Kehoe, P., Ben-Shlomo, Y., Howden, B., Lane, J. A., Coulthard, L., Blair, P., Horwood, J., Selman, L., & Clement, C. (2017). The Rationale and Design of the Reducing Pathology in Alzheimer's Disease through Angiotensin TaRgeting (RADAR) Trial. *Journal of Alzheimer's Disease*, 61(2), 803-814. <https://doi.org/10.3233/JAD-170101>

Peer reviewed version

License (if available):
CC BY-NC

Link to published version (if available):
[10.3233/JAD-170101](https://doi.org/10.3233/JAD-170101)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via IOS press at <https://content.iospress.com/articles/journal-of-alzheimers-disease/jad17010>. Please refer to any applicable terms of use of the publisher

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

The rationale and design of the Reducing pathology in Alzheimer's Disease
through Angiotensin Targeting (RADAR) Trial

Patrick G Kehoe¹, Peter S Blair², Beth Howden², David L. Thomas^{3,4}, Ian B. Malone⁴, Jeremy Horwood², Clare Clement², Lucy Selman², Hannah Baber², Athene Lane², Elizabeth Coulthard⁵, Anthony Peter Passmore⁶, Nick C Fox⁴, Ian B Wilkinson⁷, Yoav Ben-Shlomo⁸

¹ Dementia Research Group, Translational Health Sciences, Bristol Medical School, University of Bristol, Faculty of Health Sciences, Level 1 Learning & Research, Southmead Hospital, Bristol, BS10 5NB

² Bristol Randomised Trials Collaboration (BRTC), Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK

³ Leonard Wolfson Experimental Neurology Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG

⁴ Dementia Research Centre (DRC), Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK

⁵ ReMemBr Group, Translational Health Sciences, Bristol Medical School, University of Bristol, Faculty of Health Sciences, Brain Centre, Southmead Hospital, Bristol, BS10 5NB

⁶ Institute of Clinical Sciences, Block B, Queens University Belfast, Royal Victoria Hospital, Belfast, BT12 6BA

⁷ , Division of Experimental Medicine and Immunotherapeutics, School of Clinical Medicine, University of Cambridge, and Clinical Trials Unit, Addenbrookes Hospital, Box 111, Hills Road, Cambridge, CB2 0SP, UK

⁸ Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK

WORD COUNT:

Abstract word count: 282

Title Count: 16

References: 76

Tables: 1

Figures: 1

Correspondence:

Patrick Gavin Kehoe, Ph.D.

Professor of Translational Dementia Research

Dementia Research Group, School of Clinical Sciences

Faculty of Health Sciences

University of Bristol

Level 1, Learning & Research

Southmead Hospital

Bristol, BS10 5NB

Email: Patrick.Kehoe@bristol.ac.uk

Phone number: [+44-117-4147821](tel:+44-117-4147821)

Keywords: Alzheimer's disease, hypertension, vascular risk, parental history, renin angiotensin system, clinical trial

Disclosures:

Kehoe has undertaken advisory work for Novartis 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. UCL has received payment from Biogen, Eli Lilly, GSK, Janssen, Novartis, and Roche for image analysis services or consultancy by NF. NF receives no personal compensation for this. NF gratefully acknowledges support from the NIHR, the Queen Square BRU in dementia, the Leonard Wolfson Experimental Neurology Centre, the MRC, the Alzheimer's Society and Alzheimer's Research UK. The Trial Manager will keep records of financial and other competing interests for all Committee members.

Trial registration: EudraCT number 2012-003641-15; ISRCTN-ISRCTN93682878; MHRA CTA 18524/0223/001-0001

Ethical approval REC Reference 12/WA/0338

Sponsor: North Bristol NHS Trust Research & Innovation (NBT R&I) (reference 2625)

Protocol Version 8.0 – 04 March 2016

Funder: The RADAR Trial is funded by the Medical Research Council-National Institute of Health Research Efficacy and Mechanism Evaluation Programme (EME Board EME-11/47/03

Roles and responsibilities PGK, PSB, BH, AL, LC, APP, IW and YB-S all helped design and modify the protocol, PGK is the Chief Investigator (CI) of the study and BH is the trial manager who supervises the data collection at the different sites. DT and NF advised on MRI design and supervise the MRI analysis, PSB oversees the statistical analyses conducted by BK, AL provides BRTC support and JH, LS and CC designed and are responsible for the qualitative component, LC and APP provide clinical expertise on dementia, IW provides expertise on blood pressure and cardiovascular issues, YBS provides other methodological expertise. All members help decide on practical issues around running the RCT.

Trial Steering committee – Jenny Rusted (Chair), Antony Bayer, Clive Holmes, Susan Marshfield, Bill Mitchell, Eileen Winston, Ms Ly-Mee Yu, Patrick Kehoe, Beth Howden, Yoav Ben-Shlomo, Peter Blair, Athene Lane.

Data Monitoring Committee – Craig Ritchie (Chair), Sayeed Haque, Paul Gard

Abstract

Background: Anti-hypertensives that modify the renin angiotensin system may reduce Alzheimer's disease pathology and reduce the rate of disease progression. We report a phase II, two arm, double-blind, placebo-controlled, randomised trial (ISRCTN: 93682878; EudraCT: 2012-003641-15) of losartan to test the efficacy of Reducing pathology in Alzheimer's Disease through Angiotensin TaRgeting (RADAR).

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

Interventions: Randomly allocated 100mg encapsulated generic losartan or placebo once daily for 12 months after successful completion of a 2 week open-label phase and 2 weeks placebo washout to establish drug tolerability.

Outcomes: The primary outcome is the rate of whole brain atrophy as a surrogate measure of disease progression. Secondary outcomes include changes to (i) white matter hyperintensity (WMH) volume and cerebral blood flow (CBF) (also surrogate markers of cognitive decline and disease progression); (ii) performance on a standard series of assessments of memory, cognitive function, activities of daily living and quality of life.

Assessments: Major assessments (for all outcomes) and relevant safety monitoring of blood pressure and bloods will be at baseline and 12 months. Additional cognitive assessment will also be conducted at 6 months along with safety blood pressure and blood monitoring. Monitoring of blood pressure, bloods and reported side effects will occur during the open-label phase and during the majority of the post-randomisation dispensing visits.

Sample Size: 228 participants 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: Intention-to-treat analysis, estimating between-group differences in outcomes derived from appropriate (linear or logistic) multivariable regression models adjusting for minimisation variables.

Background

Currently the care costs of Alzheimer's disease are almost equal to that of cancer, stroke and heart disease combined, and are predicted to increase in the current absence of long term effective therapies (1-3). Thus there remains urgent need for better treatments to extend the quality of life of patients, their carers and to reduce the rising associated health care costs. Any treatment delaying the onset of AD by 5 years could halve its prevalence (4).

Hypertension in midlife (5, 6) and late life (7), and stroke (8) increase risk of dementia. Recently, 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 incidence of AD compared with other types of anti-hypertensive drugs. 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 (A β) peptide and tau pathology is key (11). Significant cerebrovascular pathology (CVP), such as reduced cerebral blood flow (CBF), loss of cerebrovascular autoregulation, ischaemia and white matter hyperintensities (WMHs); pathologies associated with and predictive of loss of cognitive function (12-16); is also common (11, 17, 18). Hypertension is associated with plasma levels of A β (19) and AD risk (20). Molecular pathways, likely independent of cerebrovascular mediated pathology are also probably relevant. Angiotensin converting enzyme (ACE) and neprilysin (NEP), which make AngII, are elevated in the AD brain (21, 22). ACE activity is elevated in peripheral blood in AD (23); ACE and NEP degrade A β *in vitro* and *in vivo* (2); variation in the ACE gene associated with lower plasma levels of ACE are also associated with AD risk (24). AngII promotes the synthesis of the inflammatory mediator TNF α (25, 26), and has anti-cholinergic (27, 28) and anti-glutamatergic effects (29), all of which are major sequelae of AD pathology.

Losartan, an angiotensin type 1 receptor antagonist (AT1RA) is an 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 that we, and others, have observed to be associated with reduced incidence of AD (9, 10). Losartan also improves CBF (14), a surrogate marker of cognitive performance in humans (31-33), and limits neuronal damage following ischaemia in stroke rat models (16); 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 (12).

No clinical trials studying losartan or any related AT1RA drugs as an intervention in AD have been undertaken to date. The most relevant related studies that used losartan (50mg) reported modest benefits, non-significant benefits on memory in non-demented hypertensive patients (35, 36), which were thought to be independent of BP-lowering effects (37). Yet, as a hypertension trial, cognition was not the primary outcome and thus was likely underpowered for more conventional study of cognition. To date, there are limited systematic reviews that have assessed the impact of BP-lowering on cognitive decline (38). McGuinness and colleagues previously 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 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 reported 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 scope for translation to the prognosis of AD since the study populations included were generally younger, selected according to high cardiovascular burden and cognitive assessment was not the primary outcome whereby assessment was generally less rigorous than that normally used in clinical trials of AD. In our opinion, these negative findings make any larger-scale (e.g. Phase III) multi-centre RCTs of an AT1RA in AD premature and currently unjustified without further supportive evidence.

To our knowledge, no studies have investigated losartan on MRI measures of brain atrophy, CBF, WMH and cognition in AD. One related smaller (n=100) phase II three arm US-based trial (NCT00605072) was the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial. Using only hypertensive participants with early (non-AD) cognitive impairment, it compared 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).

We have chosen losartan as our intervention because of the multi-factorial functions of AngII in the brain including vasoconstriction, reduction of acetylcholine (ACh) release, inflammation and neuronal excitotoxicity (25-29, 42). Second, selective antagonism of the AT1 receptor (AT1R) by losartan does not inhibit ACE activity, which may be important as ACE is elevated in AD (21, 22)) and can degrade A β (21, 43, 44). 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, 45-47). By testing an AT1RA in both hypertensive and normotensive AD patients, we enhance the generalizability of any finding and examine if any protective mechanisms may be operating independent of or in addition to BP-lowering effects.

RADAR will test the hypothesis that AngII blockade in mild to moderate AD with 100mg of the AT1RA losartan will reduce the rate of brain volume loss and therefore slow the clinical progression of AD. We have opted for the highest dose of losartan normally recommended and titrated directly from 25mg, reflecting standard clinical practice, to attempt maximal engagement of the intervention with its receptor whilst having provision of appropriate monitoring of blood pressure both prior to and during the course of the study.

Study Design

A two-arm, double-blind, placebo-controlled, multi-centre, randomised, trial comparing 100mg losartan or placebo effects. This will examine whether 12 months of treatment has any difference on changes in MRI brain imaging in AD patients (both hypertensive and normotensive).

Study setting

RADAR is a multi-centre study that is recruiting patients with mild-to-moderate AD from up to 25 specialist hospital trusts where patients with AD are routinely diagnosed in the UK. Sites must have prior expertise in recruitment to clinical trials of AD and capacity to provide MRI facilities to fulfil the Neuroimaging protocol (see below)

Inclusion criteria

Patients diagnosed with mild-to-moderate AD according to original NINCDS-ADRDA criteria (48). Patients must have all of the following to be considered eligible: (i) Age ≥ 55 years (to maximise generalisability of the study and avoid exclusion of younger yet otherwise eligible potential participants); (ii) A MMSE score of 15-28; (iii) A modified Hachinski score (49) of 5 or less; (iv) A previous CT, SPECT or MRI scan consistent with a diagnosis of AD; (v) The presence of a study companion who is willing to participate in the study; (vi) Capacity to consent for themselves as judged by a member of the research team with appropriate training and experience.

Exclusion Criteria

Patients will be ineligible if they have any of the following: (i) Receiving ACE-Inhibitors; AT1RAs, aliskiren or potassium sparing diuretics; (ii) Known intolerance or renal problems with ACE-inhibitors or sartans; (iii) Medically unsuitable for, or unwilling to have, an MRI scan; (iv) Consistent baseline BP of <115/70 mmHg or >160/110 mmHg; (v) A fall in BP on standing of >20/10 mmHg associated with clinically significant symptoms or a fall >30/15 mmHg; (vi) Previous cerebrovascular accident (CVA), with significant residual impairment (Transient Ischaemic Attack (TIA) is NOT an exclusion); (vii) Hypertrophic cardiomyopathy; or significant aortic valve stenosis; (viii) Estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73m²; (ix) Evidence of liver disease or significant LFT derangement (Aspartate transaminase (AST)/ Alkaline Phosphatase (AP/ALP)/ Bilirubin greater than 2 x upper limit of normal); (x) Potassium (K) greater than 6.0 mmol/L on non-haemolysed sample; (xi) Primary neurodegenerative diseases or potential causes of dementia other than AD; (xii) 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; (xiii) 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; (xiv) Participation in a previous CTIMP within 6 months of RADAR trial entry.

Intervention

Participants will be randomised to either Losartan (100 mg) once a day or an identical looking placebo using over encapsulation (St. Mary's Pharmaceutical Unit [SMPU]) for 12 months. Prior to randomization there is 3-4 week pre-randomised study open-label phase (See Figure 1). This will involve potential participants being on open-label 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. This is to ensure all patients entering the trial can tolerate the maximum dose of losartan (based on daily monitoring of BP over the open-label period in conjunction with any clinically relevant issues, including potential deviations from baseline blood measurements (as assessed by the Principle Investigator), or self-reported concerns made by participants or study companions) and have had a sufficiently long wash-out period to assess laboratory assessment of bloods prior to being randomised. There are no dose modifications after the participant has entered the randomised phase. Drug adherence is monitored by pill counts undertaken at the regular

follow-up visits (see figure 1). Normal clinical care is permitted including the use of other dementia related treatments requiring being on a stable dose for 3 months on study entry but allowing for naturalistic dose adjustment once entered.

Outcomes

Primary measures

Change in whole brain volume between MRI-based measured at both baseline and after 12 months of treatment post randomisation, measured using volumetric MRI (vMRI). This is recognised as an empirical surrogate marker of cognitive decline and AD pathology (50-55). All MRI scans will be performed using either 1.5T or 3T imaging systems with high-resolution (1mm isotropic) 3D T1- MPRAGE at all sites. The volumetric analyses of the MPRAGE images will be conducted in collaboration with the Dementia Research Centre at University College London (UCL) who provided initial advice and validation of the MRI protocol at all sites. The UCL team have developed semi-automated computerised methods to derive brain structure volumes from single time-point MRI and rates of atrophy from serial MRI (56-59) similar to those previously reported for multi-centre trials(60). Quality control (QC) of scans and QC and editing of segmentations will be carried out using the MIDAS software (57). Automated segmentations will be performed using BMAPS (58) for brains and STEPS (61), prior to manual checks and edits by if needed. Image analysts undergo training and regular validation on structure segmentation. Longitudinal change following registration is measured using a Dementia Research Centre implementation of K-means normalised boundary shift integral (KN-BSI) (62) for brains or double window KN-BSI for the hippocampus (59, 62).

Secondary measures

These will include (i) rates of AD progression as assessed by changes in cognitive assessments (including MMSE), measures of activities of daily living and quality of life; (ii) change to the level of CBF measured by arterial spin labelling (ASL) techniques; (iii) change to the level of white matter hyperintensities by MRI; (iv) change in BP; (v) measure of association between MRI measures of atrophy and rate of cognitive decline; (vi) level of drug compliance and tolerability (particular consideration to non-hypertensive patients' tolerability). ASL data will be processed using the NiftyFit software package (63) to generate quantitative CBF maps, and white matter hyperintensities automatically identified and quantified using dedicated software developed at UCL (64).

An assessor whom will be blinded to the intervention will conduct face-to-face a schedule of assessments summarised in Table 1: 11 item ADAS-Cog (65); the Neuropsychiatry Inventory (NPI) (66); the Bristol Activities of Daily Living Scale (BADLS) (67), DEMQOL and DEMQOL-Proxy (68).

Other imaging outcomes will include analysis of Cerebral Blood Flow (CBF) by arterial spin labelling (ASL) methods as a surrogate marker of cognitive performance as has already been reported in humans (31-33). Change in white matter hyperintensities (WMH) volume will be measured by T2/FLAIR to explore the efficacy of the trial medication in ameliorating white matter damage in participants, which has synergistic effects in AD (69) and predicts 1 year cognitive decline (12).

The combination of measures of atrophy, CBF and WMH volume will be important complements to the standard cognitive assessment measures and may provide further mechanistic insights to justify further pursuit of losartan or other similar related drugs in large-scale clinical trials of AD.

Participant time line

Participant pre-screening will be initially undertaken by examination of existing registers or after participants express their interest to take part, followed 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. Consent will be taken at this visit and eligibility then confirmed after initial data collection. We have designed our inclusion criteria so that although the patients have a diagnosis of AD, they should still have capacity to consent, and they continue to have the right to withdraw consent in the future. If a participant loses capacity over the time of the trial, they will remain in the trial unless their legal representative (that may also be their companion) feels this is no longer appropriate.

If a potential participant meets the eligibility criteria, they enter the open label phase (see figure 1). This establishes that they can tolerate 100 mg losartan (as described, see also Table 1) and there are no safety issues and hence reduces potential drop out secondary to either self-reported drug side effects, or clinically significant (as assessed by the Principle Investigator) deviation from protocol specified ranges of BP and blood measurement of electrolytes, creatinine and LFTs, after randomization. They then proceed to the baseline MRI and any patients who cannot have an MRI scan are then withdrawn. At this stage other baseline data is collected and randomization determines whether they are allocated to the active or placebo arm. There are then 6 further follow-up visits (hospital or home-based), mainly to ascertain safety and compliance though cognitive function is re-measured half way through the study at 6 months. At the 12 month visit they stop treatment and have a 4 day washout period before the repeat MRI scan and final assessments. (see table 1 for further details). 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 (70). Non-compliance will be discussed with the Principal Investigator or delegated clinician to determine if it is appropriate to discontinue medication.

In most cases data will be collected at a research clinic at the local site but in some cases, home visits may be undertaken. Patients who wish discontinue with the trial medication will be encouraged to stay in the trial and continue to be assessed so they can be included in the final analysis.

Participant withdrawal

Participants may voluntarily withdraw their consent for taking study medication at any time but may continue to be followed up if they wish.

Participants may be withdrawn from the study medication at any time if deemed appropriate by the local PI due to adverse blood results, recognised drug-related side effects, 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, experience of a Serious Adverse Event or any other illness/disease developed through the course of the study making further participation inappropriate or requiring emergency unblinding

Randomisation

Randomizations were done by centres either telephoning or accessing an online centralised automated system (www.sealedenvelope.com) to ensure allocation concealment. We have used a stratified randomization approach using a minimization procedure to reduce allocation imbalance (whilst retaining a random component) stratified by age and baseline hippocampal volume according to Scheltens' rating (71) and balanced according to site.

Blinding

All participants and study personnel (except Pharmacists) will be blinded to allocation by using over-encapsulation of losartan and placebo tablets. Assessment of MRI scans to

generate the primary outcome will be undertaken blinded to treatment arm. All the initial analyses will follow the statistical analysis plan and will maintain blinded codes for treatment status.

Emergency unblinding can occur if a clinician believes that their treatment decision for a participant could be influenced if the patient was receiving losartan. A 24-hour emergency unblinding service is available to all research sites through each local pharmacy service within working hours and Out of Hours (OOH) either locally or by a pharmacy nominated by the study co-ordination team. 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 (SAE) then the appropriate documentation will be completed and will be reported accordingly. Each participant will be given a Trial Participation Card with details of who their treating clinician should contact in the event of an emergency.

Data entry

All anonymised MRI data are uploaded and stored on a secure customised web-based server running XNAT 1.6.4 (www.xnat.org). Hard copies of anonymised paper based Case Report Forms (CRFs) are either sent to the Trial Co-ordinating team for data entry or directly entered onto a secure web-based database (REDCap 7.0.8 © Vanderbilt University).

Monitoring and Adverse Events

Safety monitoring will be conducted by the Chief Investigator (CI) and trial team and will report intermittently to a Data Monitoring and Ethics Committee (DMEC) that also reports to a Trial Steering Committee (TSC) that meets at least twice per year. The DMEC will examine data relating to trial processes, outcomes and adverse events. 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.

As the primary outcome only occurs at the end of follow-up, there are no planned interim analyses and no formal stopping rules as regards efficacy. If the DMEC has any concerns regarding safety they can forward their recommendation to the TSC who can review these at an unplanned TSC meeting and inform the trial management group and the sponsor whether they think the trial should be stopped prematurely.

Participants are screened at each follow-up assessment for Adverse Events (AEs) as specified by the International Conference on Harmonisation [ICH] definition. Similarly blood pressure readings will be taken at most follow-up visits. Some of the 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. More detailed information on reported adverse events that have been reported for losartan used in this study are available online (<http://www.tevauk.com/mediafile/id/40029.pdf>); however, it has a low adverse event profile (72).

Serious adverse events (SAEs), e.g. rarely occurring hypersensitivity or adverse reaction (AR) to the drug and Suspected Unexpected Serious Adverse Reactions (SUSARs), defined according to ICH definitions, will be reported and managed according to North Bristol NHS Research and Innovation Policies and Standard Operating Procedures.

In the event of an incidental neuroimaging finding, we will follow the guidance set out in the recent “Management of Incidental Findings Detected in Research Imaging” report (see: [https://www.rcr.ac.uk/docs/radiology/pdf/BFCR\(11\)8_Ethics.pdf](https://www.rcr.ac.uk/docs/radiology/pdf/BFCR(11)8_Ethics.pdf)). This is thought to be an unlikely occurrence as the inclusion criteria require that all patients should have had a previous CT or MRI scan which supported their diagnosis of AD.

Enhancing site recruitment

We will embed a qualitative component to the RADAR trial (before we have recruited 50% of the participants) to explore trial site recruitment, with the aim of enhancing the study design, conduct, organisation or training that could then lead to improvements in recruitment.

Qualitative interviews will be undertaken with a purposeful sample of research nurses and doctors responsible for screening and consent and trial participants from a range of high and low recruiting trial sites to gain insights into barriers and facilitators for recruitment. With informed consent, interviews will be audio recorded, transcribed, and imported into NVivo 10 and analysed thematically (73). Data collection and analysis will be conducted in parallel until

data saturation is reached (74). The trial management group and the TSC will be informed of the findings.

Sample Size and Analysis

Our proposed sample size is based on previous 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 (53, 55, 75). Previous data suggested 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 (76), and equivalent to a standardised effect size of 0.44 SDs. We will randomise a total of 228 participants that will leave 182 subjects for analysis assuming 20% missing primary outcome data. 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 $\alpha = 0.05$.

The analysis and presentation of the trial results will be in accordance with CONSORT guidelines (<http://www.consort-statement.org/>), 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. Similar analyses will be undertaken for the secondary outcomes (where p-values will be adjusted to account for multiple testing) and adjusting for any variables exhibiting marked imbalance at baseline to check that this does not influence the findings. There will be three additional types of analyses. 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.

Conclusion

The RADAR trial is a phase II study that will provide evidence as to whether the AT1RA losartan does or does not influence the rate of brain volume loss in patients with early AD. Regardless of the results, it should provide valuable insights into potential mechanistic pathways and give further insight into the challenges of studying this patient group, as well as inform the relative merits of using brain atrophy as a marker for disease progress. If the findings are supportive of a potential neuroprotective effect, then a larger phase III is likely to be required to provide a more precise estimate of the clinical and quality of life benefits. As this drug is relatively safe and inexpensive (being off-license), even modest clinical benefits are likely to be cost-effective.

Table 1: 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 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 companion
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 safety tests**, 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 safety tests**, do pill count and provide next trial drug	Start taking placebo drug for at least 4 days until called for baseline MRI visit
Randomisation Phase		
Baseline Visit 18-28 days after open label medication commenced)	MRI to inform randomisation and collect primary outcome measure. At same visit or within 10 days conduct cognitive assessment***; Measure Sitting and Standing BP, take bloods for safety tests** 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 safety tests**, optional samples for future research, do pill count & provide next trial drug	Take allocated drug
3 months after randomisation	Measure Sitting and Standing BP; take bloods for safety tests**, do pill count & provide next trial drug	Take allocated drug
6 months after randomisation	Cognitive assessment***, measure Sitting and Standing BP, take bloods for safety tests**, do pill count & provide next trial drug	Take allocated 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 allocated 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 allocated 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 safety tests**, optional samples for future research; do final pill count.	

* MMSE will be compared between eligibility screening visit and end of study. ** Blood safety tests will include measures of electrolytes, creatinine and LFTs according to protocol defined ranges for inclusion/exclusion
***Cognitive assessment will include ADAS-COG (participant), NPI (companion), BADLS (companion), DEMQOL (participant) and DEMQOL-Proxy (companion).

Acknowledgements

This project is supported by the Efficacy and Mechanism Evaluation (EME) Programme*, an MRC and NIHR partnership. **Disclaimer:** The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health.

*The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D Division, Public Health Agency in Northern Ireland. The authors would also like to acknowledge some early contributions in protocol development to Alan Montgomery, Risto Kauppinen, Shona Clegg as well as assistance provided by David Carmichael in the setup of the randomization system with external providers.

Legend to Figure 1

Safety bloods include measures of electrolytes, creatinine and LFTs according to protocol defined ranges for inclusion/exclusion. Cognitive assessment will include ADAS-COG (participant), NPI (companion), BADLS (companion), DEMQOL (participant) and DEMQOL-Proxy (companion). MMSE will also be compared between eligibility assessment and end of study.

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;366(9503):2112-7.
2. Kehoe PG, Miners S, Love S. Angiotensins in Alzheimer's disease - friend or foe? *Trends Neurosci*. 2009;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;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;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;21(1):49-55.

7. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. *Neurol Res.* 2006;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;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;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;18(2):240-52.
12. 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;67(11):1370-8.
13. 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.
14. 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;121(1):51-7.
15. 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;97(17):9735-40.
16. Zhao Z, Tuor UI, Barber P. Chronic treatment with Losartan and Cerebral Ischemic Tolerance. *J Exp Stroke Transl Med.* 2009;2(2):9.
17. 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.
18. Kalara RN. Linking cerebrovascular defense mechanisms in brain ageing and Alzheimer's disease. *Neurobiol Aging.* 2009;30(9):1512-4.
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;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;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;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;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;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 : official publication of the American College of Neuropsychopharmacology.* 2011;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. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2005;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;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;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;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;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;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;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;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;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;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;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;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;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. 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.
43. Miners JS, Raiker M, Love S, Kehoe PG. ACE variants and association with brain A β levels in Alzheimer's disease. *American Journal of Translational Research* 2010;3(1):8.

44. 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.
45. 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;375(3):446-9.
46. 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;117(11):3393-402.
47. 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;27(32):8628-35.
48. 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;34(7):939-44.
49. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol*. 1980;7(5):486-8.
50. Frisoni GB, Fox NC, Jack CR, Jr., Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol*. 2010;6(2):67-77.
51. 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;362(9390):1121-2.
52. 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;27(4):685-91.
53. Fox NC, Ridgway GR, Schott JM. Algorithms, atrophy and Alzheimer's disease: cautionary tales for clinical trials. *Neuroimage*. 2011;57(1):15-8.
54. Fox NC, Scahill RI, Crum WR, Rossor MN. Correlation between rates of brain atrophy and cognitive decline in AD. *Neurology*. 1999;52(8):1687-9.
55. 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.
56. Freeborough PA, Fox NC. The boundary shift integral: an accurate and robust measure of cerebral volume changes from registered repeat MRI. *IEEE transactions on medical imaging*. 1997;16(5):623-9.
57. Freeborough PA, Fox NC, Kitney RI. Interactive algorithms for the segmentation and quantitation of 3-D MRI brain scans. *Computer methods and programs in biomedicine*. 1997;53(1):15-25.
58. 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*. 2011;55(3):1091-108.
59. 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*. 2010;51(4):1345-59.
60. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370(4):322-33.
61. Jorge Cardoso M, Leung K, Modat M, Keihaninejad S, Cash D, Barnes J, et al. STEPS: Similarity and Truth Estimation for Propagated Segmentations and its application to hippocampal segmentation and brain parcellation. *Med Image Anal*. 2013;17(6):671-84.
62. Leung KK, Clarkson MJ, Bartlett JW, Clegg S, Jack CR, Jr., Weiner MW, et al. Robust atrophy rate measurement in Alzheimer's disease using multi-site serial MRI: tissue-specific intensity normalization and parameter selection. *Neuroimage*. 2010;50(2):516-23.

63. Melbourne A, Toussaint N, Owen D, Simpson I, Anthopoulos T, De Vita E, et al. NiftyFit: a Software Package for Multi-parametric Model-Fitting of 4D Magnetic Resonance Imaging Data. *Neuroinformatics*. 2016;14(3):319-37.
64. Sudre CH, Cardoso MJ, Bouvy WH, Biessels GJ, Barnes J, Ourselin S. Bayesian model selection for pathological neuroimaging data applied to white matter lesion segmentation. *IEEE transactions on medical imaging*. 2015;34(10):2079-102.
65. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-64.
66. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-14.
67. 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;25(2):113-20.
68. 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;9(10):1-93, iii-iv.
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*. 2002;103(5):481-7.
70. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269-86.
71. 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*. 1992;55(10):967-72.
72. 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. *The American journal of cardiology*. 1995;75(12):793-5.
73. Braun V, Clarke V. Using thematic analysis in psychology. . *Qualitative Research in Psychology*. 2006;3:77-101.
74. Sandelowski M. Sample size in qualitative research. . *Res Nurs Health* 1995;18 (2):179–83.
75. Thompson WK, Holland D. Bias in tensor based morphometry Stat-ROI measures may result in unrealistic power estimates. *Neuroimage*. 2011;57(1):1-4; discussion 5-14.
76. 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*. 2010;31(8):1452-62, 62 e1-2.

Figure 1: Participant procedures and data collection after ascertainment of eligibility and willingness to participate.