The TREAT CASP study

The Evaluation of blood pressure treatment stratified according to Central Aortic Systolic Pressure (CASP) in Young Hypertensive Patients

The TREAT CASP study - A Cardiovascular Screening Study Followed by a One Year Prospective Randomised Open Blinded Endpoint Clinical Trial and a one year observational follow-up study Comparing Standard Blood Pressure Lowering Therapy with Usual Care on Central Aortic Systolic Pressure and Left Ventricular Mass Index by Cardiac MRI in Young Men with Stage 1 Hypertension.

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Table of Contents

1 Administrative information

This document was constructed using the UCL Clinical Trials Unit (CTU) Protocol template Version 2.0. It describes the TREAT CASP study, sponsored by UCL and co-ordinated by UCL CTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at UCL CTU.

UCL CTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials. The SPIRIT Statement Explanation and Elaboration document version 6 can be referred to, or a member of UCL CTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Agreements that include detailed roles and responsibilities will be in place between the participating site and UCL CTU.

The Participating site will inform UCL CTU as soon as they are aware of a possible serious breach of the approved protocol or of the principles of GCP. For the purposes of this protocol a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

UCL is the trial sponsor and has delegated responsibility for the overall management of the TREAT CASP study to UCL CTU. Queries relating to UCL sponsorship of this trial should be addressed to the Director, UCL CTU, or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN Registration Applied for
Date of Registration in Primary Registry	11-08-2013.
Secondary Identifying Numbers	Other identifiers besides the trial identifying number allocated by the primary registry, if any. These include: • NIHR Portfolio ID: 14991
Source of Monetary or Material Support	National Institute for Health Research Efficacy and Mechanisms Evaluation funding stream (Funder reference EME 10-90-22)
Primary Sponsor	University College London
Secondary Sponsor	Sponsor responsibilities for Trial Management are delegated to UCL CTU.
Contact for Public Queries	ctu.enquiries@ucl.ac.uk
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Public Title	Can Blood Pressure Measured Near the Heart Indicate Which Young People With Increased Blood Pressure Benefit Most From Blood Pressure Lowering Treatment?
Scientific Title	The Evaluation of blood pressure treatment stratified according to Central Aortic Systolic Pressure (CASP) in Young Hypertensive Patients - The TREAT CASP study - A Cardiovascular Screening Study Followed By A One Year Prospective Randomised Open Blinded Endpoint Clinical Trial and a one year observational follow-up study Comparing Standard Blood Pressure Lowering Therapy with Usual Care on Central Aortic Systolic Pressure and Left Ventricular Mass Index by Cardiac MRI in Young Men with Stage 1 Hypertension.
Countries of Recruitment	UK
Health Condition(s) or Problem(s) Studied	Stratification of young men with stage 1 hypertension for blood pressure lowering therapy
Intervention(s)	**Active Treatment Arm** Losartan 50mg tablets once daily up-titrated to 100mg once daily if necessary and/or with addition of amlodipine 5mg

	tablets once daily if required to achieve BP target. **Comparator** Usual Care: No treatment. This study does not use any placebo tablet. Study Duration: 12 Months
Key Inclusion and Exclusion Criteria	Men (18-54 years) with stage 1 hypertension (blood pressure 140-159/90-99mmHg), not currently treated for hypertension and with no concurrent cardiovascular disease or overt target organ damage.
Study Type	1. Cross-sectional observational screening study followed by an interventional clinical trial & observational follow-up study. 2. Clinical Trial design: Prospective Randomised Open Blinded Endpoint (PROBE) design 3. Phase III/IV 4. Randomisation: Computer generated simple randomisation with allocation of study number and indicate treatment or no treatment
Date of First Enrolment	Anticipated June/July 2013.
Target Sample Size	500 participants recruited into the screening study with 130 then going on to be randomised into the clinical trial and 65 entering the observational follow-up study
Primary Outcome(s)	**Study primary outcome**: Change in Left Ventricular Mass Index on cardiac Magnetic Resonance Imaging (cMRI) in the randomised clinical trial comparing active treatment with usual care. Metric/method of measurement – grams per metre squared Timepoint – Baseline and Study end (12 months following treatment initiation).
Key Secondary Outcomes	**Secondary outcomes:** The following outcome measures will be assessed at baseline and study end (12 months following treatment initiation): 1. Change in Left Ventricular Mass to volume ratio on cMRI Metric/method of measurement – grams per millilitre cubed 2. Regional systolic & diastolic strain Metric/method of measurement – % change in dimension by cMRI myocardial tissue tagging 3. Interstitial Fibrosis using T1 mapping Metric/method of measurement – Fibrosis index by cMRI 4. Aortic distensibility on cMRI Metric/method of measurement (10^{-3}/kPa) 5. Aortic & Carotid wall thickness on cMRI Metric (micometers)

1.4 Roles and responsibilities

1.4.1 Protocol contributors

Name	Affiliation	Role
Prof Bryan Williams	University College London	Chief Investigator – Protocol design & writing
Dr Peter Lacy	University College London	Co-Investigator – Protocol design & writing, statistical analysis
Jane Gregg	University College London	Contributions to trial management and governance
Michelle Tetlow	University College London	Contributions to trial management and governance

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Prof Bryan Williams	University College London	Chief Investigator, responsible for the trial overall, including patient safety, data analysis and reporting the study results
Dr Peter Lacy	University College London	Co-investigator, responsible for training and data collection in specialist haemodynamic measurements, data analysis & reporting the study results
Dr Vivek Muthurangu	University College London	Co-investigator, responsible for MRI data collection & analysis
Dr Alexander Jones	University College London	Study physician responsible for patient recruitment, data collection, delivery of interventions & pharmacovigilance
Amanda Wilson, Study nurse	University College London	Responsible for study recruitment, data and sample collection, day-to-day interaction with patients
Statistician	TBA	Analysis of STOP/GO checkpoint , study endpoints and data

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Prof Bryan Williams	University College London	Chief Investigator, responsible for overall trial management & governance
Dr Peter Lacy	University College London	Co-investigator, responsible for initial trial set-up management
Jane Gregg	University College London	Responsible for day-to-day study management & governance
Michelle Tetlow	University College London	Line management and supervision of trial manager

1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Prof Tom MacDonald	University of Dundee	Independent Chair Trial Steering Committee
Dr Gerry McCann	University of Leicester	Independent Member Trial Steering Committee
Prof Richard McManus	University of Oxford	Independent Member Trial Steering Committee
Prof Bryan Williams	University College London	Chief Investigator & Member Trial Steering Committee
Dr Peter Lacy	University College London	Investigator & Member Trial Steering Committee

1.4.6 Data Monitoring & Ethics Committee

Name	Affiliation	Role and responsibilities
Prof Mark Caulfield	Queen Mary, University of London	Chair Data Monitoring & Ethics Committee
Dr Adrian Stanley	University of Leicester	Member Data Monitoring & Ethics Committee
To Be Appointed		Independent Statistician & Member Data Monitoring & Ethics Committee

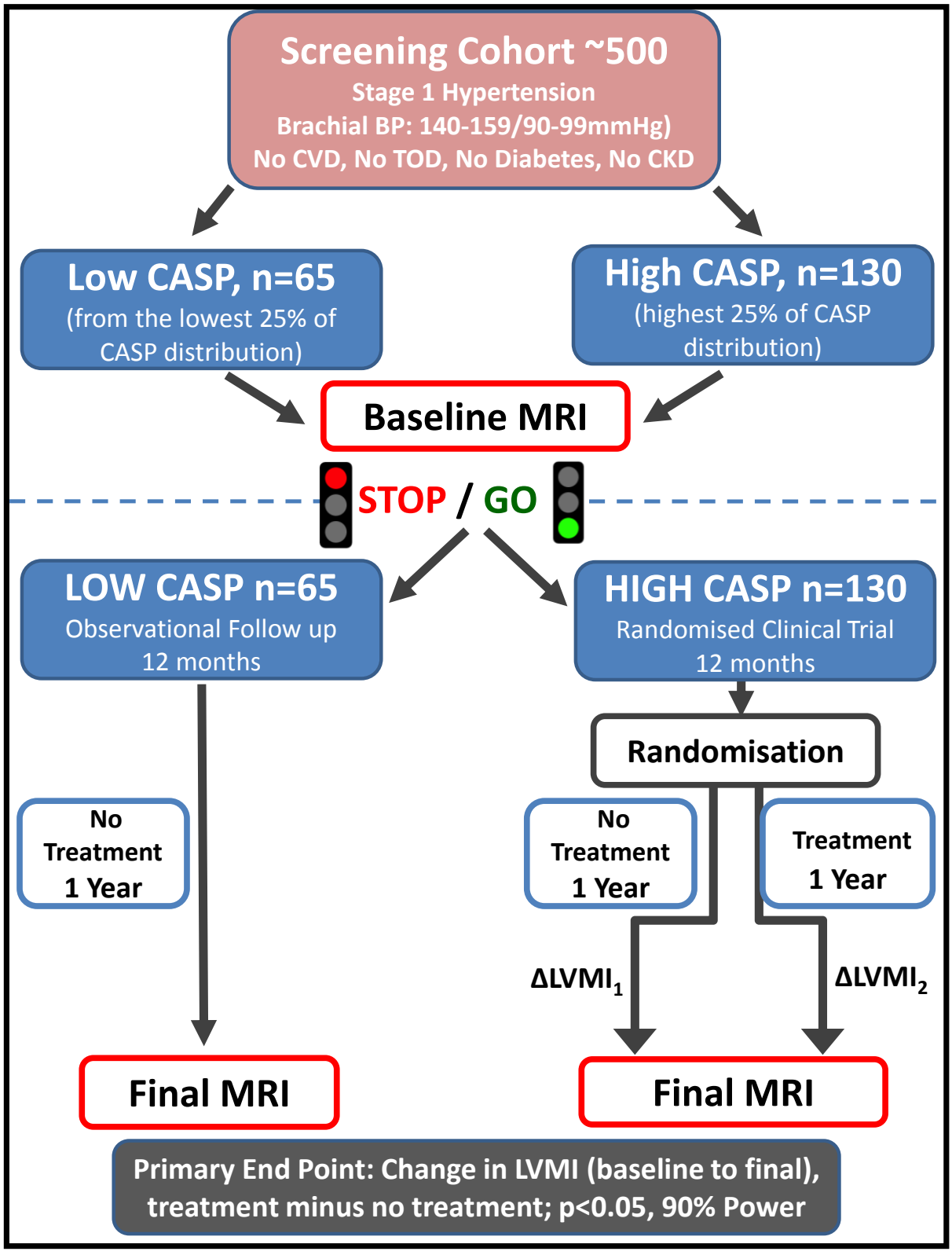
1.4.6 Quality Management Group

Name	Affiliation	Role and responsibilities
Peter Brocklehurst	University College London	UCL CTU Acting Director
Susan Tebbs	University College London	UCL CTU Deputy Director and Head of Clinical Trials Operations
Alan Bailey	University College London	UCL CTU Manager
Michelle Tetlow	University College London	UCL CTU Project Manager for QA
Clare Torud	University College London	UCL CTU Administrator
Rebecca Evans-Jones	University College London	UCL CTU Advisory Clinician
Julie Bakobaki	University College London	UCL CTU Senior Clinical Operations Project Manager for Methodology

1.4.7 Protocol Review Committee

Name	Affiliation	Role and responsibilities
Peter Brocklehurst	University College London	UCL CTU Acting Director
Rebecca Evans - Jones	University College London	UCL CTU Advisory Clinician
Laura Vallejo Torres	University College London	UCL CTU Principal Health Economist
Julie Bakobaki	University College London	UCL CTU Senior Clinical Trials Operations Project Manager for Methodology
Clare Torud	University College London	UCL CTU Administrator
Caroline Doré	University College London	UCL CTU Head of Statistics

2 Trial Diagram



Where: BP - blood pressure; CASP – Central Aortic Systolic Pressure; CKD – Chronic Kidney Disease; CVD – Cardiovascular Disease; LVMI – Left Ventricular Mass Index; MRI – Magnetic Resonance Imaging; TOD – Target Organ Damage,

3 Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACR	Albumin:Creatinine Ratio
AE	Adverse Event
ANOVA	Analysis of Variance
AR	Adverse Reaction
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BP	Blood Pressure
BrBP	Brachial Blood Pressure
BrSBP	Brachial Systolic Blood Pressure
CASP	Central Aortic Systolic Pressure
CI	Chief Investigator
CKD	Chronic Kidney Disease
cMRI	Cardiac Magnetic Resonance Imaging
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
CVD	Cardiovascular Disease
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
ECG	Electrocardigram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
FDA	(US) Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
LTFU	Lost to Follow-Up
LV	Left Ventricular
LVMI	Left Ventricular Mass Index
MAR	Missing at Ramdom
MESA	Multi-Ethnic study of Atherosclerosis
MHRA	Medicines and Healthcare products
	Regulatory Agency
MoU	Memorandum of Understanding
MRI	Magnetic Resonance Imaging
NAE	Notifiable Adverse Events
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR-EME	National Institute for Health Research – Efficacy & Mechanisms Evaluation funding stream
NPMA	N-Point Moving Average
PI	Principal Investigator
PIS	Participant Information Sheet
PROBE	Prospective Randomised Open label Blinded Endpoint
PWV	Pulse Wave Velocity
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
QMP	Quality Management Plan
QoL	Quality of Life
R&D	Research and Development
RAPW	Radial Artery Pressure Wave
RCT	Randomised Controlled Clinical Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SMS	Short Message Service
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischaemic Attack
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TOD	Target Organ Damage
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London
UCLH	University College London Hospital
WHO	World Health Organisation

4 Glossary

24-Hour Ambulatory Blood Pressure Monitoring – A technique for measuring blood pressure at regular intervals over a 24-hour period using a modified portable BP monitor.

Albumin:Creatinine Ratio – A clinical test of urine which gives an indication of kidney function

ANOVA - A statistical test comparing data from two or more different groups

ARB – Angiotensin Receptor Blocker - a type of blood pressure lowering medication

Body Mass Index – A standard index of body size

Calcium Blocker - a type of blood pressure lowering medication

Central Aortic Pressure – pressure in the ascending aorta

cMRI – cardiac magnetic resonance imaging – non-invasive imaging of the heart and large conduit arteries

ECG – Electrocardiogram, a standard clinical test evaluating the electrical activity of the heart

Estimated Glomerular Filtration Rate – A clinical blood test which gives an indication of kidney function

Left Ventricular Mass Index – A parameter measured by MRI indicating structure of the heart

Magnetic Resonance Imaging – A high-resolution non-invasive imaging technique

n-Point Moving Average – A mathematical technique for calculating Central Aortic Systolic Pressure from radial artery pressure waveforms

Prospective Randomised Open label Blinded Endpoint – a type of clinical trial design which allows a clinical trial to be performed in which both participants and study doctors/nurses involved in clinical care to know which treatments participants are taking.

Radial Artery Pressure Wave – A measurement of the pressure pulse at the wrist

Randomisation – A method which assigns people to study medication or no medication without introducing bias

Standard Deviation – A statistical measurement of data dispersion

Target Organ Damage – Evidence of structural/functional change to key organs or tissues

Titration – Adjustment of drug dose/addition of further drug to achieve BP target

5 Introduction

5.1 Background and Rationale

High blood pressure (BP) is one of the leading preventable causes of premature morbidity and mortality world-wide [1,2]. In the UK it is estimated that at least 25% of the adult population are hypertensive (defined as BP≥140/90mmHg), rising to more than 50% in people aged over 65 years [3]. The effectiveness of treatment of hypertension has one of the largest evidence bases in medicine and is the cornerstone of national strategies to reduce cardiovascular disease risk. Detection, treatment and monitoring of BP represents one of the commonest reasons for consultation in primary care and in the UK accounts for over £1billion expenditure on drug costs alone [4].

5.1.1 Hypertension in the Young

For more than a century, the diagnosis of hypertension has been based on the measurement of brachial BP using an occluding cuff, inflated around the upper arm. However, the decision to treat BP is based not only on the patients' BP but also their risk of cardiovascular disease [4] as indicated by i) the presence of established cardiovascular disease; ii) the presence of pressure-mediated damage (e.g. left ventricular hypertrophy; markers of renal disease; the presence of hypertensive retinopathy) – so called "target organ damage", or iii) high cardiovascular risk (CV risk) based on formal estimation using CV risk calculators. Age is a major determinant of risk for CV events [5]; consequently most research has focussed on assessing and treating older people, who are more likely to develop measurable clinical end-points within the typical duration of clinical trials, such as morbidity and mortality resulting from stroke and heart disease. As a result, most of the evidence base used to formulate national treatment guidelines has been acquired from people over 55 years of age and there is a paucity of research data upon which to base treatment decisions for younger people with hypertension [6-8]. This has created a major dilemma for NICE in formulating its hypertension treatment guidelines – how and when to treat younger people with hypertension? This dilemma is recognised in the current NICE guidance on treating hypertension in Primary care (NICE CG 127, 2011) which identifies as a major research priority "the need to define the best methods to stratify younger people (i.e. aged ≤40 years) with high blood pressure for treatment". In such younger people, if the brachial BP is ≥160/100mmHg (stage 2 hypertension), current guidelines recommend treatment [4]. However, for the large number of younger people with stage 1 hypertension (brachial BP 140-159/90-99mmHg), there is uncertainty about the benefits of treatment unless the patient already has evidence of overt target organ damage, established cardiovascular disease, chronic kidney disease or diabetes. It is accepted that the use of formal 10 year CV risk calculations has little validity in these younger age groups and in any case, is unlikely to accurately reflect their lifetime risk. The issue of when to treat younger people with stage 1 hypertension is not insignificant. A recent study involving over 30 years of follow-up of over 1 million young male Swedish army recruits suggested that stage 1 hypertension in young people may not be benign and is associated with an increased risk of cardiovascular mortality [9,10]. The question remains as to whether simple tools can be developed to better assess which younger people with stage 1 hypertension should be treated.

5.1.2 Inadequacies of Conventional Blood Pressure Measurement

The brachial BP (BrBP) method for measuring BP has changed little for more than a century, apart from the fact that automated oscillometric methods are progressively replacing manual auscultation. The assumption has always been that the pressure measured in the arm is

representative of the pressure throughout the circulatory system. However, it has long been recognised that pressure (particularly systolic and pulse pressure) is amplified as it moves from the aortic root to the peripheral circulation, i.e. the brachial artery [11]. If this relationship was fixed in all individuals, in all circumstances, throughout life, this amplification of pressure would not matter because the BrBP, if not an exact measurement of aortic root pressure, would always be proportional to the aortic root pressure. Unfortunately, this is not the case. We and others have shown that the amplification of brachial systolic blood pressure (BrSBP) can vary markedly and is profoundly influenced by age, gender, vascular disease (especially aortic arteriosclerosis and stiffening), heart rate and drug therapies used to treat hypertension [12-17]. Importantly, we and others have shown that the variation in the relationship between central aortic systolic pressure (CASP) and BrSBP is particularly marked in younger people and paradoxically, those with the healthiest, most compliant arterial systems [13,18], [Appendix figure 1]. The difference between CASP and BrSBP whilst typically around 10mmHg in older people, i.e. aged >55yrs, can be as much as 30mmHg in younger people aged 18-40 years [Appendix figure 2]. This can give rise to the spurious diagnosis of hypertension in younger people, based on their brachial BP, and points to the fact that brachial BP measurements are not always the ideal way to categorise hypertension in younger people or to stratify their need for BP-lowering treatment. The inaccurate diagnosis of hypertension can have important implications for younger people, not only because of the anxiety and cost of treatment but also the impact of disease labelling on insurance weighting and some forms of employment. Therefore, it is particularly important to establish the correct diagnosis in younger people so as to avoid these consequences and exposure to life-long treatment that may not be necessary.

5.1.3 Development of Methods to Non-Invasively Measure Central Aortic Systolic Pressure (CASP)

Over the past 10 years we have been investigating whether it might be possible to non-invasively measure CASP using methods that would be suitable for widespread use in Primary care. Our objective was to determine whether the measurement of CASP would provide a better means of stratifying people with hypertension for treatment, avoiding the spurious diagnosis of hypertension due to pressure amplification, especially in the young. Our hypothesis has been that if we could do it, few could argue against the proposition that the accurate measurement of CASP (i.e. the pressure in the large arteries that key organs actually experience) would be a better biomarker of risk of future vascular damage and clinical events. Various devices have already been developed which use information from the radial artery wave-form, captured non-invasively via tonometry over the wrist, to mathematically impute the aortic pressures and related haemodynamic indices. However, many of these devices are cumbersome and expensive, requiring expertise in interpretation and are thus unlikely to be sufficiently practical to change clinical practice [19].

5.1.4 Novel discovery work leading to this study:

Previous work conducted by us with the NIHR Biomedical Research Unit in Cardiovascular Disease at the University of Leicester and in collaboration with a small biotechnology company (HealthStats) from Singapore described and validated a simple, novel and non-invasive method to accurately measure CASP in man [20]. This method captures the radial artery pulse wave using a tonometer embedded within a flexible strap that is placed around the wrist. BrBP is measured in the conventional way using a cuff around the upper arm. The BrBP measurement is used to calibrate the radial artery wave-form and generates a radial artery pressure wave (RAPW). The combined information from the BrBP and RAPW is then used non-invasively to derive the CASP. This is done

using a mathematical filter, an n-point moving average (NPMA), which filters the amplification of the pressure wave revealing the true CASP value. We and others have undertaken studies directly comparing direct aortic root pressure measured at cardiac catheterisation with simultaneous non-invasive measurement of CASP using our NPMA method and this demonstrated excellent agreement and correlation (r = 0.99, r2 = 0.98) [20,21] [Appendix figure 3]. We have now incorporated this algorithm into a purpose built technology platform (CASPro) that looks similar to a conventional desk-top BP monitor and cuff with the addition of the wrist strap tonometer [Appendix figure 4]. Press of a single button measures the BrBP, captures the radial artery wave-form and instantaneously integrates the data generating i) a standard BrBP measurement, and ii) the corresponding CASP value. It is recognised that there is minimal change in diastolic pressure across the circulation [11] so brachial and central aortic diastolic pressures are assumed to be equivalent. This allows for calculation of both brachial and central aortic pulse pressures. We have used this new device to derive central aortic pressure in a clinical practice setting and the measurements take only a few minutes more than conventional brachial BP measurement. This device was also fast-tracked by the U.S. FDA for approval for clinical use and has also gained equivalent EU approvals. This study will now translate our NIHR-supported discovery work into the clinical setting.

5.1.5 Proof of concept for CASP as a biomarker of cardiovascular risk in people with hypertension

A number of studies have evaluated the value of invasively and non-invasively acquired aortic pressures versus conventional brachial pressures with regard to predicting cardiovascular target organ damage, differential effects of drug therapy and clinical outcomes [14, 22-28]. Consistent with our hypothesis, population-based studies have shown that aortic pressures are more strongly related than brachial pressure to markers of pressure-mediated target organ damage in people with hypertension, e.g. left ventricular hypertrophy (LVH), carotid intima:media thickness, and albuminuria [29,30]. In addition, we and others have shown that despite similar effects of BP-lowering drug therapies on brachial pressures, there are differential effects of different drug treatments on aortic pressures [14, 31-35]. Moreover, those treatments associated with more effective central aortic pressure lowering were also associated with a more effective reduction of clinical outcomes, especially stroke [14,22,23,26]. Other population-based observational studies have shown that when central aortic and brachial pressures have been measured, central aortic pressures have been a better predictor of clinical outcomes [27,36]. The outcome of further ongoing studies are now eagerly awaited. Together, this evidence provides proof of concept that central aortic pressure measurement could provide a more accurate biomarker of target organ damage and disease risk in people with hypertension and thus, a more effective clinical tool to stratify risk and the need for treatment. This, taken together with the aforementioned observations of marked variation between aortic and brachial pressures, especially in the young [13,18], provides the basis for our hypothesis suggesting that the simple non-invasive measurement of aortic pressures will provide a more effective means of stratifying the need of younger 'hypertensive' people for treatment.

5.1.6 Cost and Logistics Implications for Integrating Measurement of CASP into Clinical Practice

Should the current study prove its hypothesis and suggest a change in practice is warranted to better stratify younger hypertensive people with regard to their need for treatment, it is anticipated that the integration of routine clinical measurement of CASP for young people within the NHS would be relatively straight-forward and achieved at low cost. Other than the initial capital outlay in acquiring the necessary equipment (CASP monitors currently cost £4,000 per unit and cost would reduce with

bulk purchase or purchase of less sophisticated versions), on-going costs are minimal. There are no consumables associated with the equipment, training in use is easily provided and maintenance consists of periodic recalibration of the BP monitor portion of the device, similar to requirements for existing oscillometric automated BP monitors. The test itself takes little longer than a standard measurement of blood pressure and interpretation of results will be based upon evidence from outcome studies such as the current proposed study. The necessary technology for assessing CASP has been developed by a range of equipment manufacturers and market forces will drive costs down to an appropriate level for bulk purchase. Indeed, if requirement develops for the routine measurement of CASP within clinical practice, it is likely that the technology will reduce in cost to a level similar to current automated BP monitors.

5.1.7 Appropriate End-point Evaluation for studies of younger people with hypertension

One of the dilemmas in evaluating the most appropriate method to define hypertension in younger people is "which end-point to use?" For older people in whom BP-related clinical outcomes such as stroke, heart failure and ischaemic heart disease are more likely, the dilemma has been resolved by defining hypertension as "the level of blood pressure at which risk of these events is substantially increased in prospective population studies and the BP level at which treatment has been shown to reduce that risk in clinical outcome trials". Clinical outcome trials of this kind are never going to be possible in younger people with stage 1 hypertension because of the long time-course required before clinical outcomes occur. Thus, the use of intermediate or surrogate end-points is the only option to assess whether a specific level of BP is causing cardiovascular injury that would ultimately lead to later clinical morbidity and mortality [(37)]. The most logical surrogate for BP is i) a clinical consequence that can unequivocally be attributed to elevated BP and ii) has been associated with an increased risk of cardiovascular morbidity and mortality. One of the earliest consequences of high BP is remodelling of the left ventricle and vasculature. This is characterised by hypertrophy of the left ventricle and the wall of the carotid artery [(38-44)]. These can be considered to be an individual barometer of unequivocal exposure to elevated pressures. Furthermore, these structural changes have been shown to have prognostic significance with regard to risk for future cardiovascular events [(45,46)]. These early BP-related structural changes are often subclinical, i.e. not detected by routine screening in Primary care. However, they are readily detectable by non-invasive imaging, especially MRI studies [(47-49)]. Thus, in this study, we will use MRI-based detection of cardiovascular structural change as the definitive indicator of elevated pressure, to evaluate whether CASP rather than conventional brachial BP is a better way of stratifying whether BP lowering treatment is needed in younger people with type 1 hypertension, and whether treatment regresses these structural changes.

5.1.8 STUDY RISKS AND BENEFITS:

5.1.8.1 Potential Benefits of using CASP to stratify younger people for treatment for stage 1 hypertension:

1. There are approximately 1 million younger people with a possible diagnosis of stage 1 hypertension in the UK [(3)]. The simple non-invasive measurement of CASP will potentially lead to better stratification of those requiring treatment for their hypertension. This could avoid the spurious diagnosis of hypertension due to excess pressure amplification from their aortic root to brachial artery.

2. The use of CASP to stratify people for treatment could avoid the unnecessary treatment of some people with stage 1 hypertension in whom the CASP value is normal and in whom, as we propose, there may be no evidence of cardiovascular structural damage either at baseline, or after 12 months of follow-up.
3. The use of CASP to stratify people for treatment could identify those who have evidence of early cardiovascular structural damage at baseline and who would benefit most from treatment to lower blood pressure.
4. Targeting of treatment to those with the highest CASP values who show evidence of early cardiovascular structural damage could result in regression of structural damage, and over the longer term, would result in a reduced lifetime risk of cardiovascular morbidity and mortality.
5. This could lead to economic benefit and better use of health care resources i.e. improving diagnosis and targeting effective treatment to those at highest risk.
6. This study addresses a key research question identified by the current NICE hypertension guidelines [4] regarding the need for more research data on how to best stratify younger people with stage 1 hypertension for treatment.
7. MRI scanning is non-invasive and does not involve exposure to ionizing radiation. There are no known long-term side-effects from MRI. Allergic reactions to MRI contrast occur rarely (~1/10,100) and patients with significant renal failure will be excluded which essentially eliminates any risk of nephrogenic systemic fibrosis.

5.1.8.2 Potential Risks of using CASP to stratify younger people for treatment of stage 1 hypertension:

1. The use of CASP may fail to differentiate between those with and without early cardiovascular structural damage when comparing people with LOW and HIGH CASP values. This finding would eliminate the need for a clinical trial of blood pressure lowering in those with HIGH CASP values and the study would be terminated without performing a clinical trial in patients with stage 1 hypertension.
2. People identified with stage 1 hypertension and LOW CASP values may show continued progression of cardiovascular structural damage with time if left untreated for blood pressure lowering. This would suggest that people with stage 1 hypertension and LOW CASP values are not truly normotensive and might also benefit from treatment. In this respect, although CASP may have been useful in defining who has early cardiovascular structural damage at baseline it would be less useful at predicting whether structural damage will progress with time.
3. Treatment to lower BP in young people with stage 1 hypertension and HIGH CASP values could be poorly tolerated leading to study drop-out. This is unlikely however because both the brachial BP and CASP will have defined these people to be hypertensive and this will have been shown to be associated with early cardiovascular structural damage. Moreover, the proposed treatments are generally very well tolerated.
4. Treatment of people with HIGH CASP values may fail to regress or halt the progression of structural damage. This could indicate that the structural damage is irreversible, or that the treatment target was inadequate to reverse the damage or halt its progression, i.e. that lower BP targets are required. This would require further study.

5. Inclusion of younger women with stage 1 hypertension could expose women who become pregnant during the study to medications that are contraindicated during pregnancy. To avoid this and to reduce the confounding effects of the oral contraceptive pill on blood pressure, the study will only recruit younger men with stage 1 hypertension.

5.2 Objectives

The aim of this study is to evaluate whether the measurement of CASP is a better biomarker and means of stratification of blood pressure status, structural damage and the need for, and response to treatment, in younger men (aged 18-54 years) than current practice which is to classify these people as having stage 1 hypertension according to their brachial BP.

We have established prior proof of concept that; i) central aortic systolic pressure (CASP) can be simply and accurately measured non-invasively from the radial artery pulse wave [(20)]; ii) that conventional brachial systolic BP measurement may overestimate CASP by a variable but often marked degree in younger people - potentially misclassifying them as hypertensive [(13,18)]; iii) that CASP is a better predictor of left ventricular (LV) mass and other markers of hypertensive target organ damage than brachial BP [(14,22,29,30)]. Furthermore, we are addressing an unmet clinical need identified as a research priority by NICE with regard to the uncertainty about use of brachial BP alone to accurately stratify the need for BP-lowering treatment in younger people with stage I hypertension[(4)].

For practical reasons with regard to participant recruitment over the timescale of this study, younger men are defined as being between the ages of 18 and 54 years i.e. adults under 55 years of age. This upper age limit is in accordance with the NICE guideline[(4)] for stratification of people with hypertension for treatment type.

5.2.1 Explanation for choice of comparators

If this study demonstrates CASP to be a better predictor of left ventricular mass and therefore cardiovascular risk in young people than simple classification as stage 1 hypertension according to brachial BP, it follows that reducing CASP should regress left ventricular mass commensurate with a reduction in brachial BP. To investigate this, a randomised clinical trial will be undertaken in those identified to be in the highest quartile of CASP values from a cohort of people diagnosed with stage 1 hypertension. The active intervention will be BP lowering treatment, using anti-hypertensive treatments recommended by NICE guidance [(4)] and licensed for use in this age group – see section 6.4. The comparator is no treatment, which represents recommended usual care for patients with stage 1 hypertension and no other concurrent cardiovascular disease or overt target organ damage. These treatment regimens represent national guideline recommended approaches for the treatment of stage 1 hypertension in young people and are appropriate for use in this study. The use of no treatment as a comparator represents 'usual care' and avoids the unnecessary administration of placebo.

5.2.2 Study Hypotheses and Outcomes:

- We hypothesise that the non-invasive measurement of CASP will better define and stratify which younger people (18-54yrs) with stage 1 hypertension, according to their brachial BP, will have evidence of target organ damage as detected by MRI. We propose that those with the highest CASP values will have evidence of damage and are truly hypertensive, whereas

those with the lowest CASP values will have no damage, are truly normotensive and are misclassified as hypertensive according to their brachial BP values.

- We hypothesise that the non-invasive measurement of CASP in younger people with stage 1 hypertension will better define who requires treatment. We propose that only those with high CASP values will have evidence of early cardiovascular structural damage and thus require treatment and that there will be no development of target organ damage in those with low CASP values if left untreated for 1 year.
- We hypothesise that those with high CASP values will exhibit evidence of pressure-mediated cardiovascular structural damage, and that this damage will regress with treatment targeted at reducing CASP for one year, confirming the benefits of treatment in those with high CASP values.

5.2.3 Key Research Questions:

1. Is CASP a better biomarker of subtle early cardiovascular structural damage than conventional brachial BP measurement in young hypertensive people, i.e. does CASP provide incremental value versus brachial BP as a predictor of cardiovascular structural damage?
2. Is a low CASP benign in young people with stage I hypertension and thus a more reliable biomarker of their BP status - are these people truly normotensive, even though they have stage 1 hypertension according to their brachial BP values?
3. Is a high CASP more predictably associated with early cardiovascular damage than brachial blood pressure and a better indicator of true hypertension and of the potential need for treatment?
4. Does BP-lowering treatment of people with a high CASP versus no treatment, lead to better prevention/regression of cardiovascular structural damage - justifying treatment?
5. Are on-treatment CASP values a better biomarker of regression of cardiovascular structural damage than on-treatment brachial blood pressure values?

5.3 Trial Design

This study is a single centre study in two stages with a STOP/GO checkpoint between stages. The first stage (STAGE 1) of the study will comprise a screening study for 18 months, in which 500 young men with stage 1 hypertension and no other evidence of cardiovascular disease will be stratified into two groups according to non-invasive measurement of their central aortic blood pressure (the LOW and HIGH CASP groups). The second stage of the study (STAGE 2) will comprise a 12 month RCT in the HIGH CASP cohort (treatment versus no treatment) utilising a Prospective Randomised Open Blinded Endpoint (PROBE) design [(50)]. The second stage of the study will also comprise a 12 month observational follow-up study of the LOW CASP cohort which will run in parallel with the RCT. The decision to proceed to STAGE 2 (STOP/GO checkpoint) will depend on whether the first part of our hypothesis is proven, i.e. that CASP will differentiate between those with and without cardiovascular structural damage (i.e. increased left ventricular mass index), measured using cMRI.

6. Methods

6.1 Site Selection

This is a single-site, investigator-designed and investigator-led study which will be performed within clinical research facilities available at University College London/University College Hospitals London NHS Trust.

6.1.1 Study Setting

Participants with stage 1 hypertension will be identified for recruitment from patients attending the blood pressure clinic at University College Hospital London or from local general practice surgeries in the north/central London community. All study procedures will be carried out in a research outpatient facility either at University College London Hospital (Clinical Research Facility, Elizabeth Garrett Anderson Wing, UCLH) or at University College London Institute for Cardiovascular Science (Clinical Research Facility, 170, Tottenham Court Road, London). cMRI imaging will be carried out in the Institute of Cardiovascular Science British Heart Foundation funded Imaging Facility (Great Ormond Street Hospital, London).

6.1.2 Site/Investigator Eligibility Criteria

To participate in the TREAT CASP study, investigators and the trial site must fulfil a set of criteria that have been agreed by the TREAT CASP Trial Steering Committee and that are defined below. The trial site, will be issued with the applicable TREAT CASP documentation to use when applying for Site-Specific Approval (SSA).

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign a UCL CTU Investigator Agreement to include compliance with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that the site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of the drugs, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site where significant trial related duties have been delegated.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

The trial site will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to UCL CTU.

6.2 Site approval and activation

On receipt of the signed Clinical Trial Agreement or Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor which was given favourable opinion by the Research Ethics Committee (REC) and/or Institutional Review Board (IRB). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at UCL CTU.

6.3 Participants

6.3.1 Eligibility Criteria

This study will recruit young men with stage 1 hypertension, in accordance with the study hypothesis, aims and objectives.

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of recruitment. Questions about eligibility criteria should be addressed PRIOR to attempting to recruit the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this study if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

- Men aged 18-54 years.
- A diagnosis of stage 1 hypertension using conventional brachial BP measurements confirming a seated blood pressure of 140-159/90-99mmHg and/or or a day-time average greater than or equal to 135mmHg on ambulatory blood pressure monitoring.
- No current treatment for hypertension (if previously treated with anti-hypertensive medication, patients will have received no treatment for > 3 months).
- Willing and capable of giving informed consent.

6.3.1.3 Participant Exclusion Criteria

- Women of any age.
- Stage 2 hypertension, i.e. brachial blood pressure ≥160/100mmHg.
- Secondary hypertension, e.g. renal artery stenosis, Conn's adenoma phaeochromoctytoma, aortic coarctation.
- Stage 1 hypertension with evidence of overt target organ damage on routine clinical testing (e.g. ECG LVH, renal impairment, proteinuria), and/or concurrent cardiovascular disease (e.g. stroke, TIA, cardiac or peripheral vascular disease) and/or diabetes mellitus - i.e. risk factors

that would indicate that the stage 1 hypertension should be treated according to current guidance (NICE CG 127).

- Men in whom it is not possible to measure conventional brachial blood pressure.
- Atrial fibrillation or any other significant pulse rhythm irregularity in whom blood pressure measurement is difficult and unreliable.
- Regular consumption of more than 28 units of alcohol per week, or use of recreational drugs.
- Chronic inflammatory diseases requiring concomitant steroids and/or non-steroidal anti-inflammatory drugs.
- Known severe hepatic impairment.
- Known previous hypersensitivity to drugs used.
- Concurrent malignancy.
- Unwillingness to undergo, or contraindication to, MRI scanning.
- Current or recent participation (last 6 weeks) in an interventional clinical trial.
- Co-enrolment in a CTIMP or study of a non-investigational medicinal product.
- Any clinical condition for which the investigator would consider the patient unsuitable for the trial.

6.3.1.4 Eligibility Criteria for Individuals Performing the Study

This trial will be carried out by nurses, physicians, scientists and technologists experienced in the management and treatment of hypertension, experienced in techniques of non-invasive blood pressure and with experience in performing and interpreting magnetic resonance imaging.

6.3.1.5 Co-enrolment Guidance

Co-enrolment in any CTIMP or any other study of a non-investigational medicinal product is an exclusion criterion. Patients will not be permitted to enrol into a CTIMP or another study of a non-investigational medicinal product until their participation in this trial has been completed and at least 6 weeks has lapsed since the last intervention. There is no prohibition on co-enrolment into observational studies.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants, person with legal responsibility after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed or any blood is taken for the trial. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

The TREAT CASP study is in two stages and includes an initial stage 1 screening study into which all participants will be enrolled. There will be no pre-screening procedures prior to enrolment into the stage 1 screening study. Adherence to inclusion/exclusion criteria will be established from enquiring into potential participants' medical history. However, a seated measurement of brachial blood pressure may be performed during pre-screening as a part of normal clinical care.

6.3.1.7 Stage 1 Screening Study; Stratification of Participants by Central Aortic Systolic Pressure (CASP).

The first part of this study will identify ~500 men aged 18 – 54 years from the University College London Hospitals blood pressure out-patient clinic or from local General Practice surgeries, who have stage 1 hypertension based on seated conventional brachial BP measurements according to criteria set out by national NICE guidelines (BP 140-159/90-99mmHg and/or mean day-time blood pressure greater than or equal to 135/85 mmHg on ambulatory blood pressure monitoring). Potential participants will be given study specific information (participant information sheet) and will have had the opportunity to discuss potential participation in the study with a member of the research study team, prior to arranging an appointment to attend for a stage 1 screening study visit. At the stage 1 study visit we will outline what participation entails for the potential participant and answer any questions they have regarding participation in the study. We will then obtain and document informed consent to participate. Adherence to study inclusion and exclusion criteria will be ensured by questioning potential participants about their medical history, prior to enrolling the participant into the screening (stage 1) phase of the study and allocating a study specific identity. Stage 1 study participants will be recruited according to the study eligibility criteria as defined above and will have no evidence of existing target organ damage, cardiovascular disease, diabetes or chronic kidney disease. Once consented to participate in the TREAT CASP study, participants will undergo a cardiovascular health screen which will involve a number of routine clinical assessments, together with a study-specific non-invasive measurement of CASP.

Clinical assessments to be performed during the screening stage:

- Informed consent.
- Medical and lifestyle history.
- Physical examination.
- Seated Brachial BP and CASP using the CASPro device.
- Height and weight.
- Body fat composition using non-invasive bio-impedance.
- Blood tests: haematology, biochemistry, lipid profile and glucose (non-fasted), renal function (eGFR).
- Urinary albumin:creatinine ratio / urine dip stick for blood and protein.
- 12-lead ECG.
- 24hr brachial Ambulatory Blood Pressure Monitoring (Spacelabs device).

The ABPM measurement will be undertaken at screening to exclude participants with “white coat hypertension” as defined by the current NICE guidance [(4)]. This requires a minimum of 14 daytime readings, 30 minutes apart (usually 08.00hrs-22.00hrs). The daytime average is then used to define

the participants' BP status. An ABPM daytime average of ≥135/85mmHg excludes white coat hypertension. This ABPM diagnostic threshold is taken from the current NICE guidance on hypertension (NICE CG 127).

Data collected as part of the stage 1 screening study will primarily be used to stratify participants according to their central aortic systolic blood pressure and to identify those to be approached to participate further as participants in the subsequent randomised clinical trial and observational follow-up study. However, data from all stage 1 participants will also be used as cross-sectional data to investigate relationships between CASP and demographic or clinical parameters in patients with stage 1 hypertension. This will provide novel findings in patients with this condition. The Stage 1 screening phase will take up to 18 months to complete.

6.3.1.8 Defining the LOW CASP and HIGH CASP Groups - Stratification According CASP

After 500 participants have been recruited into the stage 1 screening study, data from participants will be stratified according to their CASP values. Based on the distribution of CASP values from our previous studies, we will select the upper 25% of CASP values to define the HIGH CASP group (n=130) who will be invited to participate in the RCT if the study progresses to the second stage. We will also select 65 participants with the lowest CASP values who will form the LOW CASP observational cohort and will be invited to participate in the observational follow-up study. Our preliminary data suggests that stratifying the stage 1 study population in this manner will result in an upper limit CASP value for the LOW CASP group of 129mmHg, and lower limit value for the HIGH CASP group of 141mmHg, generating a minimum CASP separation of 12mmHg between the groups. We recognise that this will most likely generate two groups with different brachial BP values as well different CASP values. However, according to current guidance, treatment would not be offered on the basis of the brachial BP value alone. Furthermore, CASP cannot be predicted from the brachial BP and we are specifically evaluating the use of CASP to stratify the patients for treatment.

We plan to screen up to 500 participants in Stage 1 of the study, however, as screening proceeds, the distribution of CASP values will be monitored and modelled by the study statistician. It is possible that fewer people will need to be screened to identify the required number of participants for the LOW CASP and HIGH CASP cohorts with the desired CASP separation.

Once identified, people in the HIGH CASP (n=130) and the LOW (n=65) groups will be invited to return to the research unit to undergo cardiac MRI for detailed evaluation of left ventricular mass index (LVMI) and cardiac and vascular structure and function. This evaluation will dictate whether the TREAT CASP study progresses to the stage 2 randomised clinical trial and observational follow-up study.

6.3.1.9 STOP/GO Checkpoint:

A STOP/GO checkpoint has been incorporated into the study design which will be evaluated before the study proceeds to the second stage. The STOP/GO checkpoint will be implemented to avoid futility in implementing the second part of the study i.e. if there is no difference in cardiac structure between the HIGH and LOW CASP cohorts there would be little likely benefit in stratifying participants by their central BP for subsequent treatment for blood pressure lowering.

Cardiac MRI (cMRI) will be used to measure left ventricular mass index in participants from the HIGH and LOW CASP groups participating in the stage 1 screening study. This data will be used to evaluate

the STOP/GO checkpoint. If a difference in LVMI is observed between participants from the HIGH and LOW CASP groups, the null hypothesis that there is no difference in LVMI between groups will be rejected and the study can proceed to the second stage. If the null hypothesis is not rejected i.e. if there is no difference in LVMI between people from the HIGH and LOW CASP groups, the TREAT CASP study will be terminated at this point. This evaluation will be used to confirm or refute the first key element of our hypothesis, i.e. whether CASP has been effective at identifying patients with and without pressure-related target organ damage, irrespective of their brachial blood pressure values.

The decision to proceed to the second stage of the study will be taken by the Trial Steering Committee. The data upon which the STOP/GO decision is made will be reviewed by an independent statistician who will provide recommendations to the Trial Steering Committee.

6.3.1.10 STAGE 2 Randomised Clinical Trial and Observational Follow-up Study:

If the conditions of the STOP/GO checkpoint are met i.e. if stratification by CASP value identifies groups with differing pressure related cardiac damage (LVMI), the study will proceed to the second stage. The second stage of the TREAT CASP study incorporates a 12 month randomised controlled trial in the HIGH CASP group using a prospective, randomised, open label, blinded end-point (PROBE) design [(50)]. The RCT is designed to evaluate whether people from the HIGH CASP group benefit from BP lowering drugs compared to no treatment (usual care) with regard to regression of their baseline cardiovascular structural damage (elevated LVMI relative to the LOW CASP group). The degree of regression of cardiovascular structural damage (LVMI) between the intervention and the usual care groups constitutes the primary outcome for the TREAT CASP study and will be evaluated following completion of the RCT (after 12 months treatment) following a repeated cMRI evaluation.

The second stage of this study also incorporates an observational follow-up of the LOW CASP group (n=65) with repeat cMRI after 12 months. This is designed to evaluate whether there is any development or progression of cardiovascular structural changes if people with LOW CASP are left untreated for 12 months.

6.4 Interventions

The active intervention for the stage 2 RCT is BP lowering using treatments recommended by NICE guidance [(4)] and licensed for use in this age group. The comparator is no treatment, which represents recommended usual care for these patients.

Active treatment will be titrated (dose/regimen adjusted) according to participants' CASP value rather than to the brachial BP value. Active treatment will be up-titrated to achieve a CASP value of <120mmHg and/or at least a 5mmHg reduction in CASP from baseline. For patients unable to tolerate higher dose medication, the treatment may be back-titrated to achieve the best CASP value tolerated.

6.4.1 Arm A

6.4.1.1 Products

BP lowering therapy for the intervention group in the stage 2 randomised clinical trial will be prescribed according to current NICE guidance for people aged <55years. Treatment constitutes an angiotensin receptor blocker (losartan 50mg once daily) for all ethnic groups other than for younger black men of African or Caribbean descent for whom a calcium antagonist (amlodipine 5mg once

daily) is the recommended initial treatment. Both of these treatments are well tolerated, generic and established medications, widely used in routine clinical practice.

Treatment will be titrated according to the CASP value rather than brachial BP values and up-titrated to achieve a CASP value of <120mmHg and/or at least a 5mmHg reduction in CASP from baseline. Combination therapy (i.e. angiotensin receptor blocker plus calcium antagonist) is also permitted if required in order to achieve blood pressure target.

6.4.1.2 Treatment Schedule

Participants in the stage 2 RCT randomised to active treatment will receive losartan 50 mg tablets once daily for 12 months. For participants of African or Caribbean descent treatment, participants will receive amlodipine 5 mg tablets once daily for 12 months.

6.4.1.3 Dispensing

All treatments will be prescribed via NHS standard prescriptions and will be sourced, stored and dispensed by the participant's local pharmacy. Payments will be made by NHS prepayment card which will be supplied to participants.

6.4.1.4 Dose Modifications, Interruptions and Discontinuations

Treatment may be up-titrated to Losartan 100mg tablets once daily and/or amlodipine 5mg tablets once daily may be added at the discretion of the study physician depending upon blood pressure achieved at follow-up visits during the 12 month treatment period. The study nurse will be permitted to prescribe the drugs. For patients unable to tolerate higher-dose medication, the treatment may be back-titrated to achieve the best CASP value tolerated. For participants of African or Caribbean descent treatment may be up-titrated to amlodipine 10mg tablets once daily and/or losartan 50mg tablets once daily may be added at the discretion of the study physician as above, but the study nurse will also be permitted to prescribe.

6.4.2 Arm B

6.4.2.1 Products

The comparator is no treatment, which represents recommended usual care for these patients.

6.4.2.2 Treatment Schedule

Not applicable, no trial-specific medicinal products will be taken on arm B.

6.4.2.3 Dispensing

Not applicable, no trial-specific medicinal products will be taken on arm B.

6.4.2.4 Dose Modifications, Interruptions and Discontinuations

Not applicable, no trial-specific medicinal products will be taken on arm B.

6.4.3 Accountability

Drug accountability will be by tablet count at patient visits. The study authors acknowledge the limitations in monitoring accountability by simple tablet count, but this represents the only practical way to estimate compliance in a community-based study with community pharmacy-based medication dispensing. Study medication is given within license and according to national guidelines – there are no anticipated medication safety issues. Given that participants are blood pressure

lowering-treatment naïve, the degree of separation in blood pressure between treatment arms will also give an indication of medication compliance.

6.4.4 Compliance and Adherence

The proposed medications are generally very well tolerated. Compliance with medication will be prompted periodically by SMS (text) messaging which we have utilised successfully in previous studies.

6.4.5 Concomitant Care

Concomitant care is permitted for study participants with the exception of other blood pressure lowering medications. The age of the study cohort together with the exclusion criteria reduces the likelihood of recruiting participants with concurrent chronic conditions.

6.4.6 Overdose of BP-Lowering Medication

Overdose of BP-lowering medication will be treated as a medical emergency. In this study treatment is open label. Normal NHS procedures for overdose will be followed in the unlikely event of overdose.

6.4.7 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to blood pressure-lowering treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable treatment toxicity or adverse event.
- Inter-current illness that prevents further treatment.
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment.
- Withdrawal of consent by the participant.

As participation in the trial is entirely voluntary, the participant may choose to discontinue treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

6.4.8 Intervention in the Observational Follow-up Study in the Low CASP Group.

The second stage of this study also incorporates a 12 month observational follow-up of the LOW CASP group (n=65) with repeat cMRI after 12 months. No medication will be administered to participants in the observational follow-up study as this represents 'usual care'. The observational follow-up study provides an opportunity to investigate whether there is any progression of cardiovascular structural change in patients with stage 1 hypertension who fall into in the LOW CASP group. The LOW CASP group will also serve as a reference against which the degree of regression in LVMI for the active intervention group of the RCT will be evaluated i.e. does BP-lowering regress LVMI to the level seen in those in the LOW CASP group? Concomitant medication will be allowed for participants in the observational follow-up study with the same stipulations as specified for participants in the RCT (see above).

6.5 Outcomes

6.5.1 Primary Outcome

THE PRIMARY OUTCOME for the TREAT CASP study is the change in left ventricular (LV) mass index from baseline to study end (12 months) in the randomised clinical trial comparing active treatment vs. no treatment. The primary outcome will be evaluated using 1.5T Cardiovascular MRI and will be expressed as grams per metre squared. Evaluation of the primary endpoint will be blind to treatment allocation. cMRI is the preferred mode of evaluation because of its excellent reproducibility, allowing adequately powered studies, with much reduced sample size and greater precision than echocardiography. Detail regarding measurement of the primary outcome variable is shown in section 6.10.1.

6.5.2 Secondary Outcomes

Secondary outcomes in the TREAT CASP study are designed to evaluate mechanisms exploring the relationship between CASP vs. conventional brachial BP on extended markers of cardiac and vascular damage both in cross-sectional evaluations at the end of the STAGE 1 screening study and in longitudinal analysis during STAGE 2, after 12 months follow-up of the LOW CASP observational cohort and the HIGH CASP RCT.

Secondary outcomes for the TREAT CASP study will be:

1. LV mass/volume ratio;
2. cMRI myocardial tissue tagging to demonstrate alterations in regional systolic and diastolic strain – early markers of hypertension-mediated damage;
3. cMRI measurement of interstitial fibrosis using T1 mapping – marker of damage as a prelude to impaired function;
4. cMRI measures of aortic distensibility and pulse wave velocity - sensitive indices of aortic stiffening. This tests our subsidiary hypothesis that increased aortic stiffness causes the detrimental increase in CASP relative to brachial BP;
5. High resolution cMRI spin echo sequences to measure carotid and aortic wall thickness;
6. Albumin excretion rate (Urinary Albumin: Creatinine ratio) as an index of early renal injury;
7. Retinal photography to document hypertensive changes in retinal small vessels.

Detail regarding measurement of the secondary outcome variables is shown in section 6.10.1.

6.6 Participant Timeline

Participants in the TREAT CASP study will initially be recruited into the stage 1 screening study. Stage 1 screening study recruitment will remain on-going from study commencement (mid 2013) until 500 participants have been screened (~18 months). At this time, data from the stage 1 screening study will be collated and used to stratify participants into the upper and lower quartiles based upon their CASP values (HIGH and LOW CASP groups). Only those participants falling into the HIGH and LOW CASP groups will then be invited to return to the research centre to undergo cardiac MRI. Once participants in the HIGH and LOW CASP groups have undergone cMRI, the STOP/GO

checkpoint will be evaluated (early 2015) to dictate whether the study proceeds to the second stage (stage 2 RCT and observational follow-up study). The study assessments in the stage 1 screening study have already been described (section 6.3.1.7) and are shown in the schedule of assessments below.

If the study proceeds to the second stage, those stage 1 participants identified as constituting the HIGH CASP group will then be invited to participate in the randomised clinical trial (n=130, early 2015). At the same time, 65 participants from the LOW CASP group will be invited to participate in the observational follow-up study. Participants entering the randomised clinical trial will commence medication at randomisation, i.e. there is no need for a wash-out/run-in period as this is a trial in treatment naïve participants. Similarly, those entering the observational follow-up study will be entered immediately at their randomisation visit.

For people participating in either the stage 2 randomised clinical trial or the stage 2 observational follow-up study, the study measurements performed during the stage 1 screening study (except for documentation of medical/lifestyle history and physical examination, see section 6.3.1.7) will be repeated both at randomisation (baseline) and at study end (study close out, 12 months). Ambulatory blood pressure monitoring will also be performed at randomisation and study end for all participants in the stage 2 randomised clinical trial and the observational follow-up study. All ABPM measurements during the stage 2 randomised clinical trial and observational follow-up study however, will use a wrist-mounted device (BPro device, Healthstats, Singapore) rather than the arm cuff device (Spacelabs) used in the Stage 1 screening study. This is because the wrist-mounted BPro device allows simultaneous monitoring of both brachial and central blood pressure over the course of 24 hours (see section 6.10.1) and will be used to monitor the change in 24-hour ambulatory blood pressure over the course of the RCT and the observational follow-up studies.

In addition to the visits planned at randomisation and study end, all participants in either the stage 2 randomised clinical trial or the observational follow-up study will be asked to return to the research centre 3 and 6 months following randomisation for measurement of their seated brachial BP and CASP and to document any adverse events. For participants in the stage 2 randomised clinical trial, further study visits will be scheduled for the actively treated group only, i.e. within the first 4 months and at 9 months, to optimise and up-titrate treatment as necessary and to ensure that the actively treated cohort in the randomised clinical trial achieve and maintain their CASP target for at least 8 months during follow-up. The schedule of study visits and study assessments in the TREAT CASP study is shown in the table below.

Participants not entering the stage 2 randomised clinical trial or observational follow-up study will complete the study following their stage 1 screening visit or their first cMRI visit and will be discharged from the TREAT CASP study.

TREAT CASP Study Schedule of Visits and Assessments

Visit	1	2	3	4	5	6	7	8	9	10
Type	Screening	MRI	Randomisation	Safety	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Close-out
Week	*	¶	0	4	8	12	16	26	38	52
Study Stage	1	1	2	2	2	2	2	2	2	2
PROCEDURE										
Signed Informed Consent	X		X							
Medical History	X									
Physical Exam	X									X
Seated Brachial BP	X		X	X	X	X	X	X	X	X
CASP	X		X	X	X	X	X	X	X	X
Height/Weight	X		X							X
Body Fat Composition (Bio-impedance)	X		X							X
Full Blood Count	X		X							X
Clinical Chemistry	X		X	X						X
Non Fasting/Fasting Glucose	X		X							X
Urinary Albumin:Creatinine Ratio	X		X							X
Urine Dip-Stick Test	X		X							X
ECG	X		X							X
24-Hour brachial ABPM (Spacelabs)	X									
24-Hour central ABPM (BPro)			X							X
Non-Mydriactic Retinal Photography			X							X
SF-36 QoL Questionnaire			X							X
Dispense Study Meds			X	X	X	X	X	X	X	X
Document Adverse Events			X	X	X	X	X	X	X	X
MRI		X								X

Text in blue indicates treatment group (1) only.

**Screening visits occur in first study year (Stage 1), prior to Stop / GO checkpoint for the subsequent RCT (Stage 2)*

¶ MRI visits occur within 3 months of subsequent randomisation

Both the randomised clinical trial and the observational follow-up study will be carried out over a 12 month period, with additional study visits scheduled during this period (see schedule of assessments, section 6.10). A repeat cMRI will be performed at the end of 12 month period (final visit, January-March 2016).

6.6.1 Early Stopping of Follow-up

If a participant chooses to discontinue their treatment, they should continue to be followed-up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the treatment. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the trial. UCL CTU should be informed of their withdrawal in writing using the appropriate TREAT CASP study documentation. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Participants who stop trial follow-up early will not be replaced.

6.6.2 Participant Transfers

As this is a single centre study, if participants move away from the study vicinity during follow-up, every effort will be made to maintain contact with them and to encourage them to return for study visits. If this is not possible, participants will be discharged from the study and not replaced.

6.6.3 Loss to Follow-up

Every effort will be made to follow patients and collect outstanding data. If follow-up appointments are missed patients will be contacted by the research nurse. If patients still fail to attend for appointments or if contacting them is unsuccessful, their GP will be contacted in an effort to re-establish contact with the patient.

6.6.4 Trial Closure

Study end is defined as the time at which the final database is locked. In the event of the conditions for the STOP/GO checkpoint not being met, the study will be terminated when data collection for the screening phase has been completed, at which time the database will be locked and the study will not proceed to the stage 2 clinical trial. In the event of early termination of the study or at the planned end of study, the study sponsor will be informed.

6.7 Sample Size

Two sample size calculations are presented for the TREAT CASP study; i) sample size to power the STOP/GO checkpoint; ii) sample size for the randomized clinical trial. As the sample size for the stage 2 RCT is critical for powering the study primary endpoint and because recruitment into the stage 1 screening study may be flexible to ensure sufficient recruitment, the sample size for the RCT is presented first.

6.7.1 Sample Size for the Stage 2 Randomized Clinical Trial

The Primary Outcome Measure for the Stage 2 randomised clinical trial is the change in left ventricular mass index from baseline to study end between the intervention group (BP lowering) and the no treatment (usual care) group. No published data is available relating to the effects of treatment upon LV mass in young men without established cardiovascular disease. Therefore the sample size for the RCT (study stage 2) is based on an analysis of previously published data investigating the effects of BP lowering treatment on MRI-determined LV mass index (LVMI) in people with existing cardiovascular disease. Analysis of data taken from 4 individual treatment studies comprising 7 active treatment arms in 627 individuals, mean age 60±3.4 years (51-54), indicates an average difference in LVMI between treatments (treatment versus no treatment) of 6.6g/m^2, SD 10.9g/m^2 [Appendix, table 2]. All treatments in the cited studies used inhibitors of the renin-angiotensin system and achieved moderate reductions in blood pressure (average reduction with treatment -8/-4.5 mmHg). Based on an anticipated difference in LVMI between treatments of 6.6g/m^2, SD 10.9g/m^2, power calculations indicate a sample size of 58 people per treatment arm will be required to show a difference with 90% power at p=0.05 in LVMI between the treatment and no treatment groups for the RCT (study stage 2). Recruitment of 65 individuals per treatment arm will allow for 10% drop-out between treatments.

6.7.1.1 Justification for the specified duration of the RCT in stage 2.

The duration of the stage 2 RCT in the TREAT CASP study is 12 months. Prior studies of LVMI change in response to BP-lowering therapy indicate that the majority of LVMI regression occurs within the first 12 months of treatment with very little additional change with longer follow-up (up to 5 years), [55,56]. This is because LVMI regression is powerfully determined by the extent of the reduction in BP on treatment, and the BP change is maximal during the first year of therapy. Thus, the anticipated change in BP with treatment and the proposed study duration has been chosen to maximise the change in LVMI within a reasonable timescale for the RCT.

6.7.2 Sample size underpinning the STOP/GO check point at the end of the stage 1 Screening Study

The inbuilt STOP/GO checkpoint to allow the study to proceed to the RCT (stage 2) is based on achieving a significant difference in LVMI as measured by MRI between people in the HIGH CASP and LOW CASP groups at the end of the screening phase (stage 1 see section 6.3.1.7).

Previously published studies indicate that LVMI is directly related to blood pressure and that the relationship between the change in systolic blood pressure and the change in LVMI approximates to the order of 1g/m^2 LVMI per mmHg SBP [57,58]. This order of magnitude of change is similar to that seen for the regression in LVMI with BP-lowering treatment in the analysis of published studies for the RCT power calculation (average reduction in SBP -8 mmHg, average reduction in LVMI with treatment -6.6 g/m^2). Preliminary data from our clinical laboratory in men with stage 1 hypertension stratified by their CASP values indicates that groups incorporating the highest and lowest 25% of the population with regard to their CASP values are separated by brachial systolic blood pressures of at least 10mmHg [Appendix, figure 7]. Based on the relationship between LVMI and BP as outlined above, this indicates a likely separation between groups in LVMI of approximately 10g/m^2. With regard to a starting value, systematic review of LVMI values by MRI in 1,032 young men from 11 published studies indicates a mean value of 78.5 g/m^2, SD 11.8g/m^2 [59-67]. Combining an estimated 10g/m^2 difference between the HIGH and LOW CASP groups with the SD for LVMI in young men, indicates a sample size of 31 per group would be required to demonstrate a difference in LVMI with 90% power at p=0.05. This indicates that a sample size of 65 individuals in the LOW CASP and 130 individuals for the HIGH CASP group should have abundant power to demonstrate a difference in LVMI at the study STOP/GO checkpoint. This will provide a robust basis to confirm or refute our hypothesis that CASP provides an effective mechanism for identifying patients with and without pressure-related target organ damage, in people with a diagnosis of stage 1 hypertension.

6.7.2.1 Consideration of variability in LVMI:

LVMI may be more variable in young people when compared to more frequently studied older populations. This could potentially impact upon the degree of separation in LV mass between the high and low CASP groups at the end of the first study phase (stage 1 screening study). However, this potential variability has already been taken into consideration in that the studies used to power the first phase of the study focus predominantly on younger people. Moreover, the power calculation used to power the STOP/GO checkpoint is sufficiently conservative to allow an increase in the standard deviation for LV mass index of up to 50%, equivalent to the highest levels for the standard deviation in LV mass in the group of studies upon which our study is powered, before power becomes marginal. Variability in LV mass could also potentially relate to the inclusion of fit

young men with physiological LVH. However, detection of overt LVH by ECG at screening is an exclusion criterion for the study.

6.8 Recruitment and Retention

6.8.1 Recruitment

Potential participants will be identified via three strategies:

1. From suitable patients referred to the blood pressure out-patient clinic at University College Hospital London. These people will be approached by the direct care team and given study specific information.
2. From general practice in association with liaison with the primary care research network following this study's adoption by the PCRN. These people will be approached via their GP who will provide potential participants with study information and details of how to contact the research centre.
3. Organisations such as the NIHR-funded Clinical Practice Research Datalink (CPRD) and University College London Partners have established large data-bases compiling anonymised patient-specific data. These resource will be used to search for potential participants who have already given consent through routine NHS procedures to be contacted to potentially participate in further research. These people will then be contacted via their GP who will provide study information and details of how to contact the research centre.
4. Advertisements will be placed in various media to attract potential participants for blood pressure screening.

6.8.2 Retention

For all participants in the clinical trial/observational follow-up study, we recognise that attending the research unit for regular follow-up visits (at approximately 3 monthly intervals) may intrude on their lifestyle. However, study visits will be made flexible in time and will be arranged at participants' convenience e.g. we will run out-of hours clinics as necessary. We will also make use of electronic media (text, SMS, Twitter, facebook) to remain in contact with participants to minimise the necessity for visits to the study centre.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

Assignment to treatment or no treatment (usual care) will be by random allocation, according to a computer generated random list (simple randomisation) using the web-based interface provided by the UCL CTU independent of the clinical research team.

6.9.1.2 Allocation concealment mechanism

Site staff will access a password protected, web-based interface which will allocate a study number and indicate treatment or no treatment. In cases where there is a problem with access to the internet, the study staff will telephone fully trained CTU staff who are not part of the study team via

a specific telephone number who will support the process for randomisation. In both cases the treatment allocation is concealed from staff involved in MRI measurements or data analysis.

6.9.1.3 Allocation Implementation

All participants from the HIGH CASP group who go on to participate in the stage 2 RCT will be assigned to the active intervention or usual care groups by the study nurse using the telephone randomisation number provided by the UCL CTU. Allocation will be implemented during participants' randomisation visit.

6.9.2 Blinding

The PROBE study design allows for an open-label trial with regard to study treatments and clinical care. Blinding of participants' treatment allocation applies only to study staff involved in MRI measurements and/or analysis. Blinding will be maintained by reference of study outcome data to participants' randomisation/enrolment numbers only, and this will be strictly enforced for study staff blinded to outcomes.

6.9.3 Emergency Unblinding

Not applicable – this is an open-label study.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Study data will be entered into a dedicated electronic database developed for the study by the University College London CTU. Separate database functions may be devised for collecting the stage 1 screening study data, the cardiac MR data and the stage 2 RCT and observational follow-up study, so that each dataset can be analysed and results produced separately as required. Some paper CRFs may also be used where appropriate.

6.10.1.1 Study Instruments.

6.10.1.2 Non-invasive Measurement of Seated Central Aortic Pressure:

Seated central aortic pressure will be measured non-invasively using the CASPro device as described under section 5.1 (introduction, subheading novel discovery work leading to this study). This device was developed by us at the University of Leicester NIHR cardiovascular BRU, in collaboration with a biotechnology company in Singapore. The device uses a sensitive pressure sensor (tonometer) to capture high-fidelity radial artery pulse waves, which are calibrated to a conventional measurement of brachial BP. Mathematical processing using a N-point moving average [(20)] is used to generate the central aortic systolic pressure (CASP).

Following five minutes seated rest, the brachial cuff is placed around the upper arm and the wrist strap tonometer is sited over the radial pulse. Three brachial BP and CASP readings for each participant are taken 1 minute apart each and the average of the last two measurements is calculated to yield the values for the data record. CASP values are then used to stratify study participants into the low or high CASP groups for the stage 1 screening study and to target treatment or follow blood pressure trends during the stage 2 RCT/observational follow-up study. The CASPro device has received a CE mark to show compliance with the Medical Devices Directive 93/42/EEC. This measurement takes no more than 5 minutes to perform.

6.10.1.3 Non-invasive Measurement of 24-Hour Ambulatory Brachial and Central Aortic Pressures:

24-hour ambulatory brachial and central aortic pressure will be measured using the BPro device. This device is similar in principle to the CASPro device, but has been miniaturised and manufactured in the form of a wrist watch. The device incorporates a sensitive pressure sensor (tonometer) mounted into an ergonomically designed articulating strap. The pressure sensor is placed accurately over the radial artery where it records pressure waveforms. Before initiating a 24-hour ambulatory monitoring session, radial waveforms are calibrated to a seated measurement of resting brachial blood pressure. Upon commencing the 24-hour ambulatory session, the device samples radial waveforms for ten second periods, every 15 minutes. Variation in waveform height over the 24-hour period is proportional to changes in the brachial BP. Published studies have demonstrated good comparability between ambulatory 24-hour brachial BP values recorded using the BPro device and ambulatory 24-hour brachial BP recorded simultaneously using a conventional cuff-based device [(68)]. The BPro device also processes calibrated radial artery waveforms using a N-point moving average in a similar manner to that described for the CASPro device, and this data is used to derive 24-hour ambulatory central aortic systolic pressure which is presented alongside the 24-hour brachial BP data.

6.10.1.4 Non-invasive assessment of Cardiac and Vascular Structure/Function Using Cardiac Magnetic Resonance Imaging (cMRI).

The main outcome measures for the TREAT CASP study are parameters of cardiovascular structure and function as determined by Cardiovascular MRI studies (cMRI). These measurements will be supervised by a Clinician with expertise and an academic interest in cMRI (Muthurangu, or by staff delegated by Dr Muthurangu as competent to do this and who are designated as study investigators and are blinded to participant treatment allocation). All cMRI scans will be performed using a cardiovascular research dedicated 1.5T MRI scanner within the UCL Institute of Cardiovascular Science Imaging Centre at the Great Ormond Street Hospital. In addition to using cMRI to evaluate changes in LVMI for the primary end-point, the cMRI studies will yield abundant novel mechanistic data from this study. Multi-parametric cMRI imaging allows quantification of the following variables;

6.10.1.5 Measurement of Left Ventricular Mass Index (LVMI) using cMRI:

Cine imaging with steady state free precession gives unparalleled assessment of cardiac volumes and function [Appendix figure 5]. The excellent reproducibility, inter and intra-observer variability of cMRI LV volumes/mass measurements allow adequately powered studies to be performed with greatly reduced sample sizes compared to echocardiography [(69)]. In the multi-ethnic study of atherosclerosis (MESA) study mass/volume ratio (the cMRI equivalent of echocardiographic relative wall thickness) demonstrated a hazard ratio for CVD events of 3.6 for those subjects aged <65 years in the highest quintile compared to the lowest [(70)]. Additionally the MESA study has shown that increased LVMI is more strongly related to subsequent heart failure but that concentric remodelling is a stronger predictor of incident coronary heart disease and stroke [(71)].

6.10.1.6 Measurement of Myocardial Strain:

cMRI myocardial tissue tagging can demonstrate alterations in regional systolic and diastolic strain (deformation), strain rates and increases in the normal wringing action (torsion) of the left ventricle, and is considered the gold standard technique for the assessment of function [(72)]. In hypertensive

patients with LVH, myocardial strain is reduced compared to normal controls despite similar measures of global LV function.

6.10.1.7 Measurement of myocardial interstitial fibrosis:

Detection of interstitial fibrosis using T1 mapping [73] and focal (replacement) fibrosis [74] is done following contrast administration. Fibrosis is an inevitable response to left ventricular hypertrophy and has been demonstrated in the majority of hypertensive patients with left ventricular hypertrophy [74] which, if unchecked, may lead to irreversible left ventricular dysfunction. Importantly in hypertensive patients, it is likely that interstitial fibrosis and diastolic dysfunction occur before overt left ventricular hypertrophy has developed [75]. cMRI T1 mapping has the potential to detect reversible left ventricular damage before any other imaging parameter.

6.10.1.8 Measurement of Aortic Distensibility and Aortic Pulse Wave Velocity (PWV) by cMRI:

Direct (aortic distensibility) and indirect (PWV) measurements of aortic stiffness will be undertaken in a single examination, utilising multiple sites along the aorta. Such measurements using MRI have previously been shown to exhibit good agreement compared to invasive measurements and show excellent reproducibility [76]. Stiffness can be determined at different levels of the aorta, which may be important for target organ damage and progression of disease. Possibly because the distance travelled between measurement sites in the aorta can be measured accurately by cMRI, differences in PWV can be detected between subjects with risk factors for CVD and healthy controls even with samples sizes less than 20 per group [77]. cMRI-measured aortic distensibility is an independent predictor of CVD morbidity and mortality in patients with chronic renal failure [78]. In the MESA study, reduced aortic distensibility in 800 middle aged and elderly subjects was related to age, hypertension, smoking and African-American ethnicity [79]. Additionally, reductions in diastolic function have been shown to be related independently to arterial stiffness for both aortic and carotid arteries [80], and LV hypertrophy in patients free of clinical CVD.

6.10.1.9 Measurement of Carotid and Aortic wall thickness:

High resolution spin echo sequences will allow assessment of carotid and aortic wall thickness [77]. Although arterial wall thickness and stiffness both increase with age, there are important differences in associated risk factors for the two measures [79] and increased stiffness can be demonstrated without any evidence of subclinical atherosclerosis on imaging [81]. These findings emphasise the fact that, although related, arterial stiffness and wall thickening are not governed by the same underlying pathophysiological processes, which may explain why arterial stiffness is an independent risk factor for CVD.

6.10.1.10 Measurement of Myocardial Perfusion Reserve:

This is an indicator of combined macro- and microvascular coronary function which can be determined with absolute quantification of blood flow. Perfusion reserve was related to age and traditional risk factors, and reductions in strain, in the MESA study [82] but the relationship to arterial stiffness and diffuse fibrosis in hypertension has not been studied to date.

6.10.1.11 Other Markers of Target Organ Damage;

In addition to cMRI derived parameters as indicators of target organ damage, other clinical markers of blood pressure related target organ damage will be evaluated in the stage 2 randomised clinical trial and observational follow-up study.

6.10.1.12 Urinary Albumin Excretion Rate:

The excretion of albumin is a sensitive indicator of renal haemodynamic stress in people with hypertension [83]. Albumin and creatinine levels will be measured using a sample of the first early morning urine and expressed as the albumin:creatinine ratio as a measure of albumin excretion.

6.10.1.13 Non-mydriatic retinal imaging:

Fundal images will be acquired using a dedicated retinal camera and used to study changes in retinal artery architecture during the RCT and observational follow-up studies (baseline and study end).

6.10.1.14 Quality of Life Assessment.

Quality of life assessment will be undertaken using a SF36 questionnaire [84] completed at baseline and study end by participants in the randomised clinical trial (HIGH CASP group) and participants in the observational follow-up study (Low CASP group).

6.10.2 Non-Adherence and Non-Retention

6.10.2.1 Compliance with Medications:

The proposed medications are generally very well tolerated. Compliance with medication will be recorded by tablet counts at routine study visits. Compliance with medication will be prompted periodically by SMS (text) and/or email messaging which we have utilised successfully in previous studies.

6.10.2.2 Study Withdrawal:

Our experience with relatively short-term studies (~1 year) involving close monitoring and follow-up e.g. MRI studies, suggests that loss to follow-up will be very low <5%. Furthermore, the patients entering the RCT will have already committed to the screening phase of the study and baseline MRI studies, increasing the likelihood of continued participation. We have incorporated 10% drop out from the RCT into our power calculations but consider the level of attrition unlikely to be this high, based on our local experience.

6.10.3 Data Management

6.10.3.1 Data Recording:

Data will be recorded at study visits as per the trial protocol. The study will use a dedicated on-line, password protected electronic case report form (eCRF) which will be designed in collaboration with the University College London CTU. Designated study investigators will have administrator rights to the system. This allows rapid update of patient details and events. The study research nurse will be primarily responsible for data collection at the study visits.

Data collected during participation in this study as well as related health records will remain strictly confidential at all times in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval. Study-specific information will be held securely on paper and electronically by the University College London Clinical Trials Unit under the provisions of the 1998 Data Protection Act. Participant's personal details will not be passed to anyone else outside University College Hospital NHS Trust. Participants will be allocated a trial number, which will be used as a code to identify them on all trial forms.

Participant's personal records will only be available to people authorised to work on the trial within the trial team and within the NHS Trust R&D Department for the purposes of audit. Records will also be made available to the trial team at UCL CTU for the purposes of monitoring. Participant's clinical data will be made available to participant's GP or other healthcare provider with the permission of the individual participant.

For participants who elect to withdraw consent from participating in the study, data collected until withdrawal will remain on file and will be included in the final study analysis.

6.10.3.2 Data Collation Analysis and Archiving:

Study data will be entered into an electronic database developed for the study by the University College London CTU. Statistical analysis will be undertaken by the study statistician as described in section 6.10.4.2 (statistical methods).

At the end of the study, data will be securely archived according to the study sponsor's standard procedures for a minimum of 10 years. Arrangements for confidential destruction will then be made.

6.10.4 Statistical Methods

6.10.4.1 Statistical Analysis Plan:

Study data will be analysed at three time points:

- At the end of the stage 1 screening study, demographic, clinical chemistry and haemodynamic study data will be analysed in a cross-sectional analysis.
- After the initial cMRI, the STOP/GO checkpoint analysis will be performed and cMRI data will be analysed together with stage 1 study data in cross-sectional analyses.
- At the end of the stage 2 RCT and observational follow-up study primary, secondary and other endpoints will be analysed and a longitudinal data analysis will be performed.

6.10.4.2 Statistical Methods – Outcomes:

STAGE 1: Central aortic systolic pressure (CASP) distribution will be used to stratify participants as potential candidates for stage 2. Participants with CASP values above the 75th percentile will be candidates for randomisation into the trial. Simple, unrestricted randomisation will be used. Those with CASP less than the 25th percentile will be offered participation in the observational follow-up part of stage 2.

STAGE 2: All analyses for outcomes in the RCT will be carried out on the basis of the originally assigned groups, whether participants complete treatment or not as per CONSORT guidelines [87]. Multilevel mixed-effects linear regression models with a maximum likelihood estimator will be used and will account for the repeated measures nature of the data. These models are inherently robust to missing data, dealing with missing values in a similar manner to multiple imputation approaches.

The principal outcome for assessment will be change in LV mass index over the 1-year follow-up period. This will be compared between the two groups without adjustment and then with adjustment for potential confounders in multivariable models. Such additional variables will include, but not be limited to, age, brachial artery systolic pressure, smoking history and measures of adiposity such as BMI. Over-fitting of models will be avoided by careful attention to the adjusted r^2

of the models. Thus, only coefficients that significantly improve the fit of the models or where a strong case for their known biological importance can be made will be included. Results will be presented in a multi-stage format so that readers can assess the unadjusted and adjusted models separately. Where predictor variables are suspected to have a non-linear influence on outcome (e.g. on LV mass index), further polynomial terms may be added (e.g. quadratic and cubic) but careful examination of model fits to raw data will be made to prevent such models from over-fitting the data in a spurious sense. Where interactions between predictor variables are suspected on the basis of biological plausibility e.g. varying influence of adiposity on LV mass index with age, the appropriate interaction terms will be added to the models to assess this. Outliers will be dealt with on a case-by-case basis and excluded if values are biologically implausible or can be found to be erroneous after reference to the raw data.

No interim analyses will be performed in accordance with the blinded nature of the study. Results will be reported as per CONSORT guidelines [87].

6.10.4.2.1 Data Manipulation:

In all cases, parametric analyses will be preferred and applied to data with normal distributions or after appropriate transformation to normality e.g. Log transformation for right-skewed data.

6.10.4.2.2 Missing Data:

For missing data appropriate procedures will be used such as multiple imputation procedures or (where y-values are (MAR) missing at random), the bootstrap approach as suggested by Efron [86].

6.10.4.2.3 Analysis of the STOP/GO Checkpoint:

It is a STOP/GO condition of the study prior to stage 2 that the high and low CASP groups must have a significant ($P<0.05$) difference in LV mass index. Student t-test comparison of the groups will be used to assess this.

6.10.4.2.4 Economic evaluations:

No economic evaluations are planned. Evaluation of cost effectiveness of the study medications in terms of quality adjusted life years (QALYs) is well established [4].

6.10.4.2.5 Additional Analyses – Subgroup:

No additional analysis in sub-groups is planned.

6.10.4.2.6 Additional Analyses – Adjusted:

No additional analysis in sub-groups is planned.

6.10.4.2.7 Analysis Population and Missing Data:

The analysis population and strategies for dealing with missing data are outlined in section 6.10.4.2 – statistical methods.

6.11 Data Monitoring

6.11.1 Independent Data Monitoring and Ethics Committee:

An independent Data Monitoring and Ethics Committee (DMEC) will be established for stage 2 of the study if the STOP/GO criteria are met and the study proceeds to stage 2. We do not anticipate any

major safety concerns with this study. The RCT in stage 2 is a single centre study, using established and licensed medications for one year duration. The DMEC will be independent of the TSC. There will be no planned interim analysis of the 12 month RCT and the role of the DMEC will be to assess safety reports and make recommendations to the TSC.

Further details of the roles and responsibilities of the Data Monitoring and Ethics Committee (DMEC) including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the TREAT CASP study DMEC Terms of Reference (ToR).

6.11.2 Interim Analyses

No interim analyses are planned.

6.11.3 Data Monitoring for Harm

This is a not a clinical trial of an Investigational Medicinal Products and treatments used in this study have well known safety profiles. Nevertheless, data on adverse events will be collected by the research nurse at routine study visits. Adverse events inconsistent with the known effects of study medication will be reported via the yellow card system through the MHRA website [87] at the judgement of the study physician and CI This data will be reported to the UCL CTU at the same time.

6.11.3.1 Safety reporting:

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***

* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (eg a silent myocardial infarction)

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (eg a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial drug administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial drug administration.)
- continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event

- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred eg elective cosmetic surgery
- Overdose of medication without signs or symptoms

6.1.3.2 Other Notifiable Adverse Events

Adverse events inconsistent with the known effects of study medication will be reported via the yellow card system [87] at the judgement of the study physician and CI.

6.11.3.3 Procedures to follow in the event of female participants becoming pregnant:

Not Applicable.

6.11.3.4 Investigator responsibilities relating to safety reporting:

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes and reported in the toxicity (symptoms) section of the Follow-up Form and sent to UCL CTU within 7 days. It is the responsibility of the study physician and CI to use clinical judgement regarding the discontinuation of treatment due to adverse events.

6.11.3.4.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1.

6.11.3.4.2 Severity or grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the WHO toxicity gradings.

6.11.3.4.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to the relevant Interventions sections of the protocol.

6.11.3.4.4 Expectedness

If there is at least a possible involvement of the medications, the investigator and sponsor must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the current IB or SPCs, or one that is more frequently reported or more severe than previously reported. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) this should be reported through the yellow card system as described above.

6.11.3.5 Notifications:

6.11.3.5.1 Notifications by the Investigator to UCL CTU

The investigator will report all notifications through the yellow card system to the UCL CTU at the same time as they are reported to the MHRA and the REC if the committee requires this information.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment:

The Quality Assurance (QA) and Quality Control (QC) considerations for the TREAT CASP study are based on the standard UCL CTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the approved protocol, the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled. A risk assessment will be completed for the TREAT CASP study and submitted to the UCL CTU Quality Management Group (QMG) for review. The QMG will feedback comments through a formal reporting system.

6.11.4.2 Central Monitoring at UCL CTU:

UCL CTU staff will review Case Report Forms (CRF) and electronic data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the TREAT CASP trial Data Management Plan.

6.11.4.3 On-site Monitoring:

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the TREAT CASP study Quality Management Plan (QMP) this will be based on the trial risk assessment. The QMP will also detail the procedures for review and sign-off of monitoring reports.

6.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.11.4.4 Trial Oversight:

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the UCL CTU trial oversight policy. UCL CTU ensures oversight by the formation of groups such as the Trial

Management Team (TMT) the Trial Management Group (TMG), the Quality Management Group (QMG) and the Protocol Review Committee (PRC). Independent members will be present on the Trial Steering Committee (TSC) and the Independent Data Committee (IDMC). For the purposes of the TREAT CASP study the IDMC will be known as the Data Monitoring and Ethics Committee (DMEC) for consistency with the terms used by the NIHR HTA.

This oversight is considered and described by exploring the trial dataset or performing a site visit and will be described in the TREAT CASP study Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day-to-day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

6.11.4.4.2 Trial Management Group

Trial management will be the responsibility of the UCL CTU trial management team. As this is a small-scale single centre study, day-to-day trial management will be undertaken at regular (weekly) meetings of the study team, chaired by the CI.

6.11.4.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, UCL CTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.4 Independent Data Monitoring Committee

The Data Monitoring and Ethics Committee (DMEC) is the only oversight body that has access to unblinded accumulating comparative data. The DMEC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the DMEC terms of reference. The DMEC will consider data in accordance with the statistical analysis plan and will advise the TSC through its independent Chair.

6.11.4.4.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to UCL CTU.

7 Ethics and Dissemination

7.1 Research Ethics Approval

The study will be submitted to be reviewed and approved by a Research Ethics Committee and will receive local approval by University College Hospital NHS Trust as necessary, prior to commencing.

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Competent Authority Approvals

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is not required in the UK.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the Research Ethics Committee at the same as they are submitted through the yellow card system if required. Guidance will be sought through the NRES website as to whether the approving REC will require this information.

7.3 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of the participating site. A copy of the local R&D approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to UCL CTU before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the UCL CTU Protocol Review Committee.

7.4 Protocol Amendments

Any necessary protocol amendments raised by the investigators will be considered by the Trial Steering Committee and if appropriate submitted to the REC for approval.

7.5 Consent or Assent

All participants will be required to provide written informed consent after reviewing the detailed study information within the patient information leaflet for at least 24 hours prior to the consent process. Consent will be requested for participation in the study and will be obtained by the study physician or Research nurse who will receive appropriate training (where necessary) from UCL CTU trial team. Participants will be advised that they may withdraw consent at any time.

During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Consent will be re-sought if new information becomes available that affects the participant's decision to consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use. A copy of the approved consent form is available from the UCL CTU trial team.

7.5.1 Consent or Assent in Ancillary Studies

Not Applicable

7.6 Confidentiality

The trial has been registered with the UCL Data Protection Officer and will follow the UK Data Protection Act.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Archiving

The investigators agree to archive and/or arrange for secure storage of the TREAT CASP study materials and records for a minimum of 10 years after the close of the trial unless otherwise advised by the UCL CTU.

7.9 Access to Data

The Chief Investigator, co-investigators and the TSC will have full access to the study data. Ownership of the study data will be the responsibility of the Chief Investigator.

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TSC. Considerations for approving access will be documented in the TSC Terms of Reference.

7.10 Ancillary and Post-trial Care

Once the study has been completed we are unable to provide continued treatment for participants in the clinical trial. However assuming a positive study outcome, we will recommend continued treatment via the participants' GP for those in the intervention group and we will recommend treatment via their GP, based on study findings, for those receiving 'usual care' i.e. no treatment.

7.11 Publication Policy

7.11.1 Trial Results

Results will be published in accordance with the UCL CTU Publication Policy. Results of both the stage 1 screening study and the stage 2 randomised clinical trial will be published in a peer reviewed medical journal. A "lay" report of the research findings and implications will also be delivered to all study participants.

The results of the trial will be disseminated regardless of the direction of effect.

7.11.2 Authorship

The CI will establish a writing group, which will include the investigators, representatives of UCL CTU and the statistician. Publication will comply with the UCL CTU publication policy.

7.11.3 Reproducible Research

The study protocol will be made available upon request to the TSC. A copy of the study protocol will also be held by the study funder the National Institute for Health Research.

8 Ancillary Studies

None planned.

9 Overview of Previous Protocol Amendments

This is the first protocol submitted for TREAT CASP, no amendments have been made.

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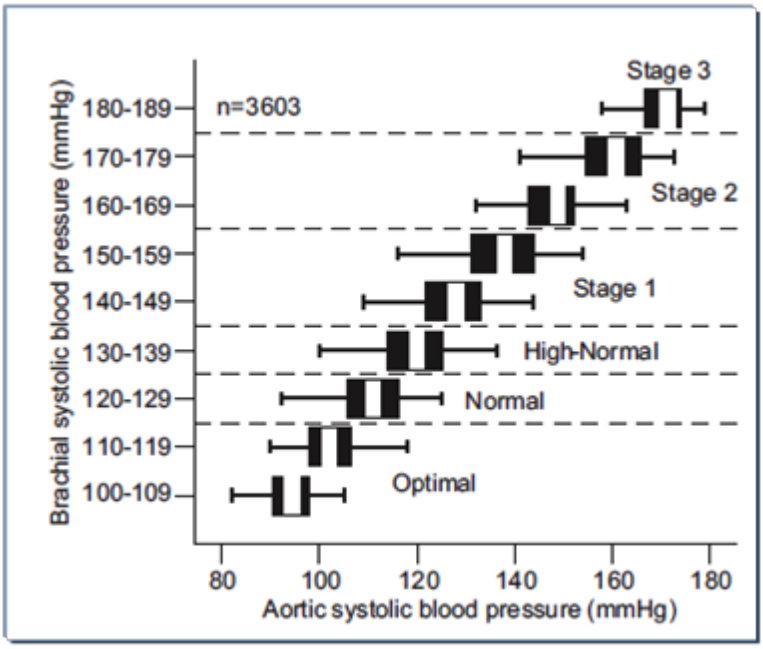
11 Appendices

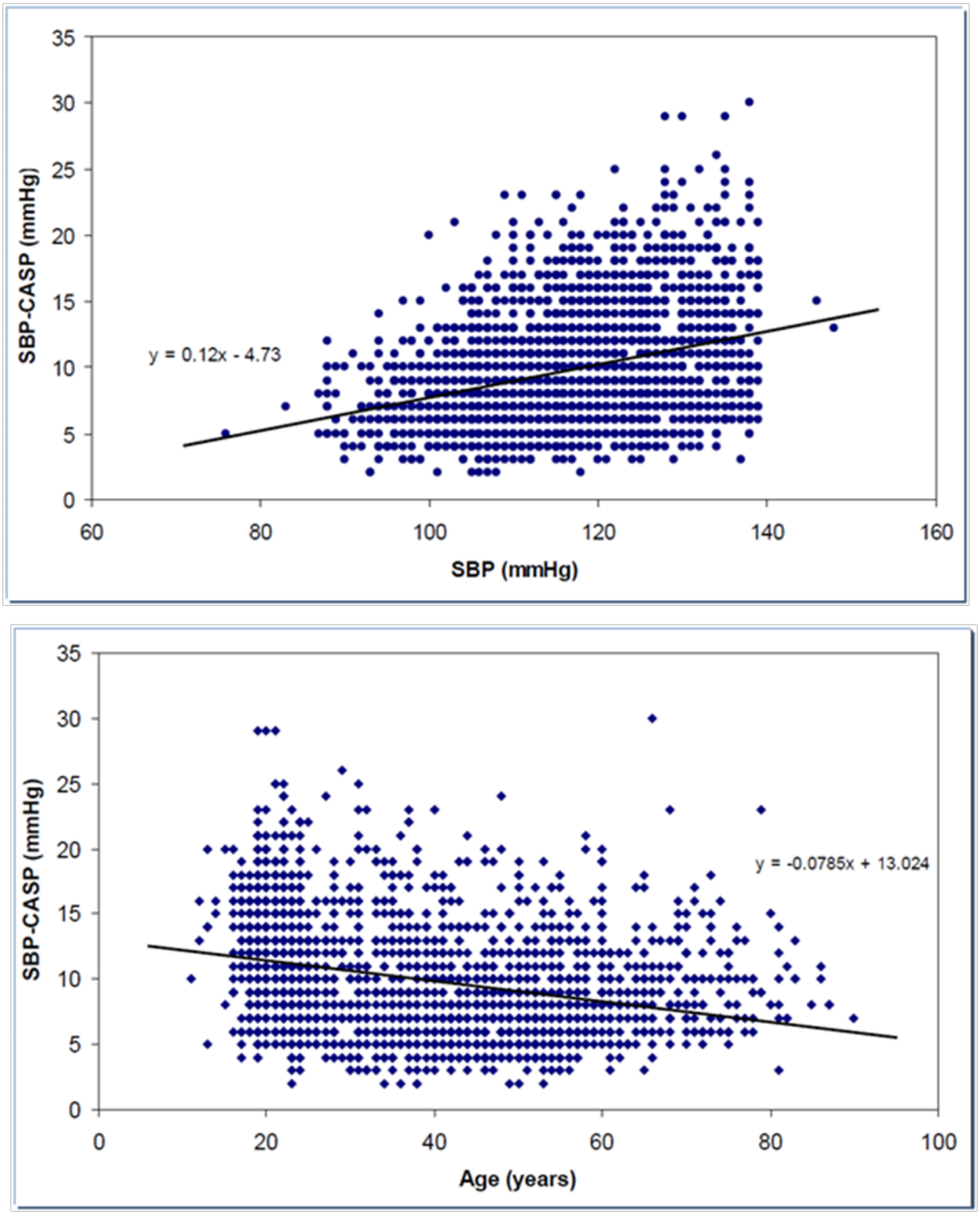
The Participant Information Sheet and Consent Form are available as separate stand-alone documents.

Appendix Figure 1.



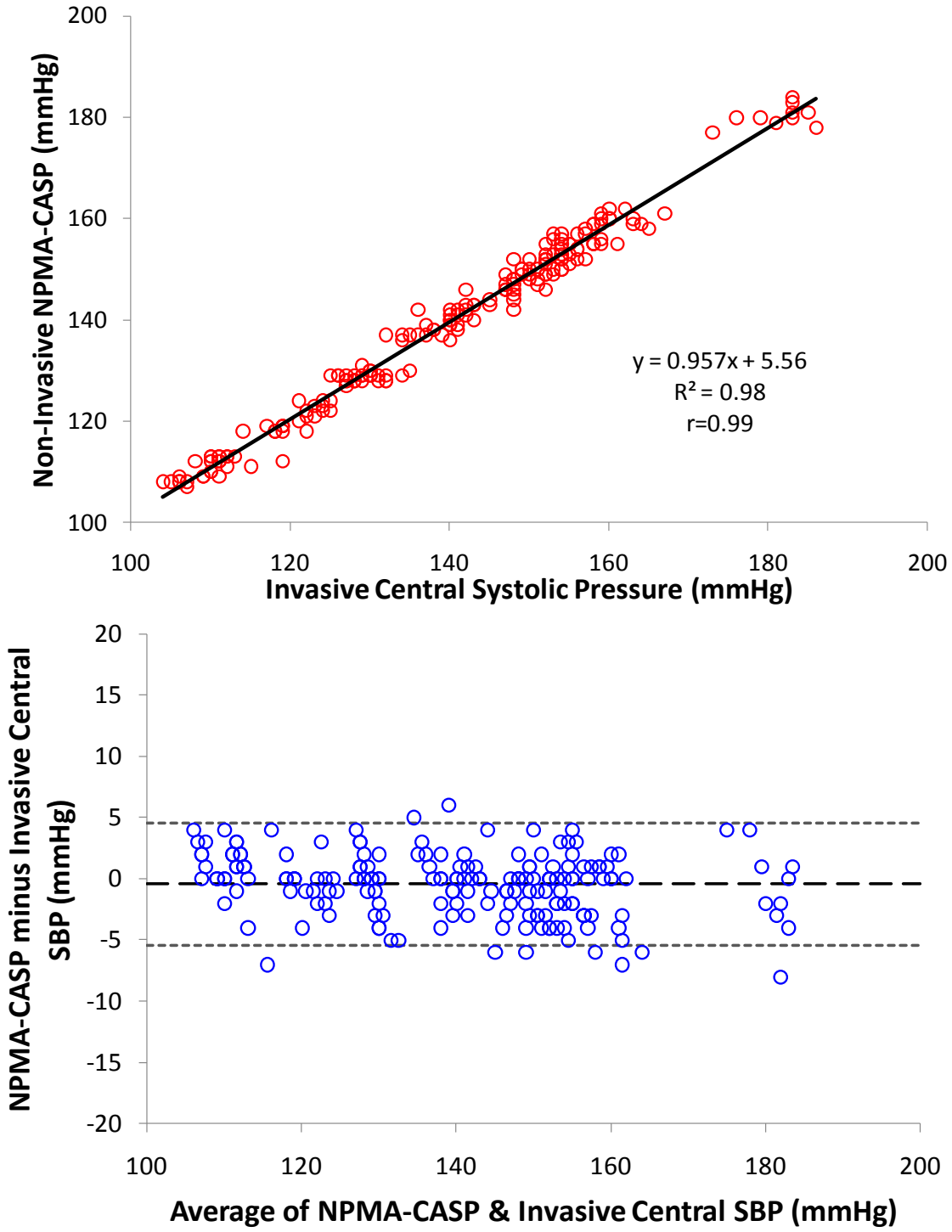
Appendix Figure 1. Box plot of central aortic systolic pressure (CASP) per 10-mm Hg increments in brachial systolic pressure in treatment naive men. The vertical line within the box represents the median, the box represents the interquartile range (50% of the distribution), and the whiskers represent the range of values. The dashed lines indicate BP classifications according to the 2007 European Society of Hypertension and of the European Society of Cardiology guidelines. Taken from McEniery *et. al*. 2008 [13].

Appendix Figure 2.



Appendix Figure 2. Scatter plots showing the difference between brachial and central systolic blood pressure (SBP-CASP) and brachial systolic blood pressure (upper panel) or age (lower panel). Data was collected from ~5,000 healthy people attending for a cardiovascular health check (unpublished data from our clinical laboratory). CASP was measured using the BPro™ device (Healthstats, Singapore).

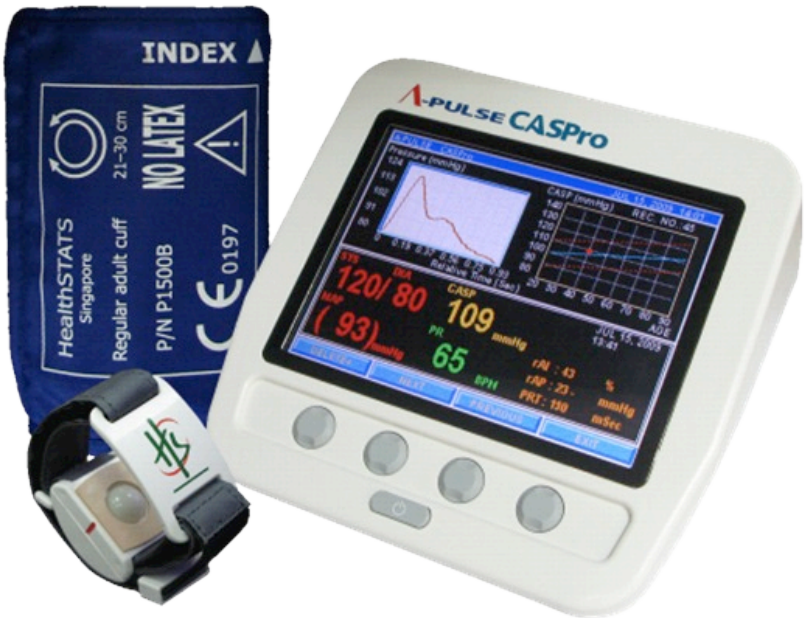
Appendix Figure 3.



Appendix Figure 3. Linear regression (upper panel) and Bland Altman analysis (lower panel) for central systolic pressure measured invasively (invasive central systolic pressure) and estimated non-invasively using moving average analysis of radial pressure waveforms acquired using a tonometer embedded within a wrist strap (A-pulse®, Healthstats, Singapore), calibrated to oscillometric brachial blood pressure (non-invasive CASP). Each data point represents each individual, ten second samplings for each patient (10 blocks per patient, 20 patients).

Appendix Figure 4.

1. **The CASPro Device**

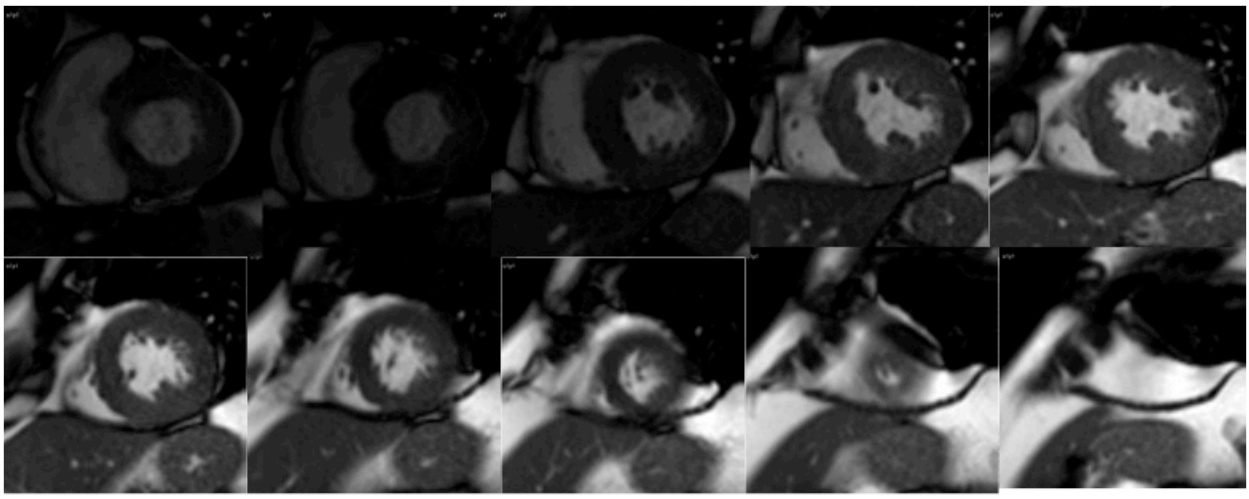


2. **The BPro Device**

Appendix Figure 4 Upper Panel: The CASPro™ device (Healthstats, Singapore) for measuring central aortic systolic pressure (CASP). The device incorporates an oscillometric blood pressure monitor together with a high fidelity tonometer incorporated into a wrist strap for measuring radial artery pressure waveforms. Radial artery pressure waveforms are calibrated to contemporaneously measured brachial blood pressure and processed using a validated N-point moving average to derive CASP.

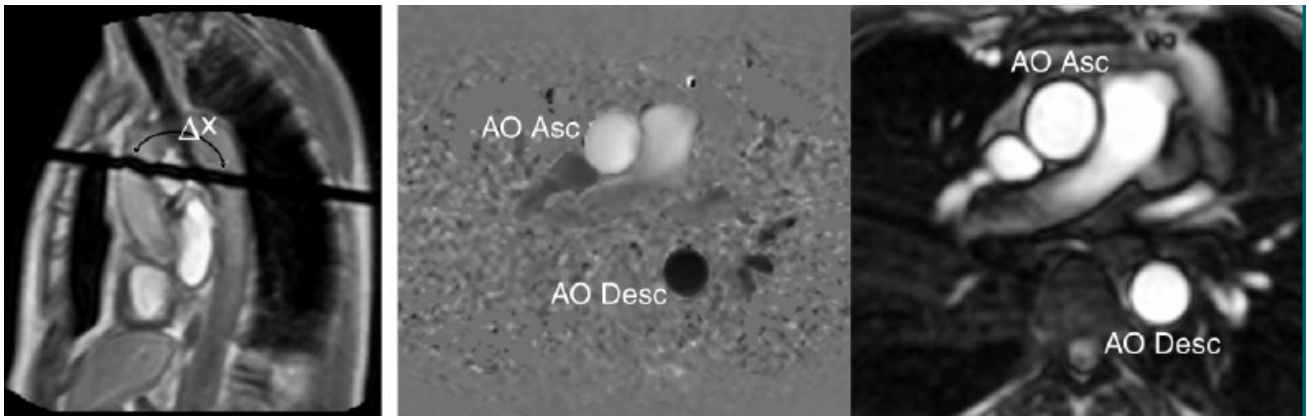
Appendix Figure 4 Lower Panel: The BPro™ device (Healthstats, Singapore) for measuring 24-hour ambulatory central aortic systolic pressure (CASP). The device incorporates a high fidelity tonometer into the articulating strap of a wrist watch device. Following calibration to a seated measurement of brachial blood pressure the device samples ten second recordings of radial artery pressure waveforms every 15 minutes across a 24-hour period. The positioning of the device over the radial artery is also shown.

Appendix Figure 5.



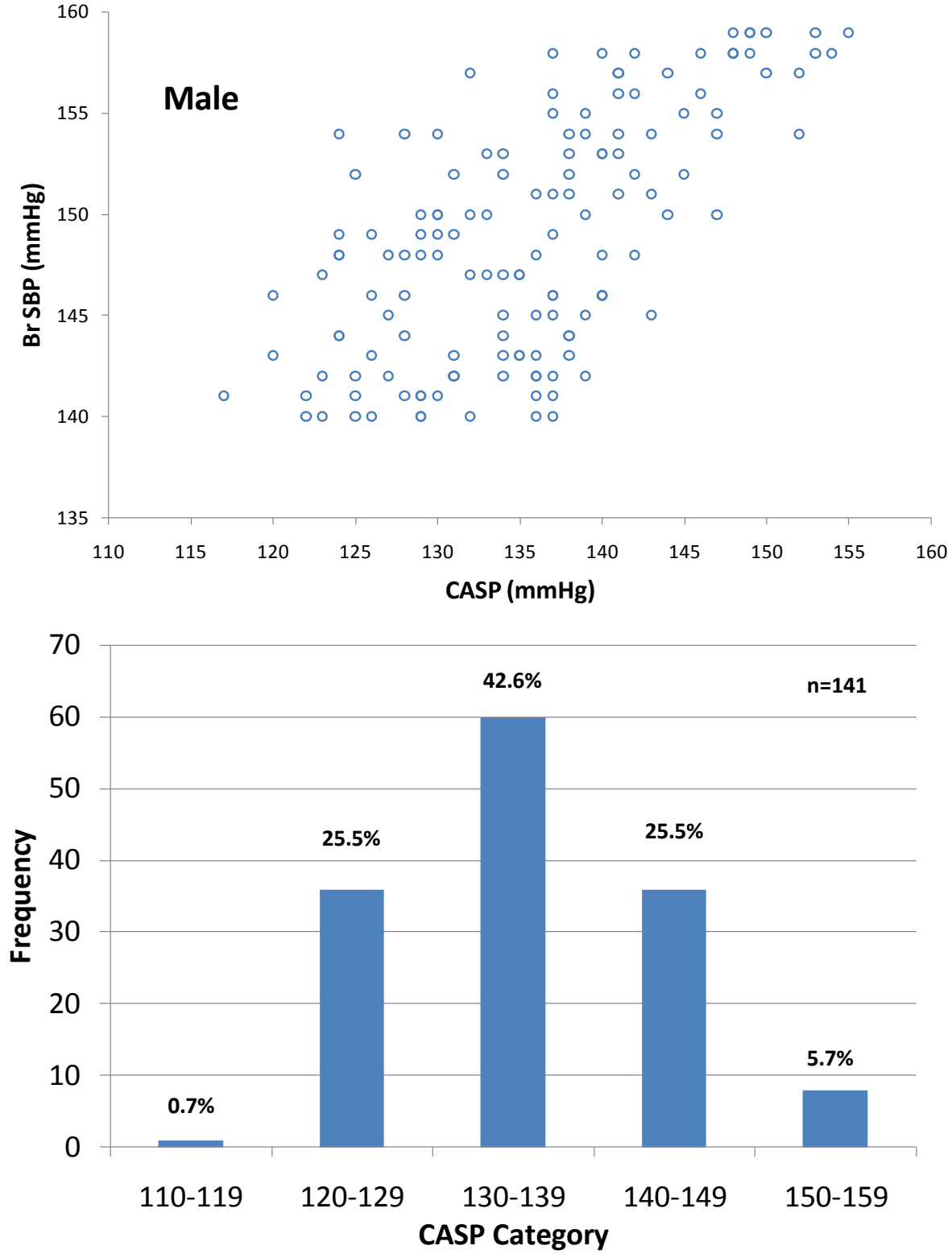
Appendix Figure 5. cMRI steady state free precession images covering entire LV from base to apex allowing accurate quantification of LV mass and function.

Appendix Figure 6.



Appendix Figure 6. Assessment of arterial stiffness by cMRI. Left panel: planning of flow measurements perpendicular to ascending and descending aorta (from sagittal oblique). Middle panel: Phase contrast image which allows calculation of flow in ascending and descending aorta and pulse wave velocity derivation. Right panel: Steady state free precession image at ascending / descending aorta allowing calculation of aortic strain/distensibility.

Appendix Figure 7.



Appendix Figure 7. Upper Panel: Relationship between brachial SBP and central aortic systolic BP (CASP) in men with stage 1 hypertension. Lower Panel: Frequency distribution for CASP deciles in men with stage 1 hypertension. Preliminary data from unpublished studies in our clinical laboratory.

Appendix Table.

A.

Study	n	Intervention	Study Duration (months)	Baseline LVMI (gm^{-2})	LVMI at Study End gm^{-2}	LVMI Change from Baseline (gm^{-2})	BP Change from Baseline (mmHg)	Participant Characteristics
Simpson *et. al*. (51)	23	BP lowering algorithm	12	65.9±11.9		4.7±7.3	-9.3/-6.1	LVH, BP normal range, Age 63, 87% male
Allay Study (52)	154	Aliskiren 300mg	9	76.8±16.5	71.9±15.7	4.9±11.7	-6.5/-3.8	↑BP, ↑LV wall thickness echo, Age 58, 73% male
Allay Study (52)	152	Losartan 100mg	9	78.0±17.4	73.2±14.3	4.8±11.9	-5.5/-3.7	↑BP, ↑LV wall thickness echo, Age 58, 73% male
Allay Study (52)	154	Aliskiren 300mg plus Losartan 100mg	9	79.1±15.9	73.3±15.0	5.8±10.9	-6.6/-4.6	↑BP, ↑LV wall thickness by echo, Age 58, 73% male
Alive Study (53)	62	Amlodipine 10mg plus Benazepril 40mg	12	80.3±15.7	70.1±16.7	10.2±12.4	-10/-5.7	↑BP, LVH by echo, Age 66, 50% male
Alive Study (53)	62	HCTZ 25mg plus Benazepril 40mg	12	79.6±15.1	72.8±20.0	6.7±11.0	-12.9/-3.5	↑BP, LVH by echo, Age 66, 50% male
Johnson *et. al*. (54)	20	Ramipril 10mg	3	82.0±18	73.0±19	9.0	-5/-4	Acute MI EF>40%, Age 58, 90% male
Study Average			*9.4*	*77.4±15.8*	*72.4±16.8*	*6.6±10.9*	*-8/-4.5*	

B.

Study	n	Intervention	Study Duration (months)	Baseline LVMI (gm^{-2})	LVMI at Study End (gm^{-2})	LVMI Change from Baseline (gm^{-2})	BP Change from Baseline (mmHg)	Participant Characteristics
Simpson *et. al*. (51)	12	Placebo	12	59.2±11.1		-2.0±6.7	-0.1/-0.2	LVH, BP normal range, Age 63, 87% male
Johnson *et. al*. (54)	15	Usual care	9	77.0±15.0	79.0±23.0	-2.0	8.0/2.0	Acute MI EF>40%, Age 58, 90% male
Study Average			*7.5*	*68.1±13.1*	*79.0±23.0*	*-2.0±6.7*	*4.0/1.0*	

Appendix Table. Influence of treatment (A) or no treatment (B) on MRI measured left ventricular mass index in published studies.