Reducing pathology in **A**lzheimer's **D**isease through **A**ngiotensin Ta**R**geting

Protocol Version 8.0 – 04 March 2016

Approvals	Reference
EudraCT number	2012-003641-15
REC Reference	12/WA/0338
ISRCTN	ISRCTN93682878
MHRA CTA	18524/0223/001-0001
NIHR Grant reference	EME- 11/47/03
Sponsored by	North Bristol NHS Trust Research & Innovation (NBT R&I)
Sponsor Reference	2625

The RADAR Trial is funded by the Medical Research Council-National Institute of Health Research Efficacy and Mechanism Evaluation Programme.

TRIAL ADMINISTRATION

Chief Investigator:

Prof. Patrick Gavin Kehoe PhD
Dementia Research Group
School of Clinical Sciences
Level 1, Learning & Research,
Southmead Hospital, BS10 5NB
Tel: 0117 414 7821
Fax: 0117 414 7822
Email: Patrick.Kehoe@bristol.ac.uk

Clinical Lead:

Prof. Ian Wilkinson DM
Clinical Pharmacology Unit
Box 110 Addenbrooke's Hospital
Cambridge
Tel: 01223 336806
Email: ibw20@medschl.cam.ac.uk

Trial and Protocol Development Group (*indicates original co-applicant)*:*

Professor Patrick Gavin Kehoe *PhD* (University of Bristol)*
Professor Yoav Ben-Shlomo *PhD* (University of Bristol)*
Dr Alan Montgomery *PhD* (University of Bristol)*
Dr Peter Blair *PhD* (University of Bristol)*
Dr Elizabeth Coulthard *PhD* (University of Bristol)*
Professor Risto Kauppinen *MD*, *PhD* (University of Bristol)*
Professor Peter Passmore *MD* (Queen's University Belfast)*
Professor Ian Wilkinson *DM FRCP* (University of Cambridge)*
Dr Athene Lane *PhD* (University of Bristol)
Mrs Hannah Baber (University of Bristol)

Trial Manager:

Bristol Randomised Trials Collaboration
School of Social and Community Medicine
Oakfield House, Oakfield Grove, Clifton
Bristol BS8 2BN
Tel: 01173 313317
Fax: 01173 313338
Email: radar-trial@bristol.ac.uk

Sponsor:

Ms Helen Lewis
NBT Lead Research Nurse
Research & Innovation
North Bristol NHS Trust
Floor 3 Learning & Research building,
Southmead Hospital, Westbury-on-Trym,
Bristol, BS10 5NB
Tel: 01173 238602
Fax: 01173 236192
Email: helen.lewis@nbt.nhs.uk

Randomisation details:

Website: www.sealedenvelope.com/radar/
Tel: 020 8099 7784

Any questions relating to this protocol should be addressed in the first instance to the RADAR Trial Manager

This protocol describes the RADAR trial and provides information about procedures for entering patients. Every care was taken in its preparation, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact the Trial Manager to confirm they have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

Protocol Authorised by:

Name & Role: Signature:

Professor Patrick Kehoe Date: 04 March 2016

RADAR Chief Investigator

Protocol Amendment History:

Trial Amendment Type & Number	Protocol Version No.	Date Issued	Author(s) of changes	Summary of changes made
Substantial Amendment 1 (S/A1)	3.0	03/06/2013	Patrick Kehoe	Revisions made for clarity and to ensure consistency with the sponsor's SOPs and previous recommendations made by the ethics committee See S/A1 summary dated 03/06/2013
Substantial Amendment 2 (S/A2)	4.0	18/07/2013	Patrick Kehoe	Addition of information pertaining to pilot imaging procedures
Minor Amendment 2	4.1	23/07/2013	Patrick Kehoe	Minor clarifications added after review by TSC, DMEC and TMG
Substantial Amendment 3 (S/A3)	5.0	28/11/2013	Patrick Kehoe	Change to minimisation details and eligibility criteria. Clarification that an additional phonecall is required to provide the outcome of the screening blood test.

Minor Amendment 3	5.1	09/04/2014	Patrick Kehoe	Minor corrections to ensure consistency with other documentation/text e.g. timing of blood tests
Substantial amendment 6 (S/A 6) NB substantial amendments 4&5 were approved by the MHRA only due to change in brand of the IMP and shelf life extension.	6.0	07/10/2014	Patrick Kehoe	Removal of exclusion criteria for severe hippocampal atrophy and inclusion of option to recruit via primary care.
Minor Amendment 4	6.0	07/10/2014	Patrick Kehoe	Submission for review of revised poster to be used in recruitment from primary care.
Minor Amendment 5	6.1	14/11/2014	Patrick Kehoe	Removal of residual references in protocol text and Appendix I of protocol to severe hippocampal atrophy as exclusion criteria that were missed in Substantial amendment 6 (S/A 6)
Minor Amendment 6	6.1	26.02.2015	Patrick Kehoe	Formatting changes to the open label diaries for BP and medication and change to the reply slip to include GP surgery.
Minor Amendment 7	6.1	12.05.2015	Patrick Kehoe	Inclusion of RADAR on 'Join Dementia Research' (JDR)
Substantial Amendment 7 (S/A7)	7.0	03/12/2015	Patrick Kehoe	Change of eligibility criteria for MMSE range from 18-28 to 15-28.
Substantial Amendment 8	8.0	04.03.2016	Patrick Kehoe	Inclusion of an embedded qualitative component.

Protocol Abbreviations

ADNI	Alzheimer's Disease Neuroimaging Initiative
ASL	Arterial Spin Labelling
BRTC	Bristol Randomised Trials Collaboration
CI	Chief Investigator
CIG	Clinical Investigators Group
CL	Clinical Lead
CBF	Cerebral Blood Flow
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
HDPE	High-density polyethylene
IMP	Investigational Medicinal Product
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NBTR&I	North Bristol NHS Research and Innovation
NIHR-EME	National Institute of Health Research Efficiency and Mechanism Evaluation
NRES	National Research Ethics Service
PI	Principal Investigator
PMG	Project Management Group
QP	Qualified Person
REC	Research Ethics Committee
SmPC	Summary of Product Characteristics
SMPU	St. Mary's Pharmaceutical Unit
TMG	Trial Management Group
TSG	Trial Steering Group
UCL	University College London
UOB	University of Bristol
vMRI	Volumetric Magnetic Resonance Imaging analysis
WMH	White Matter T2 Hyperintensities

CONTENTS

1 Project Summary

Research design: A phase II, two arm, double-blind, placebo-controlled, randomised trial.

Study population: Men and women aged at least 55 years with mild-to-moderate Alzheimer's disease (AD)

Interventions: Patients will be randomised to either 100mg encapsulated generic losartan or placebo once daily for 12 months after a 2 week open-label phase followed by up to 2 weeks placebo washout to establish drug tolerability.

Outcomes: The primary outcome will be the rate of whole brain atrophy as a surrogate measure of disease progression. Secondary outcomes: (i) white matter hyperintensities (WMH) volume and cerebral blood flow (CBF) (also surrogate markers of cognitive decline and disease progression); (ii) performance on a standard battery of assessments of memory, cognitive function, activities of daily living and quality of life. We will also bank bloods so if the trial is successful we can later study drug-induced changes to levels of plasma protein markers of AD and AngII pathway-linked AD-related.

Assessments: Major assessments (for all outcomes) and relevant safety monitoring of blood pressure and bloods will be at baseline and 12 months. An interim 6 month visit will include full cognitive assessments and safety blood pressure and bloods only. Additional safety monitoring for blood pressure, bloods and side effects will occur at weekly intervals of the active open-label phase and at 14 days, 3, 6 and 9 months post-randomisation (NB no blood test required at 9 months).

Sample Size: Based on studies conducted within the Alzheimer's Disease Neuroimaging Initiative (ADNI) to optimise protocols for imaging use in clinical trials of AD, we will recruit a sample size of 228 participants (recruited over 24 months) to provide at least 182 subjects with final assessments to provide 84% power to detect a 25% difference in atrophy rate (therapeutic benefit) change over 12 months at an alpha level of 0.05.

Analysis: We will analyse our outcome using an intention-to-treat approach, estimating between-group differences in outcomes derived from appropriate (linear or logistic) multivariable regression models adjusting for minimisation variables and value of outcome at

baseline.

Sponsorship: North Bristol NHS Trust Research & Innovation (NBT R&I). A contract between NBT R&I and the University of Bristol will outline the designation of responsibilities

2 Background Information

2.1 Existing research

Alzheimer's disease (AD) represents two-thirds of the 1-million dementia cases in the UK. Its care costs almost equal that of cancer, stroke and heart disease combined. This will double within 20 years (1). AD is currently incurable and current therapies only treat symptoms for a limited time (2, 3). AD inevitably progresses resulting in the need for very costly 24 hour care. There is urgent need for better treatments to extend the quality of life of AD patients and their carers and reduce the rising costs to the NHS of £23 billion per year. It has been estimated that *any treatment delaying the onset of AD by 5 years could half its prevalence* (4). Similarly any treatment that slows AD progression will hugely benefit escalating personal, NHS and social service burden.

Epidemiological studies have consistently shown that hypertension in midlife (5, 6), late life (7), and stroke (8) increase risk of dementia. In recent specific studies of AD, we (9) and others (10) observed that angiotensin II (AngII) targeting drugs (AngII type 1 receptor antagonists (AT1RAs) and Angiotensin Converting Enzyme inhibitors (ACEIs) had lower hazard ratios for the incidence of AD compared with other types of anti-hypertensive drugs and AT1RAs were significantly more beneficial than ACEIs. While the underlying cause of AD remains unclear, loss of acetylcholine and neurons due to the deposition in the brain of amyloid-β (Aβ) peptide, a major pathological factor is key (11). Significant cerebrovascular pathology (CVP) is also common (11-13). Examples of such CVP include reduced cerebral blood flow (CBF), loss of cerebrovascular autoregulation, ischaemia, white matter hyperintensities (WMHs), all of which are associated with and predictive of loss of cognitive function (14-18). Hypertension is associated with plasma levels of Aβ (19) and in turn AD risk (20). Yet there are also other important molecular pathways that may be independent of cerebrovascular mediated pathology. ACE and neprilysin (NEP) activity, which make AngII, is elevated in the AD brain (21, 22); ACE activity is elevated in peripheral blood in AD (23); ACE and NEP degrade Aβ *in vitro* and *in vivo* (2); variation in the ACE gene associated with lower plasma levels of ACE are associated with AD risk (24). AngII promotes the synthesis of the

inflammatory mediator TNFα (25, 26) as well as eliciting anti-cholinergic (27, 28) and anti-glutamatergic effects (29) all of which are major sequelae of AD pathology.

Losartan, an (AT1RA), is a tried, tested and effective anti-hypertension drug over a wide range of ages. Losartan crosses the blood brain barrier (30) and is of the class of AngII blocking drugs, which we, and others, have seen are associated with reduced incidence of AD (9, 10). Losartan also improves CBF (16), a surrogate marker of cognitive performance in humans (31-33), it limits neuronal damage following ischaemia in stroke rat models (18); in low doses (i.e. not reducing blood pressure (BP)), it reduces pathology and improves cognitive performance in transgenic mouse models of AD (34). Given its anti-hypertensive effect it is also likely to reduce ischaemia-mediated WMHs(14).

There have been no clinical trials studying losartan or any related AT1RA drugs as an intervention in AD to date. The most relevant related trials that used losartan (50mg) reported modest benefits on memory in non-demented hypertensive patients (35, 36) which were thought to be independent of BP-lowering effects (37). To date, only one systematic review has assessed the impact of BP-lowering on cognitive decline(38). It concluded, based on data from four randomised controlled trials (RCTs), that BP reduction was insufficient to prevent dementia and cognitive decline in hypertensive patients with no prior cerebrovascular disease. This is supported by recent secondary analysis of ONTARGET and TRANSCEND where neither the ACEI (ramipril) nor another AT1RA (telmisartan) appeared to reduce the risk of cognitive decline and any type of dementia in patients with cardiovascular disease or diabetes (39). Staessen (2011) also recently concluded in a meta-analysis of hypertension treatment trials, that BP-lowering did not reduce dementia risk in populations with high cardiovascular morbidity (40). In our opinion, these studies have limited translationability to the prognosis of AD, since study populations were generally younger, were selected according to high cardiovascular burden and cognitive assessment was generally less rigorous than that normally used in clinical trials of AD. Yet, the findings make any large scale multi-centre RCTs of an AT1RA in AD premature and currently unjustified, in our opinion, without further supportive evidence.

To our knowledge, no studies have investigated losartan on MRI measures of brain atrophy, CBF, WMH and cognition in AD. This is supported by searches of PubMed and Google scholar using a search build of “Losartan AND Alzheimer OR Memory OR Cognitive OR Cognition OR Dementia”. Identical searches of other AT1RAs revealed no trials in AD patients. One related smaller (n=100) phase II three arm US-based trial (NCT00605072) is

the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial. Using only hypertensive people with early (non-AD) cognitive impairment it will compare one year of candesartan (AT1RA) treatment with lisinopril or hydrochlorothiazide for their effect on memory and executive function, CBF (measured by Transcranial Doppler) and central endothelial function (measured by changes in CBF in response to changes in end tidal carbon dioxide)(41).

RADAR will provide important information on the potential disease modifying benefits of AngII blockage in AD. Highly sensitive intermediate and industry standard MRI measures and analyses will be used that have been shown to be predictive of future AD progression and cognitive decline(42-48) in a specific AD population,; unlike most trials to date which have recruited people with high cardiovascular morbidity at higher risk of vascular or post-stroke dementia rather than AD. Secondly, 100mg encapsulated generic losartan will be administered, offering maximal blockade of AngII and we will investigate its biological effects in both hypertensive and normotensive AD patients (see Appendix 2 for NICE guidance on the management of hypertension). Testing in AD patients, irrespective of the presence of hypertension (our past observations show about 50% of AD patients in memory clinics are hypertensive), will examine whether losartan could have much broader application than just for patients who are hypertensive. Also, if losartan is beneficial for normotensive patients, this would provide support for the hypothesis that the protective mechanisms may be operating independent of or in addition to BP-mediated effects. If the trial is successful, attempts will be made to perform subsequent additional analysis of banked plasma of blood-borne markers related to AD pathology (Aβ, acetylcholinesterase) and AngII pathway activity (ACE and NEP activity, TNFα and c-reactive protein levels - which are all also altered in AD) that will provide needed novel *in vivo* data on the effects of AngII pathway modification in AD. The RADAR trial is therefore a timely and necessary study to begin to explain the mechanisms underlying potential clinical benefits of AngII inhibition in AD and inform the design of a requisite large-scale definitive phase III trial.

2.2 Rationale for current study

This study is novel for AD patients and not part of a wider study. It is based on two assumptions in relation to the AngII pathway in the brain. First, inhibition of the multi-factorial functions of AngII in the brain including vasoconstriction, reduction of acetylcholine (ACh) release, inflammation and neuronal excitotoxicity (25-29, 49) will be of significant benefit to cognition and pathology in AD patients. Second, the selective inhibition of AngII by losartan at its receptor, rather reducing its production via ACE, as would be achieved by an ACE-

inhibitor, will ensure that ACE that is elevated in AD (21, 50, 51) is left uninhibited to degrade Aβ. This can therefore contribute to reduced levels of Aβ-related atrophy. These preferential effects of AT1RAs over ACE-inhibitors have been reviewed at length and are supported by various pharmacoepidemiological and pre-clinical studies (9, 10, 52-54).

3 Planned Intervention

Participants will be randomised to receive either 100mg of encapsulated losartan or placebo daily for 52 weeks.

4 Study Objectives

The principal research question to be addressed is whether 52 weeks treatment of Alzheimer's disease with the anti-hypertensive drug losartan has a beneficial effect on surrogate markers of disease progression.

To achieve this aim we will address the following specific objectives:

1) investigate whether losartan reduces rates of AD-associated whole brain atrophy (including related analyses of the hippocampus and ventricles), improves levels of CBF and reduces levels of WMH using sophisticated and industry standard MRI scanning and analysis.
2) examine if losartan improves patient scores in standard cognitive assessments.
3) examine the correlation between MRI measures of AD pathology and cognitive assessment scores following one year of losartan treatment.
4) explore the tolerability and safety profile of losartan in elderly normotensive AD patients to inform phase III studies.
5) explore the differences in brain atrophy rates and changes in cognitive measures, in relation to change in blood pressure levels in AD patients after AngII suppression.
6) provide an archive of stored bloods from trial participants that can be subsequently investigated in more depth, if the trial is successful.

5 Primary Hypothesis

Losartan, compared to placebo, will reduce the progression of brain pathology in both hypertensive and normotensive persons with AD.

6 Study Sites

The RADAR study will be coordinated from Bristol, sponsored by North Bristol NHS Trust and led by staff from the Schools of Clinical Sciences (SoCS) and School of Social and Community Medicine (SSCM) in the University of Bristol, with input from co-applicants based at Queen's University Belfast, the University of Cambridge and the Dementia Research Centre, UCL.

RADAR sites will require expertise in recruitment to clinical trials of AD and capacity to provide MRI facilities to collect data for the primary and secondary outcome measures of the study. The MRI capabilities of sites will be established by a combination of questionnaires to sites to express initial interest, an initial paper based audit of site imaging facilities and, in turn, individual site visits that will involve piloting by site MRI facilities of the sequence of planned MR scans on healthy volunteers. Satisfactory execution of these pilot scans, from the point of view of resultant data quality, will be important for a site to be accepted to the study.

7 Study participants and Recruitment

RADAR will recruit cases of mild-to-moderate AD, with or without hypertension - diagnosed according to original NINCDS-ADRDA criteria (55). Patients *may already be receiving a cholinesterase inhibitor or memantine therapy*.

7.1 Inclusion criteria

Patients must have all of the following to be considered eligible:

- Age≥55 years
- A MMSE score of 15-28 (equivalent to a previous Montreal Cognitive Assessment (MoCA) of 7-26). NB all patients must undergo an MMSE as part of their eligibility assessment for RADAR, but may be screened on the basis of a previous MMSE/MoCA score.
- A modified Hachinski score (56) of 5 or less
- A previous CT or MRI scan consistent with a diagnosis of AD
- The presence of an informant who is willing to participate in the study
- Capacity to consent for themselves as judged by a member of the research team with appropriate training and experience

7.2 Exclusion criteria

Patients will be excluded/ineligible if they have any of the following:

- Receiving ACE-Inhibitors; AT1RAs, aliskiren or potassium sparing diuretics
- Known intolerance or renal problems with ACE-inhibitors or sartans
- Medically unsuitable for, or unwilling to have, an MRI scan
- Consistent baseline BP of <115/70 mmHg or >160/110 mmHg
- A fall in BP on standing of >20/10 mmHg associated with clinically significant symptoms or a fall >30/15 mmHg
- Previous cerebrovascular accident (CVA), with significant residual impairment (Transient Ischaemic Attack (TIA) is NOT an exclusion)
- Hypertrophic cardiomyopathy; or significant aortic valve stenosis
- Estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73m^2
- Evidence of liver disease or significant LFT derangement (Aspartate transaminase (AST)/ Alkaline Phosphatase (AP/ALP)/ Bilirubin greater than 2 x upper limit of normal)
- Potassium (K) greater than 6.0 mmol/L on non-haemolysed sample
- Primary neurodegenerative diseases or potential causes of dementia other than AD.
- Females who have not yet reached the menopause (defined as having a period in the previous 12 months) who test positive for pregnancy, are unwilling to take a pregnancy test prior to trial entry, or are unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial
- Any severe co-incident medical disease, or other factor inhibiting compliance with the study medication or follow up schedule e.g. participant unlikely to survive the trial follow up period due to a terminal comorbid condition
- Participation in a previous CTIMP within 6 months of RADAR trial entry

8 Ethical considerations and informed consent

The main ethical considerations for this study are around informed consent; the use of an anti-hypertensive drug in normotensive AD patients; the emergence of sustained hypertension during the trial; mitigating against the risk associated with losartan and pregnancy; minimising participant burden; dealing with any serious adverse events if and

when they occur and management of unexpected findings emerging in the course of the study. To address these, consultation with service users, carers and frontline health care staff has informed both the information that will be provided to potential participants and the overall design and oversight of this study.

8.1 Consent

On issues of information provided to participants and consent our eligibility criteria are such that all participants should have capacity to self-consent which will be judged by a trained, delegated healthcare professional who will have responsibility for taking consent. It is foreseen that potentially eligible patients will be identified through local scoping exercises (notes and computer databases) facilitated by various Clinical Research Networks (CRNs) or Research Interest Registers (e.g. Scottish Dementia Clinical Research Network - SDCRN) who will contact patients informing them of our study and sending brief REC-approved information sheets regarding the study, and inviting them to contact their local study team to participate. Where local resource can support this, recruitment may also take place in primary care through displaying posters and forwarding study invitation letters asking interested patients to contact the local study team.

Those who express an interest in participating will be sent further REC-approved information to read (and raise questions about if necessary by telephone) and will be invited to undergo a brief eligibility screen telephone call (e.g. to identify any potential participants who might have issues with MRI) prior to them attending a more detailed face-to-face eligibility assessment interview at their local assessment centre (usually a memory clinic) where the information will be discussed and capacity to consent identified. At this stage consent will be obtained in accordance with the Medicines and Human Use (Clinical Trials) Regulations 2004.

The range of mini mental state examination scores that will be recruited from for this study is likely to increase the efficiency with which we identify eligible patients for the study, i.e. those who can consent for themselves but we will also involve an informant (who may or may not also be a carer) which is also important because they too will need to consent to take part as some of the assessment schedules in the study require their input.

8.2 Losartan in normotensive patients

The issues around the potential for an antihypertensive treatment being given to normotensive patients and patient burden were issues previously raised by lay members (current and former carers of AD patients) after discussions with the Chief Investigator. It will be made clear to participants, and where relevant legal representatives, that as well as testing

the effect of losartan on changes related to Alzheimer's disease, that losartan might also provide some net benefit since they are said to reduce the risk of cardiovascular disease even in people without cerebrovascular disease.(58) Furthermore, it is anticipated that normotensive patients are unlikely to have any significant effects due to the drug because their normal BP regulation mechanisms should be working well. Nonetheless participants will also be informed of the safety and monitoring measures that will be in place for both the open-label and randomisation phase. Falls should be reported as adverse events and the frequency of these will be monitored throughout the study.

8.3 Increased blood pressure during the trial

Elevated blood pressure can be transient (e.g. white-coated hypertension from the assessment) and so repeated tests in each assessment will be key. However, it is possible that some participants may be observed to have elevated blood pressure at a follow-up assessment during the study. In such instances they will be managed as normal, by the participant's primary care physician, who will be informed of the development by a RADAR researcher. Should a patient develop uncontrolled hypertension during the trial then they will be removed if the physician thinks it is appropriate and that cannot be adequately managed without knowing whether they are on active therapy.

8.4 Losartan in pregnancy

Losartan is not safe for use in pregnancy and may cause harm and even death to a developing foetus. Female participants who have had a period in the past 12 months will be required to test negative for pregnancy as part of the trial screening procedures. Pre-menopausal women will be required to take adequate precautions to prevent pregnancy for the duration of the trial and the method of contraception used will need to be documented, and judged adequate by the consenting doctor. Patients should be advised that if they were to become pregnant during the study there would be an urgent need to stop taking the medication immediately and inform the study team straight away as this would meet the criteria for a Serious Adverse Event (See Section 20).

8.5 Participant Burden

It was also noted from discussions with lay-persons that many carers and patients prefer, where possible, home visits to reduce patient burden. This reduces the number of sometimes stressful visits to busy hospital sites where parking availability is increasingly an issue and that preparation for and travel to the visits often takes as much time, if not more, than the actual assessment itself. With this in mind provision has been made in this protocol to try to

restrict the number of visits away from the home to be the eligibility (consent) visit (at a local research site (e.g. local memory clinic) where additional medical information and testing can be done if needed) prior to the open-label phase and the two MRI-linked baseline (randomisation) and end of study visits which are 12 months apart. If research sites have the capacity or willingness to conduct consent visits as a home visit then this can be arranged to the mutual convenience of both the patient and doctor taking consent. For the safety bloods, taken in the open-label phase and 14 days post randomisation, we propose these can be conducted as home visits where possible unless participants request these be done at the research site or to coincide with other normal clinical care follow-ups. For the 3, 6 and 9 month visits we will give all participants the option to be assessed at home or at the research site to ensure they are not unnecessarily inconvenienced. Similarly, if at the baseline and end of study assessments it is not possible to combine the MRI and the full assessments – participants will be given the option to have the assessment within 7 days of the MRI assessment as either a home visit or a visit to the local research site. It is important to note that before the final MRI is taken the patient must not have taken the study medication for at least 4 days.

Whilst participants are presented with flexibility regarding the location of visits (research site vs home), it is possible that participants will demonstrate better cognition at home due to familiar surroundings, which may help them to feel better orientated and relaxed. Every effort should therefore be made to ensure that the location for cognitive assessments for each participant is consistent throughout the study in order to reduce bias. If a change of location is unavoidable, the RADAR Trial Manager should be consulted.

8.6 Managing serious and other adverse events

All serious adverse events (SAEs), adverse events (AEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported and managed according to North Bristol NHS Research and Innovation Policies and Standard Operating Procedures (see Section 20).

8.7 Identification and disclosure of unexpected findings

In addition to blood pressure variations being observed, there may be instances where anomalies are identified in the course of brain imaging which forms part of the study. In such instances we will follow the guidance set out in the recent “Management of Incidental Findings Detected in Research Imaging” report which was produced by Representatives of Research Imaging Centres, Professional Societies, Regulatory Bodies, Funding Organisations, Royal

Colleges involved in research imaging and Patient Organisations in the UK. (For a copy see: https://www.rcr.ac.uk/docs/radiology/pdf/BFCR(11)8_Ethics.pdf).

In the event of any anomalies being identified, as will be the case for bloods, we will refer the patient to contact their GP to review whether any further action is required. However, we expect this to be a rare occurrence in view of the fact that Inclusion criteria for the study state that all patients should have had a previous CT or MRI scan which supported their diagnosis of AD.

9 Study Design

A two-arm, double-blind, placebo-controlled, multi-centre, randomised, trial comparing 100mg losartan or placebo effects on MRI brain imaging in AD patients (both hypertensive and normotensive) following 12 months of treatment. The randomised stage of the trial will commence after a 3-4 week pre-study open-label phase. This will involve potential participants being on active drug for 14 days (7 days at 25mg followed by 7 days at 100mg) and then 4 to 14 days washout on a placebo, to ensure all patients entering the trial can tolerate the 100mg dose of losartan and have had a sufficiently long wash-out period. After the open-label phase, patients will undergo a baseline MRI protocol and cognitive assessment and will be randomly allocated to treatment arms using an automated randomisation system recommended by the UKCRC registered BRTC, ensuring allocation concealment. Allocation will be minimised (retaining a random component) using age, and baseline hippocampal volume.

We will undertake the following steps to reduce the risk of bias in this trial: (1) allocation will be concealed using an automated system operated by a registered CTU; (2) the allocation algorithm (stratification and minimisation) will retain a random component using a computer-generated random number sequence; (3) all participants and study personnel will be blinded to allocation by using over-encapsulation of losartan and placebo tablets; (4) assessment of MRI scans to generate the primary outcome will be undertaken blinded to treatment arm; (5) we have one primary outcome in the trial, whole brain atrophy, which will be clearly stated in a protocol. We will submit the protocol for publication soon after commencement of the trial; (6) it is inevitable that some participants may be lost to follow-up or unwilling to have the final MRI scan. The primary intention-to-treat analysis will be without imputation of these missing data, but we will undertake sensitivity analyses to investigate various assumptions about the missing data and check the robustness of the primary results.

10 Randomisation

After the open-label phase, patients will undergo a baseline MRI protocol and cognitive assessment and be randomised to treatment arms using an automated randomisation system recommended by the UKCRC registered Bristol Randomised Trials Collaboration (BRTC), ensuring allocation concealment. Allocation will be minimised (retaining a random component) using age and baseline hippocampal volume. It is envisaged that participants will not receive the study drug until both the MRI and the assessments have been completed. Emergency Unblinding

When necessary, the code for a particular participant can be broken at any moment during the trial. Emergency unblinding would only occur if a clinician believed that their treatment decision for a participant could be influenced by knowledge of what the patient is taking as part of the trial. An emergency unblinding service will be available through each local pharmacy service, which will provide 24-hour coverage using both standard and Out of Hours (OOH) pharmacy staff. Requests for emergency unblinding will be documented by pharmacy staff and logged centrally by the Trial Manager. In the event that emergency unblinding has occurred, patients will discontinue taking the trial medication but remain part of the study unless they chose to withdraw.

Where possible the members of the research team (excluding trial pharmacists) should remain blinded, subject always to clinical need. The Trial Manager will ascertain why unblinding has taken place. If the participant was unblinded because of a Serious Adverse Event then an SAE form will be completed and will be reported as stipulated in Section 20 of the Protocol.

Each participant, will be given a Trial Participation Card with details of who their treating clinician should contact in the event of an emergency. A standardised procedure for emergency unblinding will be available to all research sites.

11 Sample size determination

We have based our proposed sample size on recent studies conducted by the Alzheimer Disease Neuroimaging Initiative, (ADNI) which aim to optimise levels of recruitment to clinical trials of AD that involve MRI as an outcome measure (59-61). Previous data suggest a 12-month atrophy rate among AD patients of 15.2 mL (SD 8.6 mL/year) and that a relative difference in between group atrophy rate of 25% is clinically meaningful. This is equivalent to an absolute difference in atrophy rate of 3.8 mL/year in total brain volume between the trial

arms at 12 month follow up (62), and equivalent to a standardised effect size of 0.44 SDs. We will randomise a total of 228 participants, which assuming 20% non-collection of primary outcome data will leave 182 subjects for analysis. This will provide us with 84% power to detect our target difference of 3.8 mL/year in 12 month atrophy (therapeutic benefit) with two-sided $\alpha = 0.05$. Further precision for the analysis may be afforded by adjustment for selected baseline covariates (62).

We have made the following assumptions for the sample to examine whether 10-15 centres would be sufficient to identify the required number of patients: 30% of subjects will be excluded due to potential interactions with existing prescribed drugs or other contradictions (based on a recent scoping exercise of AD patients seen at a memory clinic); 10% of eligible patients cannot tolerate or have a contra-indication for the MRI scanner (63); 10% cannot tolerate losartan in the open-label phase (perhaps overly-conservative on current evidence (64)); and that 60% of remaining patients will consent to participate in the RCT (consistent with recent phase II study in AD (65)). This requires us to identify an initial pool of around 670 prevalent patients with AD (this number varies between 573 to 803 if one alters the consent rate from 50-70% - recent studies in mild-to-moderate AD randomised 234 patients from 317 screened i.e. 74% (65)) while another randomised 278 from 518 screened i.e. 54% (63).

12 Outcome Measures

12.1 Primary measures

Change in whole brain volume after 12 months treatment after randomisation, measured using volumetric MRI (vMRI).

12.2 Secondary measures

These will include:

1) rates of AD progression as assessed by changes in cognitive assessments, measures of activities of daily living and quality of life
2) change to the level of CBF measured by arterial spin labelling (ASL) techniques
3) change to the level of white matter hyperintensities by MRI
4) change in BP
5) measure of association between MRI measures of atrophy and rate of cognitive decline

6) level of drug compliance and tolerability (particular consideration to non-hypertensive patients' tolerability) though past studies report that drop out and side effects are not a major problem (66)

We will also bank (with patients consent) additional blood plasma samples, which will be optional to participants to donate, for future possible studies of plasma protein markers of Alzheimer's disease and of the renin angiotensin system.

In addition to vMRI offering a recognised, rapid and empirical surrogate marker of cognitive decline and AD pathology (46, 67, 68), CBF also serves as surrogate marker of cognitive performance in humans (31-33). Furthermore, WMH volume is a marker of cerebrovascular damage which has synergistic effects in AD (69) while data emerging from ADNI has found that WMH volume predicts 1-year cognitive decline and is being recommended as an important covariate of interest at baseline and subsequent follow-ups in AD treatment trials (14).

Hypertension is associated with plasma levels of Aβ (19) and in turn AD risk (20) while high levels of Aβ40, in combination with low (poorly cleared from the brain) levels of Aβ42 are associated with AD (20). Plasma Aβ measures have previously been used as quantitative traits in empirical genetic studies of AD (70-72) and in previous intervention studies of AD (73, 74). Plasma AChE has also recently been proposed as a surrogate indicator of disease progression and prognosis in AD (75) while elevated ACE activity in plasma (23) and brain (51) are associated with AD. Human plasma NEP activity is untested in AD as yet but elevated brain NEP is associated with AD (22), plasma NEP reduced Aβ burden in transgenic models of AD (76) and NEP produces angiotensin metabolites that serve to counteract AngII. TNFα is a suggested biomarker for AD progression (77) and with CRP is associated with BP variability (78) both of which have reciprocal interactions with AngII and its receptors (79-82) while there have been conflicting reports of CRP variation in plasma taken from AD patients (83, 84).

The combination of measures of atrophy, CBF and WMH volume will be important complements to the standard cognitive assessment measures. These will be combined to justify further pursuit of losartan or other similar related BP-lowering drugs in AD in large-scale clinical trials. There is already observational evidence from hypertension studies that BP lowering in general and alone is insufficient to reduce rates of dementia but as yet no data from RCT. If the trial is successful we will also explore (subject to further funding) further information on disease and drug efficacy mechanisms through measures of various relevant

biomarkers that in turn could be related to the imaging and cognitive assessment data collected in the study.

13 Procedures for the assessment of effectiveness

The flow of participants through the open-label and randomised phases of the trial and time-points at which data for primary and secondary outcome measures are taken study are summarised in Appendix 1.

13.1 Patient Prescreening and Open-Label Phase

Participant pre-screening will be initially undertaken by a brief telephone check to ensure participants meet the basic criteria to warrant a visit to the research site where a face-to-face interview with a clinician will take place. At this visit eligibility to participate in the study will be explored against the study inclusion and exclusion criteria. On meeting the eligibility criteria the participants will consent to take part, at which point a measure of blood pressure and sample of blood will be taken to measure electrolytes, creatinine levels and liver function tests (LFTs) (referred to as “safety” blood). Following satisfactory safety blood test results, participants will be prescribed 25mg non-encapsulated losartan to be taken once daily for 7 days. After 7 days, another home visit will occur and will involve the patient having their blood pressure and safety blood sample taken, and then provided with 7 days worth of 100 mg non-encapsulated losartan (to be taken as one tablet per day). At the end of these 7 days a home visit will involve a blood pressure check and safety blood sample and providing the patient with 14 days of encapsulated placebo. The subsequent washout period under placebo (4 to 14 days) was noted to preserve daily routines for participants who would go on to enter the randomised phase of the trial rather than have to manage a stop start routine between the open-label and randomised phases of the study. After a minimum of 4 days into the 14 day placebo washout, arrangements will be made to have the baseline MRI and cognitive assessments unless abnormal safety bloods are recorded from the open-label phase to suggest the participant would not tolerate the longer term exposure to the drug in the main part of the study. To accommodate issues around conducting detailed baseline assessment, the availability of MRI and the need to incorporate baseline atrophy measures in the randomisation protocol before trial drugs can be dispensed – the baseline cognitive assessments and randomisation can take place within 7 days of the baseline MRI, (see Section 13.3 for further details).

13.2 Randomised phase

After completing the baseline MRI scan and safety blood tests, participants should be randomised and following the completion of the baseline cognitive assessment provided with their allocated treatment. After 14 days, another home visit will occur and will involve the patient having their blood pressure and safety blood sample taken, a pill count carried out and provision of further trial drug.

At months 3, 6, 9 and 12 a blood pressure check and pill count should be carried out, along with further provision of the trial drug. Safety bloods samples are required at 3, 6, and 12 months. At months 6 and 12 only,cognitive assessments are also required. Participants also have the option of donating an additional blood sample for future research at their final 12 month visit. Participants should be contacted at 12 months to schedule the final MRI assessment and ensure a minimum of 4 days with no study medication prior to the MRI. Cognitive assessment may take place on the same day as the MRI or after, but both should be attempted up to a maximum of 14 days after the participant stops taking the drug. (see Section 13.3 for further details).

13.2.1 Primary Outcome Measure - Measurement of brain atrophy

The primary analysis of vMRI to assess efficacy will be based on change from baseline to 12 months follow-up. Atrophy is highly correlated with cognitive decline in AD (42, 46, 59, 60, 68). All MRI scans will be performed using either 1.5T or 3T imaging systems with high-resolution, high signal-to-noise T1- MPRAGE technique at all sites. The volumetric analyses of the MPRAGE images will be conducted in collaboration with UCL. The UCL team have been pioneering the application of vMRI in dementia imaging in a quantitative manner and have specialised in developing validated (semi-)automated computerised methods to derive hippocampal and other brain structure volumes for ageing research (43-45, 85). vMRI will also provide novel and further supportive evidence of the efficacy of losartan on very specific aspects of AD pathology which may not be directly influenced by BP regulation. The analysis methods to be applied were recently used in recent phase 2 clinical trials of Bapineuzemab in mild-to-moderate AD (65) and of memantine in a more severe AD cohort (63).

13.2.2 Secondary Outcome Measures

Additional imaging measures taken at the same time as the vMRI will include analysis of Cerebral Blood Flow (CBF) by arterial spin labelling (ASL) methods at all sites with appropriate MRI capability that will be assessed by the Imaging Lead for the RADAR study during site set-up visits. The assessment of MRI capability of both primary and secondary

MRI outcome measures will involve a piloting by sites of the RADAR MRI measures, under the supervision of the RADAR Imaging Lead, on consented healthy volunteers, that will be recruited separately to any of the patient recruitment phases. In addition to these pilot scans for site eligibility verification at the beginning of the study, similar scans on the same volunteers will be performed at each site at the end of the study and potentially on an interim basis for MRI quality purposes.

CBF will be assessed as a surrogate marker of cognitive performance as has already been reported in humans (31-33). Measures of WMH volume will be taken to explore the efficacy of the trial medication in ameliorating white matter damage in participants. WMH has previously been reported as a marker of cerebrovascular damage that has synergistic effects in AD (69) and predicts 1year cognitive decline (14).

Measures of cognitive assessments will also be conducted at baseline and after 6 and 12months of treatment. All cognitive assessments will be conducted face-to-face by an assessor who will be blinded to the intervention. At the end of study there will be exploration of differences between treatment groups on a series of validated cognitive assessment tools as follows: the 11 item ADAS-Cog (86); the Neuropsychiatry Inventory (NPI) (87); the Bristol Activities of Daily Living Scale (BADLS) (88), DEMQOL and DEMQOL-Proxy (89).

13.3 Summary of visits and assessments for RADAR trial

Visit	Researcher role	Participant role
Pre-Screening phase		
Early eligibility assessment	Gather medication records to verify no potential drug conflicts Brief telephone assessment	Consent on initial reply slip that medical records can be assessed to make sure there are no conflicts with the study medication. Answer a few brief questions to ensure eligibility is likely for a face to face visit
Screening Visit		
Eligibility Assessment	Mini Mental State Exam (MMSE) take baseline bloods for electrolytes, creatinine and LFTs	Give consent of their intention to enter study subject to interview to ascertain eligibility, including blood levels check. Await confirmation to enter open-label phase (within 7 working days from blood test).,
Follow up phone call (within 7 days of eligibility assessment	Feedback blood test results and confirm whether patient can proceed. If suitable, arrange for collection of study medication and BP machine.	Collection of study medication by participant or informant
Open Label Phase		
N/A	N/A	Take 25mg dose of drug for 7 days, maintain diary of BP check, drug taking and any side effects
7 day visit	Measure Sitting and Standing BP, take bloods for electrolytes and creatinine, do pill count and provide next trial drug	Take 100mg of drug for 7 days, maintain diary of BP check, drug taking and any side effects
14 day visit	Measure Sitting and Standing BP, take bloods for electrolytes, and creatinine, do pill count and provide next trial drug	Starting taking placebo drug for at least 4 days until called for baseline MRI visit (= 18-28 days), maintain diary of BP check, drug taking and any side effects
Randomisation Phase		
Baseline Visit 4-14 days after open label medication commenced)	MRI to inform randomisation and collect primary outcome measure. At same visit or within 10 working days conduct cognitive assessment*; take bloods for, electrolytes and creatinine and optional samples for future research and provide allocated drug (week 1 25mg, week 2 100mg)	Take allocated drug
14 days after randomisation	Measure Sitting and Standing BP, take bloods for electrolytes and creatinine; optional samples for future research, do pill count & provide next trial drug	Take drug
3 months after randomisation	Measure Sitting and Standing BP; take bloods for electrolytes and creatinine, do pill count & provide next trial drug	Take drug
6 months after randomisation	Cognitive assessments*,measure Sitting and Standing BP, take bloods for electrolytes and creatinine, do pill count & provide next trial drug	Take drug
9 months after randomisation	Sitting and Standing Measure BP; do pill count & provide next trial drug (no bloods to be taken at this time)	Take drug
12 months after randomisation	Initiate contact to participant to stop taking trial drug to provide at least 4 study drug free days (no dose reduction is required).	Stop taking trial drug
End of Study 12 months + 4 days after randomisation	MRI & MMSE. At same visit or within 10 working days conduct cognitive assessment*, measure Sitting and Standing BP, take bloods for electrolytes and	

	creatinine; optional samples for future research; do final pill count.	

*Assessments will include ADAS-COG (participant), NPI (informant), BADLS (informant), DEMQOL (participant) and DEMQOL-Proxy (informant). Please see the Working Practice Guidelines for further instructions regarding these assessments.

14 Optional Blood Sample Collection

Three blood tubes are required at each of the baseline and day 14 visits within the randomised phase as well as a further three at the end of study visit for all patients who have consented to this optional part of the study. All centres should participate in the collection of blood samples and will need to obtain the relevant consumables for this locally according to the RADAR Working Practice Guidelines.

Further details on processing, storage and transfer of blood samples are given in the RADAR Working Practice Guidelines that should be followed for all samples taken in relation to the RADAR trial.

It is envisaged that all banked blood samples will be made available for other high quality ethics committee approved research. It should be made clear to participants that the donation of these samples is optional and their decision will not affect their ability to participate in the RADAR trial. Furthermore, if these samples are being taken at the same time as the study safety blood samples, these optional samples should be taken after the main study bloods.

15 Investigational Medicinal Product Description

15.1 Open-label Phase

Commercially available UK licensed losartan tablets will be sourced by each participating centre, according to local arrangements. Participating pharmacies will dispense and label the medication according to Annex 13 requirements (Volume 4, Good manufacturing practice). A label template is provided in the site pharmacy file.

Current SmPCs for the products will be maintained in the pharmacy file by the responsible pharmacists at each site.

Placebo matched capsules will be manufactured, packaged and labelled by St. Mary's Pharmaceutical Unit (SMPU) of 20 Fieldway, Cardiff, CF14 4HY, in accordance with EU Good Manufacturing Practice.

15.2 Randomised Phase

Trial specific supplies of losartan 25mg, losartan 100mg and placebo matched capsules will be manufactured, packaged and labelled by SMPU.

Study Medication will be shipped by SMPU to the responsible pharmacist at site under appropriate temperature controlled conditions.

The medicinal products will be over-encapsulated to maintain blinding and presented in HDPE containers with a child resistant, tamper evident closure, by the SMPU.

15.3 Dosing Regimen

Open-label phase: losartan 25mg once daily for 7 days (week 1), then losartan 100mg once daily for 7 days (week 2), followed by Placebo once daily for 4 to 14 days.
Each site pharmacy will label the containers with week 1 and week 2 to assist subject compliance during the dose escalation.

Randomised Phase: Losartan/placebo 25mg daily for 7 days, then losartan/placebo 100mg daily for 11 months and 3 weeks.

15.4 Drug Accountability

Investigational Medicinal Product (IMP) will be stored by each site pharmacy according to the manufacturer's instructions and dispensed in accordance with the investigator's prescription.

Accurate records of all IMP received, dispensed, returned and destroyed will be maintained on the Drug Inventory Log by the responsible pharmacist at each site according to Good Clinical Practice. Records must be made available to the study monitors on request.

Any unused, partially used or expired IMP can be destroyed by the local pharmacy, with the authority of the sponsor and by providing a record of destruction.

15.5 Subject Compliance

Participants will be asked to store the medication according to the manufacturer's instructions. At each visit, research staff will perform a capsule count and return any unused medication to the site pharmacy. Participants who have taken between 80-120% of the expected number of tablets will be considered compliant. Non-compliance should be discussed with the Principal Investigator or delegated clinician to determine if appropriate to discontinue medication.

15.6 Labelling

Study drug supplied by SMPU will be labelled in accordance with Annex 13 (Volume 4, Good manufacturing practices, Annex 13, Manufacture of investigational medicinal products). Labelling of the drug supplied from local stock in the open-label phase is the responsibility of the local site Pharmacy according to local guidelines and adherence to GCP. A template label will be provided in the site pharmacy file.

16 Withdrawal and discontinuation of participants

16.1 Stopping study medication early

16.1.1 At the participant's request

Participants may voluntarily withdraw their consent for taking study medication at any time but clarification should be sought as to whether the participant is willing to continue with trial follow up (see sections 16.3 and 16.4).

16.1.2 As clinically indicated

Participants may be withdrawn from the study medication at any time if deemed appropriate by the local PI/delegated clinician, including the following circumstances:

- adverse blood test results (particularly levels of creatinine indicating renal dysfunction - we will allow for a 25% increase from baseline before exclusion or an absolute increase of more than 40mmol/L)
- hypersensitivity to the drug, incident dizziness or postural syncope (dependent on the level of severity and reported tolerability)
- emergent claustrophobia or inability to undergo an MRI
- loss of capacity and absence of legal representative to confirm continuing assent
- the development of uncontrolled hypertension or hypotension that cannot be adequately managed without knowing whether the participant is on active therapy
- non-compliance with study medication (see Section 15.5)
- experience of a Serious Adverse Event (see Section 20)
- any other illness/disease developed through the course of the study making further participation inappropriate or requiring emergency unblinding

In the following circumstances participants will be required to cease the study medication immediately:

- pregnancy
- experience of a severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing). In this instance the participant must tell their general practitioner immediately or go to the casualty department of their nearest hospital. This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than 1 out of 1,000 patients.

16.2 Withdrawal from open-label phase

Participants who discontinue the open-label phase for any of the reasons described above, or for any other reason at the discretion of the local PI, will not be eligible to proceed to the randomisation phase of the study. The reason for discontinuation should be recorded on the CRFs and any unused medication return to the research team. Participants will not be required to complete any further trial follow up other than in relation to any Serious Adverse Events.

16.3 Withdrawal from randomisation phase

Participants who discontinue the trial medication during the randomisation phase will remain in the study unless they voluntarily withdraw consent, and it should be confirmed that they are willing to continue with the trial follow up. Unless the patient requests otherwise, all CRFs should be completed, regardless of treatment actually received, as analyses of all outcome data will be on the basis of intention to treat (i.e. all randomised patients). A trial deviation form should be completed to record details of the deviation from treatment allocation. As described below, patients are however, free to withdraw consent for participation at any time without giving a reason.

16.4 Withdrawal from trial follow-up

A trial deviation form should be completed in the unlikely event that the patient withdraws consent for further follow-up data to be collected. If this situation is suspected, clarification should be sought to ensure that the patient is not simply withdrawing from the study medication. Clarification should also be sought as to whether the participant is withdrawing from MRI data collection, cognitive assessments, or all follow up. If the participant withdraws from one data collection method, but not the other, they should remain within the trial, in order to capture as much data as possible for the intention to treat analysis.

In the extremely unlikely event that the patient wishes to have their data removed from the trial completely (the implications of this should be discussed with the patient to ensure that this is their intent) this should be indicated as such on the trial deviation form.

17 Statistical Plan

The analysis and presentation of the trial will be in accordance with CONSORT guidelines, with the primary comparative analyses being conducted on an intention-to-treat basis and due emphasis placed on confidence intervals for the between-arm comparisons. A full analysis plan will be developed prior to completion of data collection, prior to commencing data analysis and will be approved by the Trial Steering Committee.

Descriptive statistics of demographic and clinical measures will be used to examine balance between the arms at baseline. The primary comparative analyses will employ multivariable regression models to compare group mean atrophy rates at follow up, adjusted for baseline volume and stratification/ minimisation variables. The comparison will be presented as an absolute difference in mean 12-month atrophy rate in the losartan group compared with placebo, along with 95% confidence intervals. In addition to carrying out similar analyses for the secondary outcomes (where p-values will be adjusted to account for multiple testing), and repeating any such primary analyses adjusting also for any variables exhibiting marked imbalance at baseline to check that this does not influence the findings, the secondary analyses for this trial will take three general forms. First we will undertake sensitivity analyses using both multiple imputation methods and simple methods making different assumptions to investigate the potential impact of missing data. Second the effect of compliance with treatment will be investigated using allocation-respecting methods such as complier averaged causal effects (CACE) modelling. Third appropriate interaction terms will be entered into the primary regression analyses for atrophy rates in order to conduct pre-specified subgroup analyses according to baseline volume, previous history of hypertension and treatment on anti-dementia drugs. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, the results of these essentially exploratory analyses will be presented using confidence intervals and interpreted with due caution.

18 Data Management

All IT systems supported and maintained by the University of Bristol Information Services will have infrastructure including server and server-based applications and desktop system maintenance. All NHS IT systems will be similarly supported. Server-based applications supported by University of Bristol Information Services and used by BRTC include:

• Web-based systems (Content Management and Microsoft Information Services).
• Central database systems (including Microsoft SQL Server 2008R2 on development and clustered production platforms).
• Central file storage on robust data systems with file versioning and recovery and mirroring on a second site.
• Backup services, on all data and server systems. This includes remote storage of backups on tape.
• Sealed Envelope randomisation service is a commercial operation, in operation since 2001 and has been used in Clinical Trials by many organisations.

18.1 Confidentiality

The personal data recorded on all documents will be regarded as confidential, and any information that would allow individual patients to be identified will not be released into the public domain.

Principal Investigators (PIs) must keep a separate log of patients' trial numbers, names, addresses and NHS numbers. The PI must maintain trial documents, which are to be held at the participating centre (e.g. patients' written consent forms), in strict confidence and ensure the patients' confidentiality is maintained.

The University of Bristol will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. Representatives of the University of Bristol, North Bristol Trust and the regulatory authorities are required to have access to patient notes for quality assurance purposes. Patient confidentiality will be respected at all times.

Data will be stored using an SQL Server database system maintained by University of Bristol Information Services. Access to this system and the data will be permitted only to authorised personnel. Patient identifiable data will be further restricted using access control methods and encrypted password, to those involved in analysis. All paper records that contain patient identifiable data will be stored in a secure locked cabinet.

18.2 Trial documents

Trial documents to be stored in PDF including appropriate version control and date of issue.

18.3 Case report forms

A proportion of data entry will be double keyed and validated as described in the Data Management Plan. Original data entry will be retained for 10 years.

18.4 Records retention

Patient identification codes will be held by BRTC for 15 years, all other data sources will be stored for 10 years after the close of the study. Databases will be routinely backed up on a daily basis.

18.5 Auditing and inspection

All electronically stored data will be held on systems which have inbuilt audit control showing what changes have been made to primary data overtime, a record of what the original data-point was, and record which user account made changes. Paper based data will be version controlled and scanned for electronic back up storage. All data will be managed according to the Sponsor's Standard Operating Procedures or University of Bristol procedures (under formal agreement) and data will be made available to the Sponsor for quality control and quality assurance auditing purposes.

19 Safety

19.1 Risks and benefits

The main risks are contraindications to the drug and tolerability of losartan in normotensive patients. Our inclusion/exclusion criteria, combined with the use of an open-label phase and careful blood and BP monitoring will hopefully reduce the likelihood of such events. If losartan is found to reduce pathology rates in AD, then this data will provide robust evidence upon which a large phase III trial, with clinical outcomes as the primary outcome, would be justified. Our current study will inform how to test in a future phase III RCT whether losartan, could serve as a very inexpensive (3-4 pence per day) add-on therapy for AD in the absence of any long-term treatments. Generally losartan is very well tolerated and the average BP of our patient group is likely to be around 130-140 mmHg systolic (slightly elevated over younger people)(90), and hence this BP lowering drug should be better tolerated. Furthermore, losartan and related antihypertensives are generally thought to reduce risk of cardiovascular disease in general which has a net health benefit to reducing cardiovascular events and mortality. This combined with the fact that they are likely to lower BP less markedly in people with lower BP (or normotensives), means that small or negligible BP changes might be expected in the normotensive participants such that they should not be problematic. Indeed,

hypotension (i.e. blood pressure lower than normal) is only considered to be a problem if it has a negative effect on the body e.g. cause light-headedness, dizziness, weakness, blurred vision, fatigue and fainting that will require monitoring in this study. However aside from being influenced by certain medications, hypotension (transient or otherwise) can also be caused other factors including blood loss, heat and dehydration, emotional stress and infection. In contrast, in hypertensives, any reduction in BP is deemed a good outcome in terms of lowering cardiovascular events and mortality. Thus the low risk from taking losartan could be significantly outweighed by the potential to continue on this readily available (and very cheap) treatment, beyond the study, if losartan is found to be effective. Participant's wishing to continue taking the study medication after the trial ends should be encouraged to discuss this with their GP, but there will be no guarantee this will be made available.

There is a risk associated with the use of losartan in pregnancy (see Section 8.4), but due to the age restriction for the trial it is unlikely that women of child bearing potential will be recruited. For patients who are still having periods, a negative pregnancy test result will be required prior to trial entry and it will be the responsibility of the local consenting clinician to ensure that women of childbearing potential entering the study are taking appropriate precautions to prevent pregnancy for the duration of the trial.

19.2 Assessment of safety

Losartan has been reported in numerous studies to have a good safety profile and high tolerability exceeding that of many other anti-hypertensive drugs and in some cases placebo as well (91). Of the most common adverse events reported in trials, only dizziness was reported more often in losartan treated patients (2.4%) compared with placebo (1.3%) but this was still lower than other anti-hypertensives. First-dose hypotension also rarely occurred with losartan and withdrawal effects (such as rebound hypertension) were not observed in clinical trials. Of further benefit losartan did not produce any clinically important differences in the clinical or laboratory safety profiles when studied in various demographic subgroups for age, gender, or race (64).

19.3 Methods and timings of assessment, recording and analysis of safety parameters.

An initial open-label phase to this study will involve an upward titration of the losartan dose from 25mg to 100mg losartan (in line with NICE and BHF guidelines). At the end of each of these 7 day dose periods safety bloods will be taken and assessed and compared with baseline bloods that will be taken at the time of consent. The visit after at least 4 days of

washout (on placebo) from the open-label phase, will serve as the baseline assessment for the randomisation part of the study. Here again study baseline bloods will be taken and repeat safety bloods taken at 14 days from randomisation (i.e. corresponding to 7 days of treatment on the higher dose of losartan or placebo following a blind run-in for 7 days at 25mg losartan or placebo). Given that all patients in the randomisation stage will have successfully completed the open-label phase (i.e. tolerated the drug) that included safety bloods at both losartan doses, to reduce patient burden in terms of blood sampling, the taking of safety bloods after 7 days at the higher dose was deemed sufficiently safe for monitoring purposes.

Additional brief visits at 3 and 9 months, as well as the 6 month assessment follow-up, will be used as opportunities to dispense medications and in doing so check compliance, side effects, BP and general health. Safety bloods measuring creatinine and electrolytes will be taken at all visits except for the 3 and 9 months visits post-randomisation (See Appendix I). From the open-label phase all participants will be instructed on potential side effects of the medication and will be encouraged to discuss any concerns with their local GP or research contact (see Section 20.2.5). All participants will also be given portable validated automated sphygmomanometers to check their BP during the open-label phase. This self-monitoring was suggested by a number of lay members and carers with whom the trial concept has been discussed and would serve to provide some reassurance, particularly amongst participants who may not have prior hypertension.

20 Adverse Events

20.1 Definitions

20.1.1 Adverse Events (AE)

AEs are defined as any untoward medical occurrence in a clinical trial participant. An AE does not necessarily have to have a causal relationship with the study treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP. (International Conference on Harmonisation [ICH] definition). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. In all instances it will be up to the physicians responsible for the participants care at this time, to determine whether the person's change in health is related to the trial and whether emergency un-blinding and/or cessation of the treatment might be necessary (see below for further details). In the event of the patient being

unblinded or the treatment ceased this would be recorded but the patients would remain in the study.

Examples of rare but serious adverse events would include hypersensitivity or allergic reaction to the drug. Other more common tolerability issues include: dizziness, altered renal function indicated by adverse creatinine or electrolyte levels (allowing up to a 20% increase from baseline) or unresolved postural syncope. For a more detailed list of reported adverse events that have been reported for losartan Principal Investigators should refer to the most recent version of the Summary of Product Characteristics for the brand of losartan used and keep a copy in their site pharmacy file. However we anticipate that the generally low adverse event profile of losartan (64) and our open-label phase will eliminate most subjects likely to experience adverse events of this nature from the main trial phase.

All AEs will be recorded in the Case Report Form (CRF) for the duration of the participant's involvement in the study.

20.1.2 Serious Adverse Event (SAE)

A SAE is defined by ICH as any untoward medical occurrence that at any dose of the study medication meets any of the following conditions:

- *Results in the death of the participant*
- *Is life-threatening*

  The term "life-threatening" 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 that hypothetically might have caused death if it were more severe.

- *Requires inpatient hospitalisation or prolongation of existing hospitalisation*

  for any event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of these outcomes (for example, oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse), the PI and/or Trial Clinical Lead should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting.

  Exceptions to this are hospitalisations for:

  - social reasons in absence of an adverse event
  - the in-clinic protocol procedures

- surgery or procedure planned before entry into the study or for elective treatment of a condition present prior to study entry (must be documented in the CRF).

- *Results in persistent or significant disability / incapacity*

  Any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

- *Is a congenital anomaly / birth defect*

  Exposure to the study drug before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

20.1.3 Adverse Reaction (AR)

An AR is considered to be associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below.

- *Not related*: An AR that is not related to the use of the drug
- *Doubtful*: An AR for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely
- *Possible*: An AR that might be due to the use of the drug and for which an alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable and therefore, the causal relationship cannot be excluded
- *Probable:* An AR that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by IMP withdrawal). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s)
- *Very likely:* An AR that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s) or concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by IMP withdrawal and re-introduction)

20.2 Adverse Events Procedures and Reporting

20.2.1 All Adverse Events

All AEs will be recorded after the commencement of randomised treatment and within 30 days of the last administration of the trial drug. Reporting of AEs will follow the procedures and

documentation provided by North Bristol NHS Trust and trial specific Working Practice Guidelines.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded in the source document and the CRF, together with any measures taken. PIs must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. North Bristol NHS Trust as the Sponsor is accountable for appropriate reporting of adverse events to the regulatory authorities and delegates this task to the University of Bristol.

20.2.2 Serious Adverse Events (SAEs)

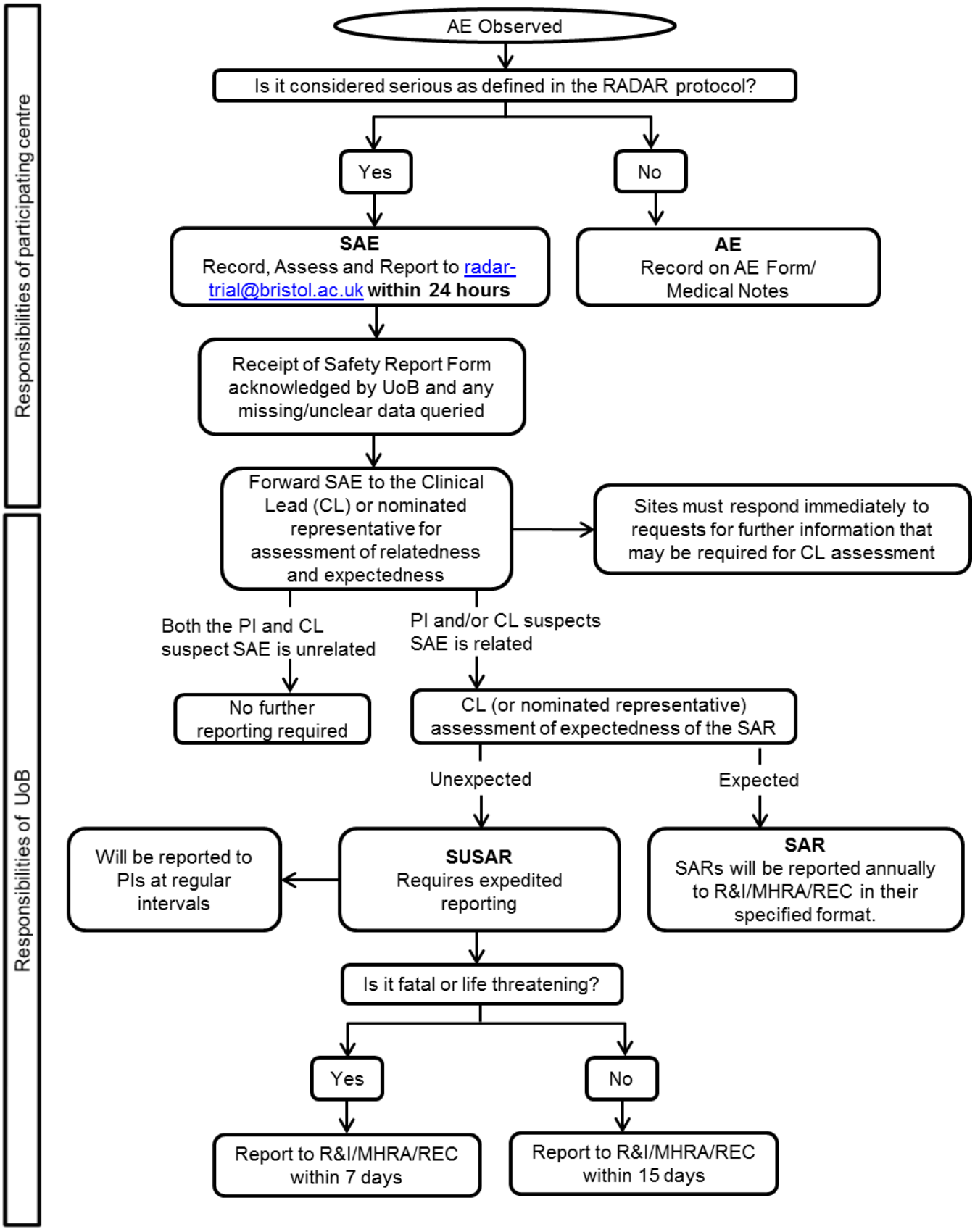
All SAEs will be reported by email to radar-trial@bristol.ac.uk by investigational staff within 24 hours of their knowledge of the event. All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- the event resolves
- the event stabilizes
- the event returns to baseline, if a baseline value is available
- the event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- when it becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

20.2.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All relevant information about a SUSAR that occurs during the course of the study and is fatal or life-threatening will be reported as soon as possible to the MHRA and the relevant ethics committee by The University of Bristol (UoB), on behalf of the Sponsor. The expectedness of an adverse event will be determined by whether or not it is listed in the *Summary of Product Characteristics.* When the outcome of the serious adverse reaction is not consistent with the applicable product information or concomitant comorbidities/diseases, this adverse reaction should be considered as unexpected. Side effects documented in the SmPC that occur in a more severe form than anticipated are also considered to be unexpected*.*

20.2.4 Flow diagram for SAE reporting, and action following report



20.2.5 Procedures for eliciting reports of, and for recording and reporting AEs and intercurrent illnesses

Participants should be encouraged to contact their GP in the first instance if they have any medical concerns, and in addition sites will provide local contact details where someone involved in the study may be contacted within office hours. Participants will be issued with a card giving brief information that the person is taking part in a trial, the trial identifier number, the relevant telephone number to contact their local research team and a 24hr emergency number that GPs or emergency doctors can ring to request emergency unblinding, from the hospital pharmacist.

In the event of a person feeling unwell whilst in the study they will be advised, in the first instance, to contact their GP or local research contact (within normal office hours). It will be the responsibility for the local Principal Investigator (or delegate) to determine whether the nature of the patient's illness may be related to the trial drug or not. The emergency contact details for unblinding may be used by anyone involved in the clinical care of the patient when unblinding is necessary to the participant's welfare. It will be the responsibility of the local PI and site pharmacist, and if possible involving input from the trial clinical lead, to determine whether unblinding is required (see Section 10.1).

In the event that surgery may be required, the intervention may be stopped briefly if there is a risk of any drug interactions. However, treatment should resume as soon as possible and a record made of the nature and duration of any interruption to taking the drug.

In terms of recording other potential side effects and intercurrent illnesses, a standardised list of questions will be asked and responses recorded at the various interim and main assessment visits which will occur 14 days, 3, 6, 9 and 12 months from baseline.

20.2.6 The type and duration of the follow-up of subjects after AEs

Subjects who self-report persistent tolerability issues will be followed up by telephone within 24-48 hours, by a member of the local research team to explore if there has been improvement.

If a GP referral was decided upon then there will be a mutually agreed level of follow-up by telephone with participants after the GP visit.

If a participant was told to discontinue treatment, the participant will be followed up daily by telephone for up to 72 hours for perceived drug-related events, commensurate with the time by which most active drug will have washed out (92, 93) and they will remain in the study.

Other self-reported issues, mentioned at interim visits will be followed up on a weekly basis for up to one month to see if there is a resolution of reported effects, at which point a decision will be made on what is an appropriate course of action in relation to a subject's involvement in the trial. Subjects who develop generalised dizziness and/or postural syncope will be monitored for the level of severity. A decision to discontinue treatment will be based upon self-reported levels of severity and perceived levels of any impairment or concern voiced by participants or if there is a clear indication to clinical members of the study team that continuation with treatment is against the best interests of the patient.

21 Embedded Qualitative Component

21.1 Rationale

The qualitative component of the RADAR trial will explore trial site recruitment pathways and potential sources of recruitment difficulties and facilitators with the aim of providing suggested changes to aspects of study design, conduct, organisation or training that could then lead to improvements in recruitment.

Many Randomised Controlled Trials (RCTs) face recruitment challenges for a variety of reasons including patient understanding of trial processes such as randomisation (Maughan et al. 2014), patient and health professional preference for particular treatments (Nelson et al. 2013, Harrop et al. 2013, Noble et al. 2014) and barriers to communication across trial sites. AD trials face additional challenges including the inherent vulnerability of older cohorts, progression of the disease and ensuing lack of capacity requiring additional recruitment of a study partner or informant, complex medication regimes excluding potential participants and a need to balance patient burden with safety monitoring (Grill & Karlawish 2010).

Robust evidence for effective recruitment strategies within RCTs is prevalent (Treweek et al.2010). However, qualitative research has been used to understand recruitment in specific trials, (de Salis et al. 2008); Wade et al. 2009, Howard et al. 2009, Paramasivan et al. 2011 and Mills et al. 2011) and has been shown to improve recruitment in some cases (Donovan et al. 2002, Donovan et al. 2009).

21.2 Qualitative study aims and objectives

To explore RADAR recruitment processes within and across trial sites to identify potential sources of difficulties and highlight facilitators to recruitment with the aim of providing suggested changes to aspects of study design, conduct, organisation or training that could then lead to improvements in recruitment.

To achieve this, aim the study has the following objectives.

- To review screening and recruitment figures across trial sites and highlight the main areas of participant exclusion/dropouts.
- Review patient and trial staff facing documentation for identification of potential recruitment barriers and provide recommendations for improved clarity and understanding.
- Explore recruitment pathways at trial sites and highlight barriers and facilitators to RADAR recruitment through questionnaires and interviews with trial staff.
- Understand trial decliner's experience of trial recruitment processes and reasons for non-participation.
- Explore and highlight potential hidden challenges to recruitment in-situ at trial sites during screening and consent sessions with patients.

21.3 Qualitative study design

A range of qualitative methods with be employed to address study objectives including review and revision of patient and trial staff facing documentation, questionnaire and semi-structured interviews with trial team members, semi-structured interviews with trial decliners and in-situ audio-recordings of recruitment screening and consent appointments. Data sets will be triangulated and analysed using a thematic approach (Braun and Clark, 2012).

21.4 Participant sampling and recruitment

21.4.1 Trial Staff (interviews)

Up to 27 trial staff will be purposively sampled to represent each trial site and include a range of research nurses and doctors responsible for screening and consent (12 sites x 2 recruiter staff = 24 total) as well as Trial Management Group members including the Chief Investigator and other closely involved in the design, management and co-ordination of the trial (x3). Purposive sampling is a non-probability sampling technique which allows the researcher to select, according to known characteristics of the phenomenon and population, instances likely to produce the most valuable data (Silverman, 2014).

The Chief Investigator will contact members of the trial team (site recruiters and TMG members) they feel the qualitative researcher would benefit from discussing recruitment with and obtain permission to pass on contact details. Contact details of those who are interested will be passed to the qualitative researcher, who will then contact the individuals to provide more information about the study and arrange a date and location for the interview.

21.4.2 Trial Decliners (interviews)

Up to 15 patients who decline to consent to the trial or their informants will be interviewed to explore their understanding of the trial processes and reasons for declining participation. Demographic information will be collected and reported descriptively but not used as sampling criteria. Trial decliner participants will continue to be recruited in the order they consent until 10-15 patients or informants across a range of trial sites have been interviewed.

Trial decliners will be informed of the optional interview study at the point of initial trial recruitment. Information about the interview study will be included in the main trial information sheet and a statement and tick box agreement for further contact from the research team included in the tear off reply slip. For those who express an interest in taking park in an interview, the qualitative researcher will arrange an interview at a mutually convenient time and place.

21.4.3 Staff and Patients (audio-recording of screening and recruitment consultations)

A minimum of one screening and one consent session will be audio-recording at each site (x24 sessions). The CI/TM will contact staff involved in recruiting patients into the trial and briefly explain the purpose of the study. They will ask whether they are able and willing to record screening and recruitment sessions, and if so, if they give their permission for the qualitative researcher to contact them. If an individual agrees their details will be passed to the qualitative researcher who will contact them to provide more information about the study and arrange audio-recording of future recruitment sessions. Participating staff will ask patients who are eligible for the trial whether then can record consultations and will provide them with the information sheet and written consent form after the consultation. This will allow the patient sufficient time to carefully read the information sheet and decide whether they want the qualitative researcher to access their recording.

21.5 Data Collection

21.5.1 Trial documentation review

Patient facing documentation including Participant Information Sheets and Consent Forms will be reviewed by the qualitative research team to identify aspects that are unclear or potentially open to misinterpretation and assess the clarity of the lay presentation of evidence provided. Recommended revisions will be made and presented for discussion with PPI representatives for a patient facing view. These PPI representatives will be asked to provide any further recommended changes which they feel may increase clarity and understanding and lead to improved recruitment.

Trial staff facing documentation will be reviewed by the qualitative team to identify aspect that are unclear and potentially open to misinterpretation and assess whether documentation is in line with the current protocol. Documentation will be discussed with recruiting staff as part of the questionnaire and interviews.

21.5.2 Recruitment pathway questionnaire

Through discussions with the Chief Investigator and Trial Manager the most appropriate person to describe recruitment processes at trial sites will be identified and sent a recruitment pathway questionnaire. The questionnaire will request trial site specific information about the patient pathway throughout the whole recruitment process, from identification of potential participants to commencement of treatment. Information about which staff and in what capacity they are involved will also be requested. Questionnaire data will be used to assess complexity of participation (patients and trial staff), compliance with the trial protocol and variation between sites. Questionnaire responses will inform later interviews with trial staff.

21.5.3 Interview conduct

Interviews with trial staff will be conducted by telephone or face to face, in a location of the participants' choice and informed consent will be gained immediately before the interview. Interviews with patients will be conducted by telephone only due to geographical dispersment of trial sites. For face-to-face interviews participants will be asked to complete a written consent form. For telephone interviews the researcher will verbally explain consent to the participant before the interview starts and, if the participant confirms their agreement to the interview, the verbal consent agreement will be repeated and audio recorded.

A flexible topic guide will be used in order to assist questioning during in-depth individual interviews. The topic guide will be devised to ensure that the primary issues are covered across all interviews, but do not dictate data collection.

The topic guide will incorporate considerable flexibility to enable participants to introduce new issues unanticipated by the researchers. Topic guides will be modified as necessary throughout the course of the study to reflect findings as they emerge. The researcher will use open-ended questioning techniques to elicit participants' own experiences and views of key events and participants will be asked to provide examples. With informed consent from participants, interviews will be recorded using an encrypted digital voice recorder, transcribed and anonymised to protect confidentiality.

Interviews with trial staff are expected to last approximately 45 minutes. Interviews with patients are expected to last approximately 10-25 minutes.

21.5.4 Recording of screening and consent sessions

All trial sites will be asked to record at least one screening telephone call (conducted with a researcher nurse) and one consent session (conducted with a doctor). One main point of contact will be identified per centre and digital audio-recorders will be provided (anticipated 1 per site). Audio recordings may be transcribed in whole or part depending on information required for analysis reasons. Audio-recordings will be keep strictly confidential with any transcribed sections anonymised to protect confidentiality. Both recruiters and patients will be asked to complete informed consent.

21.6 Data Analysis

Interview audio files will be fully transcribed, anonymised, checked for accuracy and imported into the NVIVO qualitative data management and analysis software to aid data management. Analysis will begin shortly after data collection starts, and will be ongoing and iterative. Analysis will inform further data collection: for instance, analytic insights from data gathered in earlier interviews will help identify any changes that need to be made to the topic guide for use during later interviews. Thematic analysis (e.g. Braun and Clarke, 2006), utilising a data-driven inductive approach (Boyatzis, 1998), will be used to scrutinise the data in order to identify and analyse patters and themes of particular salience for participants and across the dataset using constant comparison techniques (Glaser and Strauss, 1967; Charmay, 2006)

Firstly, interview transcripts will be individually read and re-read to gain familiarity with the data and initial ideas noted, from which an initial coding framework will be developed. The transcripts will then be examined on a line-by-line basis with inductive codes being assigned to the segments of the data that provide insights into aspects of recruitment barriers or facilitation within RADAR. The coding frame will be developed and new data will be compared initially to previous data, and then to the properties of emerging categories that contain the main themes. The data will be scrutinised for differences and similarities within the themes across interviewees, seeking disconfirming as well as confirming cases. One researcher will lead the analysis, but the other team members will independently code a sub-sample of transcripts, and all will meet to discuss the preliminary coding framework and themes, to ensure that the emerging analysis is trustworthy and credible and to maximise rigour.

Audio-recordings of appointments will be analysed as described above for interviews. Particular attention will be paid to identify and document aspects of informed consent and information provision that is unclear, disrupted or hinders recruitment. Recordings will be listened to by the qualitative research team and notes made about the content of the session,

including the basic content covered, the order of presentation of RADAR arms and other treatment options, time spent on interventions and controls, and time spent describing both the trial design and randomisation process. An assessment will be made as to whether the appointment is recruiter or participant led and also the degree to which there is evidence that the participant has understood the key issues of equipoise, randomisation, option to choose treatment and option to withdraw at any time.

21.7 Ethical Issues

The voluntary nature of participation in qualitative interviews and audio-recording of sessions will be made clear in information given to participants. Participants will be asked to provide their written or audio recorded verbal informed consent to take part prior to interview commencing. Where audio-recordings of recruitment sessions are made verbal consent prior to recording will be taken with full informed consent taken after the session to forward recordings to the qualitative research team. All participants will be assured of the confidentiality of the data collected, and will be asked for permission to publish anonymised quotations from the interviews. In the event of disclosure by the patient during the interview about any unmonitored health condition or concern the researcher will direct them to their relevant clinician for advice. Should any concern over patient safety or care be disclosed during trial staff and or patient interviews this will be highlighted to the Chief Investigator who will then take appropriate action.

All data collected will be used only for purposes in line with study aims and objectives. Confidentiality will be adhered to at all times. Transcripts of all audio-recordings will be anonymised, providing participants with pseudonyms and ensuring that any identifiable individuals or institutions discussed during interviews are anonymised sufficiently to ensure they cannot be readily identifiable. Audio recordings will be labelled and stored with a code to protect anonymity. The presentation and reporting of qualitative data will remove any information that may lead to the identification of individuals. The pseudonyms will be linked to the participants in a ‘code breaker’ database, which will be password protected and stored on a University of Bristol computer. Only the qualitative researchers working on the study will have access to this information.

Digital audio recordings will be transcribed by Bristol Transcription Service, a University of Bristol approved transcription company and a confidentiality agreement will be signed prior to this work commencing.

Interviews and recruitment sessions will be audio recorded using university approved encrypted digital audio recorders. The digital data collected will be stored on secure University of Bristol password protected computers. Data in written form, such as written consent forms, will be stored in locked filing cabinets in secure University of Bristol offices. Data will be encrypted in accordance with the University of Bristol Information Security Policies whenever it is transmitted electronically or otherwise conveyed (http://www.bristol.ac.uk/infosec/policies/).

Storage of all data with comply with the Data Protection Act and University of Bristol's data protection policies. Electronic audio recordings and consent forms will be held for 10 years or until the study is finished, whichever occurs sooner. After this period electronic audio recordings will be deleted and consent forms will be disposed of using the University of Bristol's confidential waste service. In accordance with the University of Bristol's 'Guidance on the Retention of Research Records and Data for studies involving human participants, their tissue and/or human data' (Research Governance Team, Research Data Services, 25th March 2015), anonymised, analysed data – e.g. NVIVO database and summaries of data will be retained for a minimum of ten years.

21.8 Patient and Public Involvement (PPI)

PPI representatives will be recruited from the Dementia Health Integration Team (HIT) Patient and Public Involvement panel to aid in the review and amendment of patient facing trial documents.

21.9 Qualitative Study Timeframe

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Literature Review																
CONSORT Review																
Trial Docs review																
Questionnaire to sites																
Interviews with staff																
Interviews with patients																
Recording of recruitment sessions																
Feedback and training workshop																

21.10 Presentation of findings

The qualitative research team will present a summary of anonymised findings emerging from triangulation of data sets to the CI and TMG, identifying any aspects of trial design and conduct that could be hindering or facilitating recruitment with the supporting evidence.

Feedback will include generic and RADAR specific advice for improving trial recruitment and will form part of a feedback and training workshop with trial sites.

21.11 Qualitative Study References

Boyatzis, R. Transforming qualitative information: Thematic analysis and code development. (1998). Thousand Oaks, CA: Sage.

Braun V, Clarke V. (2006) Using thematic analysis in psychology. Qualitative Research in Psychology;3:77-101.

Braun, V. & Clarke, V. (2012) Thematic analysis APA handbook for research methods in psychology. Vol 2. Research Design. American Psychology Society.

Charmay K. (2006) Constructing grounded theory: a practical guide through qualitative analysis. London: Sage.Feder G, Davies RA, Baird K, Dunne D, Eldridge S, Griffiths C, Gregory A, Howell A,

de Salis, I, Tomlin, Z, Toerien, M, and Donovan, JL. (2008) Qualitative research to improve RCT recruitment: Issues arising in establishing research collaborations, Contemp Clin Trials, 29, p.663-670.

Donovan JL, Lane JA, Peters TJ, Brindle L, Salter E, Gillatt D, Powell P, Bollina P, Neal DE, Hamdy FC for the ProtecT Study Group (2009) Development of a complex intervention improved randomization and informed consent in a randomized controlled trial. J Clinical Epidemiology, 62:29-36.

Donovan JL, Mills N, Smith M, Brindle L, Jacoby A, Peters T, et al. Improving the design and conduct of randomised trials by embedding them in qualitative research: ProtecT study. BMJ 2002; 325:766-770.

Glaser BG, Strauss AL. (1967) The discovery of grounded theory. Chicago: Aldine.

Grill J A & Karlawish J. (2010) Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. Alzheimer's Research Therapy, 2, 24, p1-11.

Howard L, de Salis I, Tomlin Z, Thornicroft G, and Donovan JL. (2009) Why is recruitment to trials difficult? Recruitment difficulties in an RCT of supported employment. Contemp Clin Trials, 30 (1), p.40-46.

Maughan T S et al. (2014) Feasibility study testing four hypotheses with phase II outcomes in advanced colorectal cancer (MRC FOCUS3): a model for randomised controlled trials in the era of personalised medicine? British Journal of Cancer, 110, 9, p2178-2186.

Mills N, Donovan JL, Wade J, Hamdy FC, Neal DE, Lane JA. Exploring treatment preferences facilitated recruitment to randomized controlled trials. J Clin Epidemiol 2011; 64: 1127-1136

Nelson A et al. (2013) QUALZICE: a QUALitative exploration of the experiences of the participants from the ZICE clinical trial (metastatic breast cancer) receiving intravenous or oral bisphosphonates. Trials, 14, 325.

Noble S et al. (2014) A feasibility study to inform the design of a randomised controlled trial to identify the most clinically and cost effective anticoagulation length with low molecular weight heparin in the treatment of cancer associated thrombosis (ALICAT): study protocol, Trials, 15, 122.

Paramasivan S, Huddart R, Hall E, Lewis R, Birtle A, Donovan JL. Key issues in recruitment to randomized controlled trials with very different interventions: a qualitative investigation of recruitment to the SPARE trial. Trials 2011; 12: 78.

Silverman D (2014) Doing Qualitative Research. 4th edition. London: Sage.

Treweek S, Mitchell E, Pitkethly M, Cook J, Kjeldstrøm M, Taskila T, Johansen M, Sullivan F, Wilson S, Jackson C, Jones R. Strategies to improve recruitment to RCTs. 2010 Cochrane Collaboration. John Wiley & Sons.

Wade J, Donovan JL, Lane JA, Neal DE, and Hamdy FC. (2009) It's not just what you say, it's also how you say it: opening the 'black box' of recruitment appointments in RCTs. Soc Sci Med 68:2018-28.

22 Definition of the end of trial

The end of the RADAR trial will be defined as the last visit for the last patient recruited to the trial.

23 Quality Control and Quality Assurance

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical study data are credible. This research study will be run in accordance with GCP.

This project will be sponsored by North Bristol NHS Trust where the CI has a contract of employment. The management and the progress reporting of the project will be very much aligned to the recommendations made in the Department of Health and Medical Research Council's Clinical Trials Tool Kit.

Working Practice Guidelines (WPG) will describe the mechanisms for ensuring the quality of the MRI data, cognitive assessments and blood samples collected.

23.1 RADAR Governance Structure

23.1.1 Project Management Group (PMG)

The PMG will comprise the PI, the trial manager (TM) and relevant members of the BRTC to discuss the day-to-day operations of the trial both locally and across all sites as well as working towards all other related functions during the trial. The PMG will have weekly meetings between the PI and the local clinical field will be to monitor Bristol recruitment while further meetings with the Trial Manager will monitor activity and progress of all sites. These meetings will be used to update the trial management group (TMG).

23.1.2 Trial Management Group (TMG)

The TMG will meet approximately every 4-6 weeks, or as required and will comprise RADAR Investigators (i.e. applicants of the original trial grant), a representative from NBT R&I and the TM and will co-opt in members from the PMG, participating sites, or the BRTC as may be required. Co-Investigators, further afield will be encourage to attend these intermittently face-to-face but will be given the option to participate by teleconference. The TMG will monitor the progress of the trial against planned objectives and will liaise and support the PMG in planning and delivering the trial.

23.1.3 Clinical Investigators Group (CIG)

The CIG comprises the RADAR Investigators, the Principal Investigators (or delegated representatives) from each RADAR site, the TM, members of the BRTC and other project staff from sites as deemed appropriate. The CIG will meet periodically (2-3 times over the course of the study) to serve as update meetings on trial progress to discuss issues and provide feedback and updates on analysis.

23.1.4 Trial Steering Committee (TSC)

The PI and key members of the trial team will also meet with the Trial Steering Committee (TSC) that will meet at the beginning of the study and approximately six-monthly thereafter to provide independent oversight of the trial. The TSC will comprise of an independent chair and two other external independent experienced researchers (one being a methodologist) and observers from the NIHR-EME programme will also be invited to attend. We will also include at least one lay member (service user and/or a carer) recruited locally from either the Alzheimer's Society Research Network or another Bristol-based dementia charity. This will serve to build on the service user feedback used in the early design and conceptualisation of this study.

The specific tasks of the TSC will be:

(i) To approve the trial protocol

(ii) To approve necessary changes in the protocol based on considerations of feasibility and practicability

(iii) To receive the report from the Data Monitoring and Ethics Committee (DMEC)

(iv) To resolve problems brought to it by the co-ordinating centre Bristol

(v) To approve trial reports and papers for publication

The BRTC template TSC charter will outline these tasks and original signed copies of the charters will be kept in the Trial Master File along with a record of committee members.

23.1.5 Data Monitoring and Ethics Committee (DMEC)

The DMEC will examine data relating to trial processes, outcomes and adverse events, and will report to the TSC. The DMEC will comprise an independent chair and at least two other independent expert members including a medical statistician. The schedule of DMEC meetings will be staggered so that feedback is available for the TSC.

The BRTC template DMEC charter will outline these tasks and original signed copies of the charters will be kept in the Trial Master File along with a record of committee members.

23.2 Site Set-up and training

Start-up visits at each site, including pilot MRI measures and training where necessary in the secondary outcome cognitive assessment tools, will be performed before each site commences enrollment in the study. They will be coordinated through the PMG.

RADAR research days involving the CIG will be held intermittently throughout the trial to ensure that all sites participating in RADAR are fully appraised of issues including recruitment, CRF completion rates any baseline analyses and further training needs. These meetings will also serve as opportunities for all the leading Investigators and researchers to discuss protocol and data collection issues. Study Monitoring by Sponsor

23.2.1 Direct Access to Source Data / Documents

The Principle Investigator (PI) will allow monitors (from NBTR&I as the Sponsor), persons responsible for the audit, representatives of the Ethics Committee and of the Regulatory Authorities to have direct access to source data / documents. This is reflected in the Participant Information Sheet (PIS). Study monitoring will be undertaken by NBTR&I using theirmonitoringstandardoperatingproceduresandpolicies (http://www.nbt.nhs.uk/research/researcher-resources/running-completing-studies).

23.2.1.1 Before the Study

The PI will allow the Monitor to visit the site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

23.2.1.2 During the Study

The PI will allow the Monitor and/or the Sponsor to:

- Inspect the site, the facilities and the material used for the study
- Meet all members of his/her team involved in the study
- Consult all of the documents relevant to the study
- Check that the CRFs have been filled out correctly
- Directly access source documents for comparison of data therein with the data in the CRFs
- Verify that the study is carried out in compliance with the protocol and local regulatory requirements
- Carry out study monitoring at regular intervals, depending on the recruitment rate, and arranged between the PI and Monitor
- All information dealt with during these visits will be treated as strictly confidential

23.3 RADAR project team self-monitoring

The normal day-to-day running of the trial will be monitored across all sites by face-to-face and/or teleconference meetings as well as email (fort-nightly during the early recruitment phase moving to monthly as recruitment becomes more established). A similar pattern will be adopted when sites are transitioning to the commencement of follow-ups.

23.3.1 Access to Source Data / Documents at remote sites

Each participating centre will provide access to source data and study documentation to facilitate the monitoring objectives outlined above.

24 Insurance

Sponsorship of the RADAR trial by NBTR&I will mean the study is covered by North Bristol NHS Trust's Insurance cover (Scheme number: T492) which forms part of the NHS Litigation Authority. All participating sites in RADAR will require NHS R&D approval locally that similarly will include appropriate insurance cover.

25 Annual reports

25.1 Annual Progress Reports

Annual progress reports (APR) will be submitted to the main REC (Research Ethics Committee). The first report will be submitted 12 months after the date on which the favourable opinion was given. Annual progress reports will be submitted on the anniversary date for which favourable opinion was given and thereafter until the end of the study. A copy will also be sent to the NBTR&I and the Research Governance Team of the University of Bristol. Submissions will be made using forms available on the NRES website http://www.nres.npsa.nhs.uk/ and will be sent to the REC within 30 days of the end of the reporting period.

25.2 Development Safety Update Report

A Development Safety Update Report (DSUR) will be provided on the anniversary of the granting of Clinical Trial Authorisation (CTA) for the study and sent to the MHRA and the main REC within 60 days of this date. A copy will also be sent to NBTR&I and the Research Governance Team of the University of Bristol.

The main objective of a DSUR is to present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation. Standard Operating Procedure ISOP- H12 from North Bristol NHS Trust will be adhered to regarding the submission of the DSUR.

The DSUR sent to the main REC will be accompanied by a CTIMPs Safety Report Form available from http://www.nres.npsa.nhs.uk/ and as outlined in the NHS REC SOP.

26 End of study reports

End of study reports will be provided to the Research Ethics Committee and will also be submitted to NIHR within 14 days of the study completion, as contractually agreed. Final reports will also be provided to the Sponsor NBT R&I.

27 Publication Policy

The TMG (and where appropriate collaborators) will take an active part in the preparing and reviewing of all manuscripts and reports generated during, or as a result of this study. In line with contractual agreements with NIHR the authors will inform NIHR of any publications at least 28 days prior to publication.

27.1 Definition of authorship

An author is considered to be someone who has made substantive *intellectual* contribution to a study. Many journals consider it best practice that everyone who is listed as an author should have made a substantial, direct, intellectual contribution to the work. Honorary or guest authorship is not acceptable.

27.1.1 Authorship Procedure

The baseline criteria for this research, for both authorship and acknowledgments for peer reviewed publications and conference contributions, is that:

A. Authors must meet *all* of the following criteria:
   - substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data
   - drafting the article or revising it critically for important intellectual content
   - final approval of the version to be published.

B. No-one should be omitted from the authorship list if he/she meets the three criteria described above.

C. Some journals allow authorship of multi-centre projects to be attributed to a group. However all members of the group who are named as authors must still fully meet the above criteria for authorship as described above.

D. Other collaborators or members of the research group who may have contributed to some but not all of the criteria above will be listed in the Acknowledgments (see F below).

E. The individual authors will jointly make decisions about authorship before submitting the manuscript for publication. The lead author, corresponding author or the guarantor must be prepared to explain the presence and order of these individuals to the editor of a journal. Authorship and order of authorship (see G below) will be agreed in advance, in the early stages of the research.

F. All contributors who do not meet the criteria for authorship will be listed in an Acknowledgments section. Examples of those who might be acknowledged include:

   - persons who have contributed materially to the paper but whose contributions do not justify authorship. These may be listed under such headings as “participating

investigators" and their function or contribution should be described - for example, "served as scientific advisors," "critically reviewed the study proposal," or "collected data/material". Because readers may infer their endorsement of the data and conclusions, these persons must give written permission to be acknowledged.

- a person who provided purely technical help, provided general comments on the manuscript or writing assistance, or a departmental chair who provided general support.
- editors can ask corresponding authors to declare whether they had assistance with study design, data collection, data analysis, or manuscript preparation. Authors should therefore disclose in the acknowledgements section the identity of any individuals who provided this assistance and any entities that supported the work in the published article.
- financial support should also be acknowledged and, if appropriate, the grant identified.
- material or logistical support, in particular giving recognition to support provided in developing countries, should always be acknowledged.

G. Order of authorship

- the authors shall decide the order of authorship together. Contributors should discuss authorship issues frankly at the start of the work for each anticipated publication and not wait to raise concerns at submission time.

- authors shall specify in their manuscript a description of the contributions of each author and how they have assigned the order in which they are listed so that readers can interpret their roles correctly.

- the corresponding author or guarantor shall prepare a concise, written description of how the order of authorship was decided.

- examples of authorship order include:

    - descending order of contribution.

    - placing the person who took the lead in writing the manuscript, or doing the research, first and the most experienced contributor in the field last

    - alphabetical

- random order

H. If an individual leaves the project the question of contribution to publications and authorship should be discussed in advance of their departure to minimise misunderstandings and to agree how this will be managed.

27.1.2 Data access requests and future analyses

Given the nature of the study and data collected there may be scope for members of the RADAR Clinical Investigators Group to conduct additional analyses. It is the intention of the RADAR Investigators to be as collaborative as possible in such regards. In such instances formal requests for data will need to be made in writing, to the RADAR CI in the first instance, for discussion amongst the TMG and in turn the TSC. In the event of publications arising from such analyses those responsible will need to provide the TSC a copy of any intended manuscripts for their approval prior to submission. In such instances authorship will need to take a format such as "[name], [name] and [name] on behalf of the RADAR Clinical Investigators Group" or something similar which will be agreed by the TMG. In line with contractual agreements with funding agencies notification of any such publications will also need to be made known to the funders 28 days prior to the publications becoming publically available.

28 Dissemination Policy

In addition to provision of annual and final reports, as well as presentations at scientific meetings and publication of findings in scientific literature, all participants in the trial will be sent a summary of the final results of the trial which will contain a reference to the full paper. A copy of any related journal articles will also be available on request from the Dementia Research Group University of Bristol. Furthermore, depending on the final findings of the trial the RADAR Investigators may also seek further dissemination funding from other sources e.g. the Alzheimer's Society, to maximize the level of dissemination to both potential service users and professionals.

29 Conflicts of interest

Kehoe has undertaken advisory work for Pharma in the development and use of dual acting inhibitors of Angiotensin Receptor Blockers and Neprilysin for the treatment of different forms of cardiovascular disease. Passmore has received fees for lectures on hypertension and angiotensin converting inhibitors and angiotensin receptor blockers. The Trial Manager will keep records of financial and other competing interests for all Committee members.

30 References

1. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005 Dec 17;366(9503):2112-7.
2. Kehoe PG, Miners S, Love S. Angiotensins in Alzheimer's disease - friend or foe? Trends Neurosci. 2009 Dec;32(12):619-28.
3. Piau A, Nourhashemi F, Hein C, Caillaud C, Vellas B. Progress in the development of new drugs in Alzheimer's disease. J Nutr Health Aging. 2011;15(1):45-57.
4. Gillette Guyonnet S, Abellan Van Kan G, Andrieu S, Aquino JP, Arbus C, Becq JP, et al. Prevention of progression to dementia in the elderly: rationale and proposal for a health-promoting memory consultation (an IANA Task Force). J Nutr Health Aging. 2008 Oct;12(8):520-9.
5. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001 Jun 16;322(7300):1447-51.
6. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000 Jan-Feb;21(1):49-55.
7. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. Neurol Res. 2006 Sep;28(6):605-11.
8. Honig LS, Tang MX, Albert S, Costa R, Luchsinger J, Manly J, et al. Stroke and the risk of Alzheimer disease. Arch Neurol. 2003 Dec;60(12):1707-12.
9. Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM. Associations of Anti-Hypertensive Treatments with Alzheimer's Disease, Vascular Dementia, and Other Dementias. J Alzheimers Disease. 2011 Jun 27;26(4):699-708.
10. Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ. 2010;340:b5465.
11. Miners JS, Baig S, Palmer J, Palmer LE, Kehoe PG, Love S. Abeta-degrading enzymes in Alzheimer's disease. Brain Pathol. 2008 Apr;18(2):240-52.
12. Buee L, Hof PR, Bouras C, Delacourte A, Perl DP, Morrison JH, et al. Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related dementing disorders. Acta Neuropathol. 1994;87(5):469-80.
13. Kalaria RN. Linking cerebrovascular defense mechanisms in brain ageing and Alzheimer's disease. Neurobiol Aging. 2009 Sep;30(9):1512-4.
14. Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvey D, Beckett L, et al. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. Arch Neurol. 2010 Nov;67(11):1370-8.
15. Hanon O, Latour F, Seux ML, Lenoir H, Forette F, Rigaud AS. Evolution of blood pressure in patients with Alzheimer's disease: a one year survey of a French Cohort (REAL.FR). J Nutr Health Aging. 2005;9(2):106-11.
16. Hong KS, Kang DW, Bae HJ, Kim YK, Han MK, Park JM, et al. Effect of cilnidipine vs losartan on cerebral blood flow in hypertensive patients with a history of ischemic stroke: a randomized controlled trial. Acta neurologica Scandinavica. 2010 Jan;121(1):51-7.
17. Niwa K, Younkin L, Ebeling C, Turner SK, Westaway D, Younkin S, et al. Abeta 1-40-related reduction in functional hyperemia in mouse neocortex during somatosensory activation. Proc Natl Acad Sci U S A. 2000 Aug 15;97(17):9735-40.
18. Zhao Z, Tuor UI, Barber P. Chronic treatment with Losartan and Cerebral Ischemic Tolerance. J Exp Stroke Transl Med. 2009;2(2):9.
19. Lambert JC, Dallongeville J, Ellis KA, Schraen-Maschke S, Lui J, Laws S, et al. Association of plasma ass peptides with blood pressure in the elderly. PLoS One. 2011;6(4):e18536.

20. van Oijen M, Hofman A, Soares HD, Koudstaal PJ, Breteler MM. Plasma Abeta(1-40) and Abeta(1-42) and the risk of dementia: a prospective case-cohort study. Lancet Neurol. 2006 Aug;5(8):655-60.
21. Miners JS, Ashby E, Van Helmond Z, Chalmers KA, Palmer LE, Love S, et al. Angiotensin-converting enzyme (ACE) levels and activity in Alzheimer's disease, and relationship of perivascular ACE-1 to cerebral amyloid angiopathy. Neuropathol Appl Neurobiol. 2008 Apr;34(2):181-93.
22. Miners JS, Baig S, Tayler H, Kehoe PG, Love S. Neprilysin and insulin-degrading enzyme levels are increased in Alzheimer disease in relation to disease severity. J Neuropathol Exp Neurol. 2009 Aug;68(8):902-14.
23. Akatsu H, Ogawa N, Kanesaka T, Hori A, Yamamoto T, Matsukawa N, et al. Higher activity of peripheral blood angiotensin-converting enzyme is associated with later-onset of Alzheimer's disease. J Neurol Sci. 2011 Jan 15;300(1-2):67-73.
24. Lehmann DJ, Cortina-Borja M, Warden DR, Smith AD, Sleegers K, Prince JA, et al. Large meta-analysis establishes the ACE insertion-deletion polymorphism as a marker of Alzheimer's disease. Am J Epidemiol. 2005 Aug 15;162(4):305-17.
25. Benicky J, Sanchez-Lemus E, Honda M, Pang T, Orecna M, Wang J, et al. Angiotensin II AT(1) receptor blockade ameliorates brain inflammation. Neuropsychopharmacology. [Comparative Study
Research Support, N.I.H., Intramural
Research Support, Non-U.S. Gov't]. 2011 Mar;36(4):857-70.
26. Zhou J, Ando H, Macova M, Dou J, Saavedra JM. Angiotensin II AT1 receptor blockade abolishes brain microvascular inflammation and heat shock protein responses in hypertensive rats. J Cereb Blood Flow Metab. 2005 Jul;25(7):878-86.
27. Barnes JM, Barnes NM, Costall B, Horovitz ZP, Ironside JW, Naylor RJ, et al. Angiotensin II inhibits acetylcholine release from human temporal cortex: implications for cognition. Brain Res. 1990 Jan 22;507(2):341-3.
28. Barnes JM, Barnes NM, Costall B, Horovitz ZP, Ironside JW, Naylor RJ, et al. Angiotensin II inhibits cortical cholinergic function: implications for cognition. J Cardiovasc Pharmacol. 1990 Aug;16(2):234-8.
29. Rogawski MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. CNS Drug Rev. 2003 Fall;9(3):275-308.
30. Culman J, von Heyer C, Piepenburg B, Rascher W, Unger T. Effects of systemic treatment with irbesartan and losartan on central responses to angiotensin II in conscious, normotensive rats. Eur J Pharmacol. 1999 Feb 19;367(2-3):255-65.
31. DeKosky ST, Shih WJ, Schmitt FA, Coupal J, Kirkpatrick C. Assessing utility of single photon emission computed tomography (SPECT) scan in Alzheimer disease: correlation with cognitive severity. Alzheimer Dis Assoc Disord. 1990;4(1):14-23.
32. Imran MB, Kawashima R, Awata S, Sato K, Kinomura S, Ono S, et al. Tc-99m HMPAO SPECT in the evaluation of Alzheimer's disease: correlation between neuropsychiatric evaluation and CBF images. J Neurol Neurosurg Psychiatry. 1999 Feb;66(2):228-32.
33. Shiraishi H, Chang CC, Kanno H, Yamamoto I. The relationship between cerebral blood flow and cognitive function in patients with brain insult of various etiology. J Clin Neurosci. 2004 Feb;11(2):138-41.
34. Danielyan L, Klein R, Hanson LR, Buadze M, Schwab M, Gleiter CH, et al. Protective effects of intranasal losartan in the APP/PS1 transgenic mouse model of Alzheimer disease. Rejuvenation Res. 2010 Apr-Jun;13(2-3):195-201.
35. Fogari R, Mugellini A, Zoppi A, Derosa G, Pasotti C, Fogari E, et al. Influence of losartan and atenolol on memory function in very elderly hypertensive patients. J Hum Hypertens. 2003 Nov;17(11):781-5.

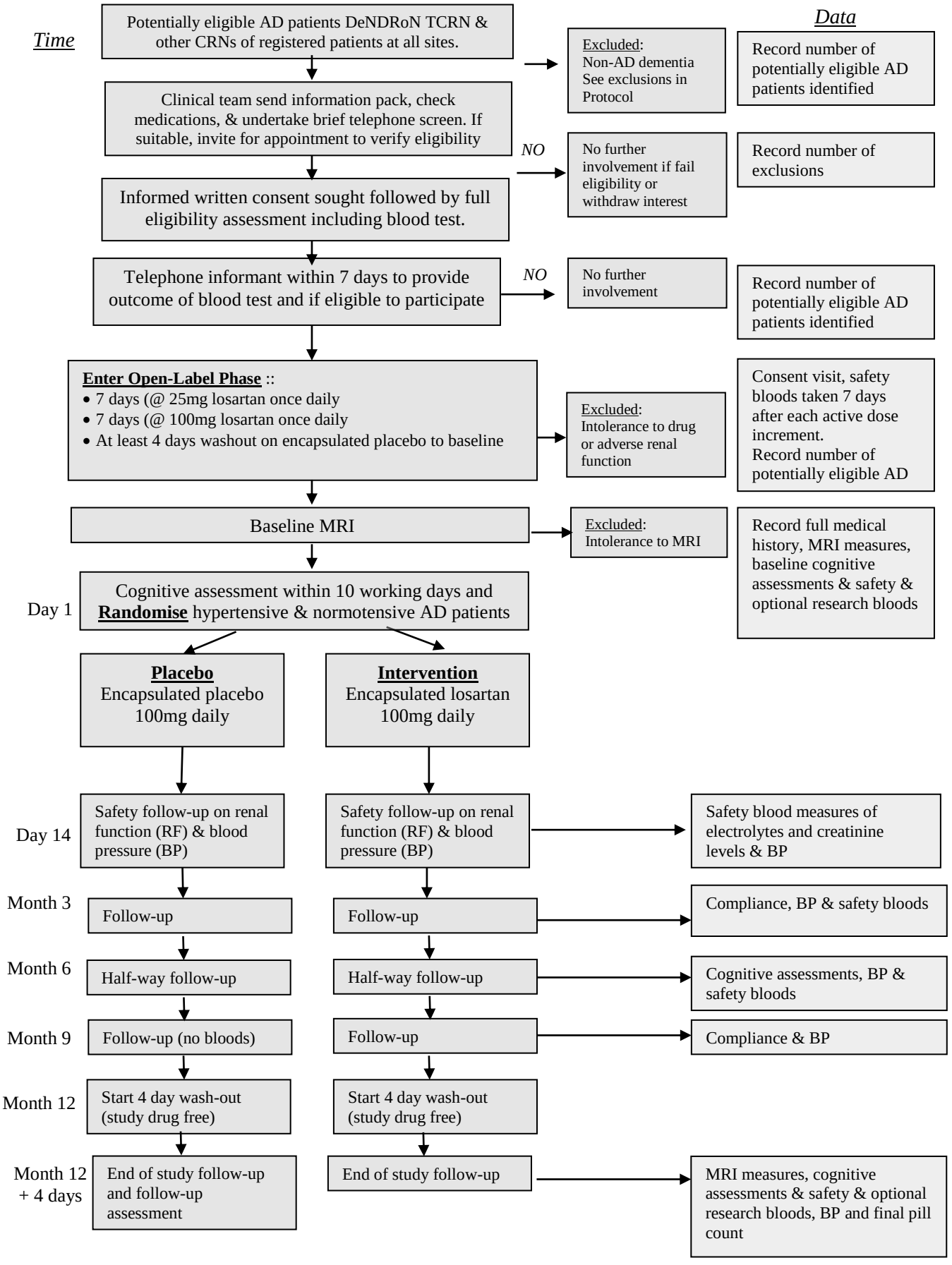
36. Tedesco MA, Ratti G, Mennella S, Manzo G, Grieco M, Rainone AC, et al. Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. Am J Hypertens. 1999 Nov;12(11 Pt 1):1130-4.
37. Tedesco MA, Ratti G, Di Salvo G, Natale F. Does the angiotensin II receptor antagonist losartan improve cognitive function? Drugs Aging. 2002;19(10):723-32.
38. McGuinness B, Todd S, Passmore AP, Bullock R. Systematic review: Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. J Neurol Neurosurg Psychiatry. 2008 Jan;79(1):4-5.
39. Anderson C, Teo K, Gao P, Arima H, Dans A, Unger T, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol. 2011 Jan;10(1):43-53.
40. Staessen JA, Thijs L, Richart T, Odili AN, Birkenhager WH. Placebo-controlled trials of blood pressure-lowering therapies for primary prevention of dementia. Hypertension. 2011 Feb;57(2):e6-7.
41. Hajjar I, Hart M, Milberg W, Novak V, Lipsitz L. The rationale and design of the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial in elderly hypertensives with early cognitive impairment: role of the renin angiotensin system inhibition. BMC Geriatr. 2009;9:48.
42. Fox NC, Scahill RI, Crum WR, Rossor MN. Correlation between rates of brain atrophy and cognitive decline in AD. Neurology. 1999 May 12;52(8):1687-9.
43. Freeborough PA, Fox NC. The boundary shift integral: an accurate and robust measure of cerebral volume changes from registered repeat MRI. IEEE Trans Med Imaging. [Research Support, Non-U.S. Gov't]. 1997 Oct;16(5):623-9.
44. Freeborough PA, Fox NC, Kitney RI. Interactive algorithms for the segmentation and quantitation of 3-D MRI brain scans. Comput Methods Programs Biomed. 1997 May;53(1):15-25.
45. Leung KK, Barnes J, Modat M, Ridgway GR, Bartlett JW, Fox NC, et al. Brain MAPS: an automated, accurate and robust brain extraction technique using a template library. Neuroimage. [Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.]. 2011 Apr 1;55(3):1091-108.
46. Chan D, Janssen JC, Whitwell JL, Watt HC, Jenkins R, Frost C, et al. Change in rates of cerebral atrophy over time in early-onset Alzheimer's disease: longitudinal MRI study. Lancet. 2003 Oct 4;362(9390):1121-2.
47. Hashimoto M, Kazui H, Matsumoto K, Nakano Y, Yasuda M, Mori E. Does donepezil treatment slow the progression of hippocampal atrophy in patients with Alzheimer's disease? Am J Psychiatry. 2005 Apr;162(4):676-82.
48. Hua X, Lee S, Hibar DP, Yanovsky I, Leow AD, Toga AW, et al. Mapping Alzheimer's disease progression in 1309 MRI scans: power estimates for different inter-scan intervals. Neuroimage. 2010 May 15;51(1):63-75.
49. Barnes JM, Barnes NM, Costall B, Horovitz ZP, Naylor RJ. Angiotensin II inhibits the release of [3H]acetylcholine from rat entorhinal cortex in vitro. Brain Research. 1989;491(1):136-43.
50. Miners JS, Raiker M, Love S, Kehoe PG. ACE variants and association with brain Aβ levels in Alzheimer's disease. American Journal of Translational Research 2010;3(1):8.
51. Miners S, Ashby E, Baig S, Harrison R, Tayler H, Speedy E, et al. Angiotensin-converting enzyme levels and activity in Alzheimer's disease: differences in brain and CSF ACE and association with ACE1 genotypes. Am J Transl Res. 2009;1(2):163-77.
52. Mogi M, Li JM, Tsukuda K, Iwanami J, Min LJ, Sakata A, et al. Telmisartan prevented cognitive decline partly due to PPAR-gamma activation. Biochem Biophys Res Commun. 2008 Oct 24;375(3):446-9.

53. Wang J, Ho L, Chen L, Zhao Z, Zhao W, Qian X, et al. Valsartan lowers brain beta-amyloid protein levels and improves spatial learning in a mouse model of Alzheimer disease. J Clin Invest. 2007 Nov;117(11):3393-402.
54. Zou K, Yamaguchi H, Akatsu H, Sakamoto T, Ko M, Mizoguchi K, et al. Angiotensin-converting enzyme converts amyloid beta-protein 1-42 (Abeta(1-42)) to Abeta(1-40), and its inhibition enhances brain Abeta deposition. J Neurosci. 2007 Aug 8;27(32):8628-35.
55. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939-44.
56. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol. 1980 May;7(5):486-8.
57. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. [Research Support, Non-U.S. Gov't]. 1992 Oct;55(10):967-72.
58. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Ann Neurol. 2009 Aug;66(2):200-8.
59. Fox NC, Ridgway GR, Schott JM. Algorithms, atrophy and Alzheimer's disease: cautionary tales for clinical trials. Neuroimage. 2011 Jul 1;57(1):15-8.
60. Hua X, Gutman B, Boyle CP, Rajagopalan P, Leow AD, Yanovsky I, et al. Accurate measurement of brain changes in longitudinal MRI scans using tensor-based morphometry. Neuroimage. 2011;57:10.
61. Thompson WK, Holland D. Bias in tensor based morphometry Stat-ROI measures may result in unrealistic power estimates. Neuroimage. [Comment
Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.]. 2011 Jul 1;57(1):1-4; discussion 5-14.
62. Schott JM, Bartlett JW, Barnes J, Leung KK, Ourselin S, Fox NC. Reduced sample sizes for atrophy outcomes in Alzheimer's disease trials: baseline adjustment. Neurobiol Aging. [Comparative Study
Multicenter Study
Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.]. 2010 Aug;31(8):1452-62, 62 e1-2.
63. Wilkinson D, Fox NC, Barkhof F, Phul R, Lemming O, Scheltens P. Memantine and brain atrophy in Alzheimer's disease: a 1-year randomized controlled trial. J Alzheimers Dis. 2012;29(2):459-69.
64. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. Am J Cardiol. [Clinical Trial
Comparative Study
Controlled Clinical Trial]. 1995 Apr 15;75(12):793-5.
65. Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology. [Clinical Trial, Phase II
Multicenter Study
Randomized Controlled Trial
Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't]. 2009 Dec 15;73(24):2061-70.

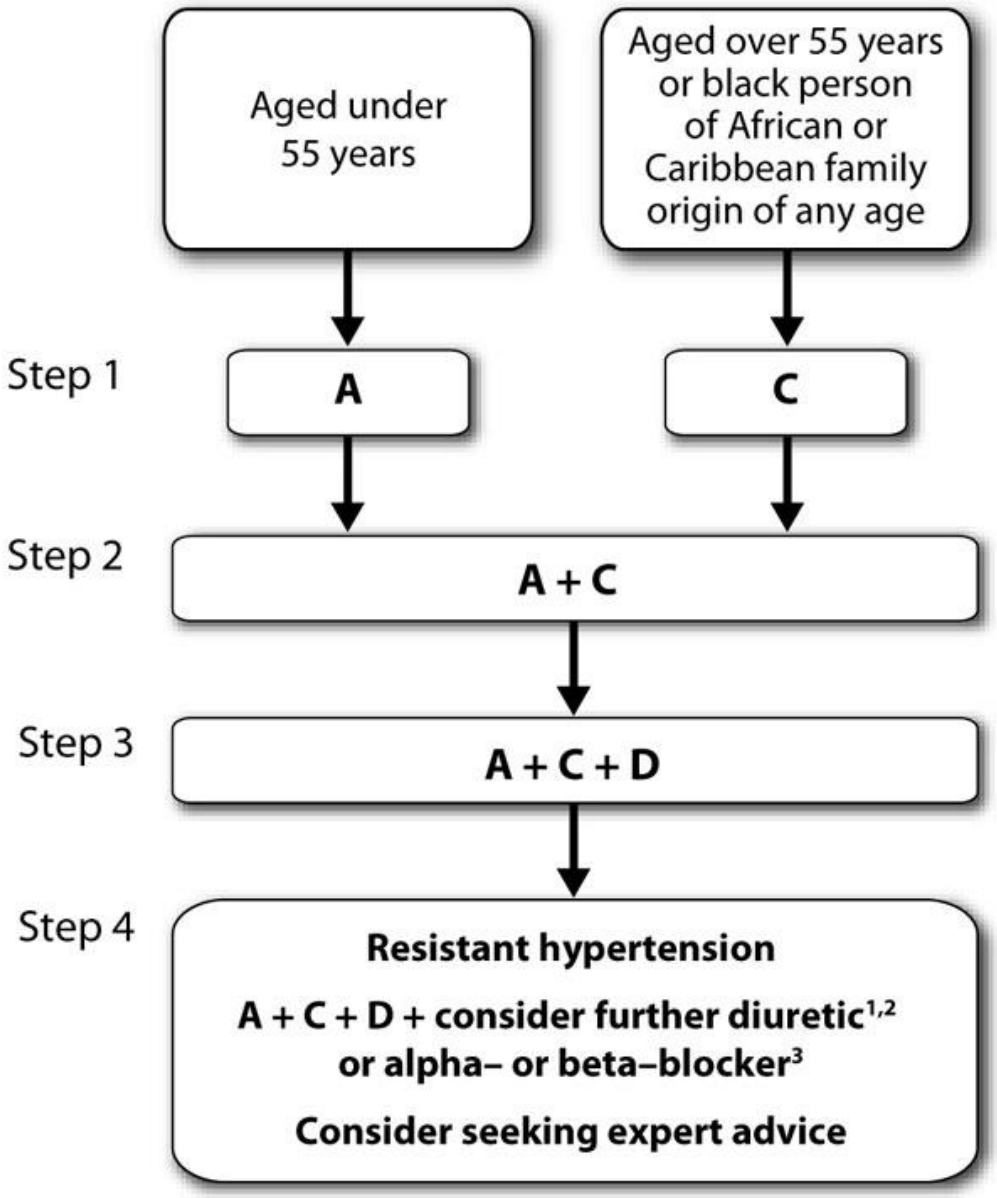
66. Stangier J, Su CA, Roth W. Pharmacokinetics of orally and intravenously administered telmisartan in healthy young and elderly volunteers and in hypertensive patients. J Int Med Res. 2000 Jul-Aug;28(4):149-67.
67. Frisoni GB, Fox NC, Jack CR, Jr., Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol. 2010 Feb;6(2):67-77.
68. Jack CR, Jr., Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging. 2008 Apr;27(4):685-91.
69. Zekry D, Duyckaerts C, Moulias R, Belmin J, Geoffre C, Herrmann F, et al. Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. Acta Neuropathol. [Research Support, Non-U.S. Gov't]. 2002 May;103(5):481-7.
70. Ertekin-Taner N, Allen M, Fadale D, Scanlin L, Younkin L, Petersen RC, et al. Genetic variants in a haplotype block spanning IDE are significantly associated with plasma Abeta42 levels and risk for Alzheimer disease. Hum Mutat. 2004 Apr;23(4):334-42.
71. Ertekin-Taner N, Graff-Radford N, Younkin LH, Eckman C, Adamson J, Schaid DJ, et al. Heritability of plasma amyloid beta in typical late-onset Alzheimer's disease pedigrees. Genet Epidemiol. 2001 Jul;21(1):19-30.
72. Ertekin-Taner N, Ronald J, Feuk L, Prince J, Tucker M, Younkin L, et al. Elevated amyloid beta protein (Abeta42) and late onset Alzheimer's disease are associated with single nucleotide polymorphisms in the urokinase-type plasminogen activator gene. Hum Mol Genet. 2005 Feb 1;14(3):447-60.
73. Basun H, Nilsberth C, Eckman C, Lannfelt L, Younkin S. Plasma levels of Abeta42 and Abeta40 in Alzheimer patients during treatment with the acetylcholinesterase inhibitor tacrine. Dement Geriatr Cogn Disord. 2002;14(3):156-60.
74. Relkin NR, Szabo P, Adamiak B, Burgut T, Monthe C, Lent RW, et al. 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiol Aging. 2008 Feb 20.
75. Garcia-Ayllon MS, Riba-Llena I, Serra-Basante C, Alom J, Boopathy R, Saez-Valero J. Altered levels of acetylcholinesterase in Alzheimer plasma. PLoS One. 2010;5(1):e8701.
76. Liu Y, Studzinski C, Beckett T, Murphy MP, Klein RL, Hersh LB. Circulating neprilysin clears brain amyloid. Mol Cell Neurosci. [Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't]. 2010 Oct;45(2):101-7.
77. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al. Systemic inflammation and disease progression in Alzheimer disease. Neurology. [Comparative Study
Research Support, Non-U.S. Gov't]. 2009 Sep 8;73(10):768-74.
78. Abramson JL, Lewis C, Murrah NV, Anderson GT, Vaccarino V. Relation of C-Reactive Protein and Tumor Necrosis Factor-Alpha to Ambulatory Blood Pressure Variability in Healthy Adults. The American journal of cardiology. 2006;98(5):649-52.
79. Li M, Liu J, Han C, Wang B, Pang X, Mao J. Angiotensin II induces the expression of c-reactive protein via MAPK-dependent signal pathway in U937 macrophages. Cell Physiol Biochem. [Research Support, Non-U.S. Gov't]. 2011;27(1):63-70.
80. Ruiz-Ortega M, Ruperez M, Lorenzo O, Esteban V, Blanco J, Mezzano S, et al. Angiotensin II regulates the synthesis of proinflammatory cytokines and chemokines in the kidney. Kidney Int Suppl. [Research Support, Non-U.S. Gov't]. 2002 Dec(82):S12-22.
81. Vongpatanasin W, Thomas GD, Schwartz R, Cassis LA, Osborne-Lawrence S, Hahner L, et al. C-reactive protein causes downregulation of vascular angiotensin subtype 2 receptors and systolic hypertension in mice. Circulation. [Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't]. 2007 Feb 27;115(8):1020-8.
82. Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation. [Research Support, Non-U.S. Gov't]. 2003 Apr 8;107(13):1783-90.

83. O'Bryant SE, Waring SC, Hobson V, Hall JR, Moore CB, Bottiglieri T, et al. Decreased C-reactive protein levels in Alzheimer disease. J Geriatr Psychiatry Neurol. [Comparative Study
Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't]. 2010 Mar;23(1):49-53.
84. Zaciragic A, Lepara O, Valjevac A, Arslanagic S, Fajkic A, Hadzovic-Dzuvo A, et al. Elevated serum C-reactive protein concentration in Bosnian patients with probable Alzheimer's disease. J Alzheimers Dis. 2007 Sep;12(2):151-6.
85. Leung KK, Barnes J, Ridgway GR, Bartlett JW, Clarkson MJ, Macdonald K, et al. Automated cross-sectional and longitudinal hippocampal volume measurement in mild cognitive impairment and Alzheimer's disease. Neuroimage. [Comparative Study
Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't]. 2010 Jul 15;51(4):1345-59.
86. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984 Nov;141(11):1356-64.
87. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994 Dec;44(12):2308-14.
88. Bucks RS, Ashworth DL, Wilcock GK, Siegfried K. Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale. Age Ageing. 1996 Mar;25(2):113-20.
89. Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. Health Technol Assess. 2005 Mar;9(10):1-93, iii-iv.
90. Falaschetti E, Chaudhury M, Mindell J, Poulter N. Continued improvement in hypertension management in England: results from the Health Survey for England 2006. Hypertension. [Research Support, Non-U.S. Gov't]. 2009 Mar;53(3):480-6.
91. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan compared with atenolol, felodipine and angiotensin converting enzyme inhibitors. J Hypertens Suppl. [Comparative Study
Meta-Analysis]. 1995 Jul;13(1):S77-80.
92. Christen Y, Waeber B, Nussberger J, Porchet M, Borland RM, Lee RJ, et al. Oral administration of DuP 753, a specific angiotensin II receptor antagonist, to normal male volunteers. Inhibition of pressor response to exogenous angiotensin I and II. Circulation. [Clinical Trial
Comparative Study
Research Support, Non-U.S. Gov't]. 1991 Apr;83(4):1333-42.
93. Munafo A, Christen Y, Nussberger J, Shum LY, Borland RM, Lee RJ, et al. Drug concentration response relationships in normal volunteers after oral administration of losartan, an angiotensin II receptor antagonist. Clin Pharmacol Ther. [Clinical Trial
Controlled Clinical Trial
Research Support, Non-U.S. Gov't]. 1992 May;51(5):513-21.

Appendix 1: Flow diagram showing the proposed recruitment, data collection and progression of participants through the trial



Appendix 2: Summary of drug therapy guidance (taken from NICE guidance on the management of hypertension (page 36, NICE clinical guideline 127, August 2011). - See more at: http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf



Key:

A = ACE inhibitor or low-cost A2RA. Consider a low cost A2RA, in preference to an ACE inhibitor, in combination with a calcium channel blocker in black people of African or Caribbean family origin at step 2

C = Calcium channel blocker (C). This is preferred but consider a thiazide-like diuretic (D) if C is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure.

D = thiazide-like diuretic: Offer chlortalidone (12.5–25 mg once daily) or indapamide (1.5 mg modified-release or 2.5 mg once daily) in preference to bendroflumethiazide or hydrochlorothiazide if diuretic therapy is to be changed or initiated.

Notes:

1. Consider a low dose of spironolactone or higher doses of a thiazide-like diuretic.
2. At the time of publication (August 2011), spironolactone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.
3. Consider an alpha- or beta-blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective.