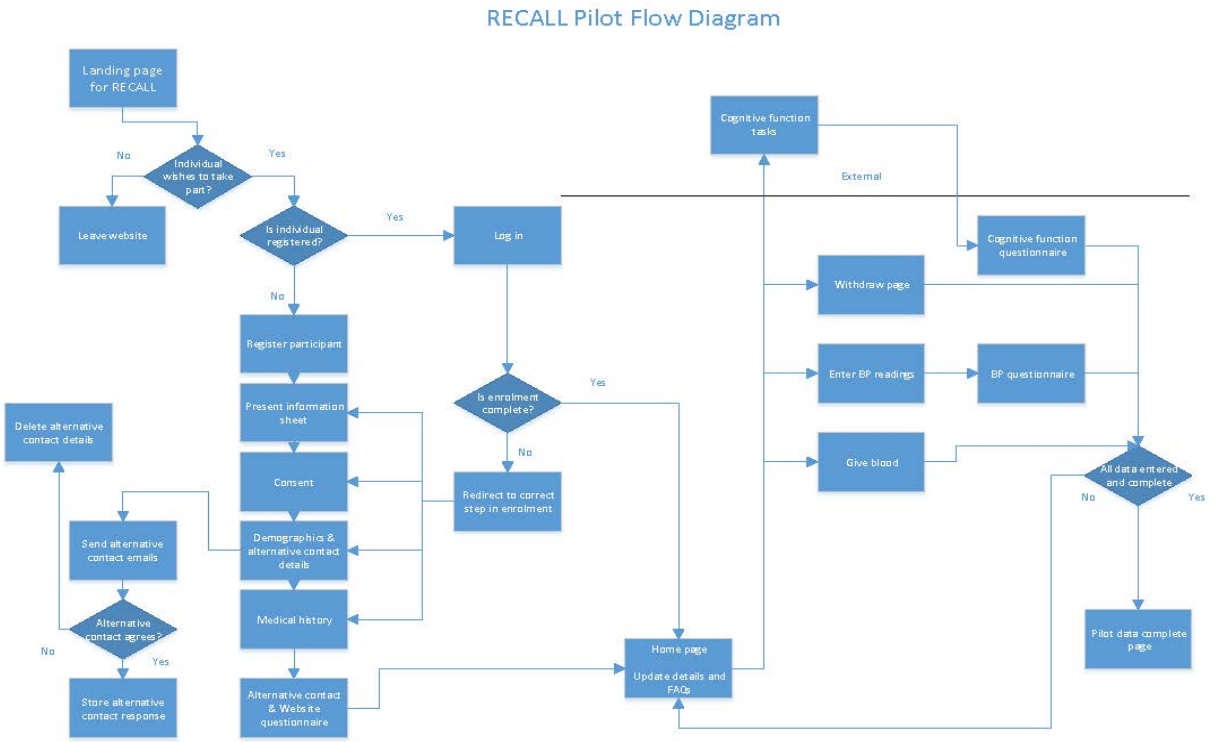
Participants will be given the opportunity to complete a feedback questionnaire after finishing each section of the study on-line. Questionnaires will also be presented to participants at the end of the trial if they have not completed sections, or if they withdraw from the study.

4.2 STUDY DESCRIPTION

Potential participants will be invited to visit a study web page by letter of invitation. On this study webpage they can read the participant information documentation and then complete an electronic informed consent form. Participants will then be asked to complete questions on their demographics, medical history, and lifestyle.

Consenting participants will be supplied with a home blood pressure monitor (HBPM) and detailed instructions on how to use it. They will then be asked to submit a set of readings (modified version of NICE guidance) [1].

4.3 STUDY FLOWCHART



4.4 STUDY SAFETY ASSESSMENTS

No Investigational Medicinal Produce (IMP) will be used in this feasibility study. Study procedures will involve direct participant data entry, online cognitive function testing and home blood pressure monitoring. All of these have been previously undertaken in other situations without significant safety concerns [2,3].

4.5 TISSUE

One blood sample will be collected, analysed and discarded at the same visit in this study.

4.6 INCIDENTAL FINDINGS

Any incidental findings (e.g. previously undiagnosed condition) considered to be clinically significant will be reported to the participant's GP by the CI with the consent of the participant.

4.7 STUDY POPULATION

Adults aged 60 years or over.

4.8 NUMBER OF PARTICIPANTS

We estimate that at least 100 participants from at least 5 practices will be required to fully test the methodology.

4.9 INCLUSION CRITERIA

- Aged 60 years or over
- Valid email address (per participant) and able to access the internet

4.10 EXCLUSION CRITERIA

- GPs may exclude participants who they deem unsuitable to participate
- Clinical diagnosis of dementia, treatment with medication for dementia or cognitively unable to follow the protocol (investigator opinion)

5 PARTICIPANT SELECTION AND ENROLMENT

Any patient registered with a Tayside GP practice participating in the study and meeting the inclusion/exclusion criteria will be eligible to register their interest in participating.

5.1 IDENTIFYING PARTICIPANTS

GP practices in Tayside will be approached by letter, inviting them to act as PIC sites for this feasibility study. Participating practices will be asked to write to all permanently registered patients aged 60 years old or over. The search list will be examined by one or more practice physicians in order to remove from the list any patients who has a clinical diagnosis of dementia, treatment with medication for dementia or cognitively unable to follow the protocol (investigator opinion). Also any patients they deem unsuitable to participate or in the opinion of the physician should not be invited to take part in the study.

The invitation letters from GPs will be sent using the Docmail system (a secure mail merge approved for NHS use) telling them about the study and inviting them to visit the study website. This methodology has been used successfully in recruiting the TIME online study of antihypertensive dosing time [4].

5.2 CONSENTING PARTICIPANTS

Potential participants who visit the study website will be presented with brief online information about the study. If they wish to participate, they will be asked to register

their email address and a personal password. These will be used to identify unique website users.
Once registered, the participant will be asked to read and download the participant information sheet (which will be available to all website visitors) and ask any questions of the study team by email or telephone. After the participant has read the PIS, and answered an automatically generated question to ensure that they have understood it, they will be presented with the online consent form. This is completed by indicating assent to each section and providing an electronic signature. After completing the consent form and agreeing that submitting this constitutes a legal signature, patients will be able to download a copy of their completed consent form. They can then proceed to provide all other requested information.

5.3 SCREENING FOR ELIGIBILITY

Potential participants will be asked to enter their date of birth and select their registered GP practice from a drop-down list.

5.4 WITHDRAWAL PROCEDURES

Participants can withdraw from the pilot study at any time and for any reason. They will be encouraged to do this themselves via the study website, but withdrawal by contacting the study team will also be possible. At the time of withdrawal, participants will be invited to complete a questionnaire to provide the study team with information about why they are withdrawing from the study.

5.5 IMPACT OF COVID-19 ON STUDY DELIVERY

The study was approved for an additional 9 month's extension by the Sponsor. As a result of the COVID-19 pandemic, study recruitment was paused in March 2020. However, the study website remained open for participants to register and for post consented participants to complete the online assessments. The impact of the COVID-19 pandemic on both the short- and long-term delivery of both standard healthcare and clinical studies within the NHS is unknown. However, in order to eliminate/reduce a potential negative impact of the COVID-19 pandemic on the RECALL Pilot study, a number of mitigation strategies may need to be implemented. These strategies have been designed to: (i) allow the continuation of online recruitment to the study (ii) accommodate participants who would prefer to avoid attending a hospital for completion of the required blood sample (iii) acknowledge the COVID-19 restrictions placed on primary care practices by providing alternative sites for taking blood samples (iv) allow the use of community hubs or other suitable facility for taking blood samples (v) allow the study team to adopt a pragmatic approach to face-to-face study visits whilst following government guidance. This may mean allowing for a delay in obtaining blood samples to ensure participant and staff safety.

6 DATA COLLECTION & MANAGEMENT

6.1 DATA COLLECTION

A dedicated study eCRF website will be used to collect the study data. This system will be developed by MEMO Research who have experience in such systems for clinical trials. Data entered directly on the eCRF website will be considered to be source data. Caldicott approval will be sought to permit the storage of patient-specific data on the secure study database.

Participant-reported data will be collected by a series of web-based questions, games and tasks, and questionnaires. Participant-reported data will include demographic data, relevant past medical history and family history, concomitant medications, details of two alternative contacts and blood pressure readings. This will be requested at the point of consent, and participants will be given the opportunity to update this during the study.

Patient-reported data will be entered by participants directly.

Participants will be asked to complete various questionnaires to provide feedback on their experience of participating in the study.

Research Nurses will enter the results of the blood test taken using the i-STAT Alinity Device.

Participants may be contacted to request clarification of data points. Any changes to data points will be logged and justified.

Participants will complete the cognitive function test via the CBS portal. The pseudo-anonymised data will be held by CBS on a secure system and transferred to MEMO Research via a secure API.

The eCFR will be the web profile with different levels of access. Access level will be role specific.

6.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, TASC SOP53 Data Management Systems in Clinical Research.

The data management system (DMS) will be a bespoke system designed in-house (MEMO Research).

The DMS will be based on the protocol and eCRF for the study and individual requirements of the investigators. The eCRF will collect only information that is required to meet the aims of the study and to ensure the eligibility and safety of the participant. The study database will be compliant with TASC SOP53 Data Management Systems in Clinical Research.

The database is managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the study team.

Database lock will be conducted in compliance with TASC SOP32 Locking Clinical Study Databases.

7 STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE CALCULATION

This is a feasibility study to test proposed methods for a large online study of dementia prevention. No formal sample size calculation has been done. We estimate that at least 100 participants from at least 5 practices will be required to fully test the methodology.

7.2 PROPOSED ANALYSES

Descriptive statistics (e.g. range, mean, standard deviation, percentage) for each outcome will be generated to support the planning (including sample size calculation) of a large randomised study. A statistical analysis plan will be prepared.

7.3 MISSING DATA

This will be covered in the statistical analysis plan.

7.4 TRANSFER OF DATA

No patient data will be removed by the study team from GP practices. All data will be entered on the study web portal directly by participants using either unique links sent to personal validated email addresses, or username and password login.

Cambridge Brain Science (CBS) are fully GDPR compliant. Their application is hosted and managed entirely by CBS and is not installed outside of the CBS infrastructure. They require no patient identifiable information to analyse the cognitive assessments. A unique CBS code will be generated for each participant by the RECALL Pilot website and this code will be used to generate all links to CBS. Participants will carry out the online cognitive function tests and CBS will send us the scores against the participants CBS code. Only MEMO Research will hold the link between the CBS code and an identifiable patient.

8 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 STUDY MANAGEMENT GROUP

The study will be co-ordinated by a Study Management Group (SMG), consisting of the Chief Investigator (CI), a Study Manager and IT programmer. The SMG will maintain minutes of formal meetings and a delegation log will be in place at the coordinating centre.

8.2 INSPECTION OF RECORDS

The CI, and all institutions involved in the study, will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

9.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

9.2 CONFIDENTIALITY AND DATA PROTECTION

The CI and trial staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All trial records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate personal data will have limited access measures via usernames and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated trial staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

9.3 INSURANCE AND INDEMNITY

The University of Dundee and Tayside Health Board are Co-Sponsoring the study. The University of Dundee has a policy of public liability insurance which provides legal liability to cover damages, costs and expenses of claims.

Tayside Health Board is a member of the NHS Scotland Clinical Negligence and Other Risks Insurance Scheme (CNORIS) which gives legal liability cover of NHS Tayside for this trial/study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

The Sponsor does not provide study participants with indemnity in relation to participation in the Study but has insurance for legal liability as described above.

10 ADVERSE EVENTS

10.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: ● results in death ● is life threatening ● requires hospitalisation or prolongation of existing hospitalisation ● results in persistent or significant disability or incapacity ● is a congenital anomaly or birth defect ● or is otherwise considered serious

10.2 RECORDING AND REPORTING AE

As this is a low risk feasibility study, no formal collecting or reporting of AE or SAEs will be conducted.

11 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS AND BREACHES OF GCP OR PROTOCOL

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the TMF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office.

12.2 STUDY RECORD RETENTION

Archiving of study documents will be for five years after the end of study.

12.3 END OF STUDY

The end of study is defined as database lock. The Sponsor, CI and/or the SC have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

13.2 PUBLICATION

The study report will be used to support the planning of a formal randomized clinical trial. The report may also be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

14 REFERENCES

1 NICE Update of clinical guidelines 18 and 34 Hypertension The clinical management of primary hypertension in adults Clinical Guideline 127 Methods, evidence, and recommendations August 2011. NICE 2011. https://www.nice.org.uk/guidance/cg127/evidence/full-guideline-248588317

2 Rorie DA, Rogers A, Mackenzie IS, *et al.* Methods of a large prospective, randomised, open-label, blinded end-point study comparing morning versus evening dosing in hypertensive patients: the Treatment In Morning versus Evening (TIME) study. *BMJ Open* 2016;**6**. doi:10.1136/bmjopen-2015-010313

3 Owen AM, Hampshire A, Grahn JA, *et al.* Putting brain training to the test. *Nature* 2010;**465**:775–8.

4 Rorie DA, Flynn RWV, Mackenzie IS, *et al.* The Treatment In Morning versus Evening (TIME) study: analysis of recruitment, follow-up and retention rates post-recruitment. *Trials* 2017;**18**:557.