Study Title: Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK D) Trial

Internal Reference No: RH/BARACK D/0003

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Signatures:

Investigator Agreement

"I have read this protocol and agree to abide by all provisions set forth therein.
I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice."

Chief Investigator:	Investigator Signature:	Date:
Professor Richard Hobbs		24th March 2015
Senior Trial Manager (Oxford):	Investigator Signature:	Date:
Dr Ben Thompson	Ben Thompson	24th March 2015

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee.

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AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Ethics meeting response	2.0	21st March 2013	Ben Thompson	Removal of gift voucher and addition of travel expenses at request of Ethics committee and addition of "Lay Title".
Substantial Amendment number 1	3.0	7th March 2013	Ben Thompson	Synopsis – trial phase corrected. Synopsis and section 5.2 – primary endpoint clarified. Section 5.5 and Schedule – Blood sample detail updated. Section 5.6 – Home BP Measurement section updated following further expert clinical input. Section 6.3 – correction of Study Treatment Compliance monitoring detail. Section 8 – Statistics section updated and clarified. Schedule – Concomitant Medications monitoring schedule updated. Throughout – minor changes to correct typos and provide clarification.
Minor Amendment number 1	3.1	19th September 2013	Ben Thompson	Change of funder from NIHR School for Primary Care Research to NIHR HTA

				(confirmed as minor amendment by Ethics Committee co-ordinator).
Substantial Amendment number 2	4.0	26th November, 2013	Ben Thompson	Add two questionnaires to measure patient's overall quality of life
Substantial Amendment number 9	5.0	10th June, 2014	Ben Thompson	Alteration of search strategy and eGFR inclusion criterion to improve patient identification. Introduction of additional screening visit to improve patient identification. Improved patient invitation strategy. Minor clarifications throughout following feedback now trial is recruiting.
Substanital Amendment number 12	6.0	27th January, 2015	Ben Thompson	Alteration of inclusion criterion eGFR range to 30 – 50 ml/min/1.73m^2 to encompass larger than anticipated measurement error/fluctuations following initial recruitment. Change in sample size to reflect alteration to eGFR range. Update to causality assessment definitions in "Safety Reporting" section. Minor clarifications throughout.

Protocol amendments should be submitted to CTRG as sponsor before submission to the ethics committee or MHRA.

1 SYNOPSIS

Study Title	Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK D) Trial: a prospective randomised open blinded endpoint trial to determine the effect of aldosterone receptor antagonism on mortality and cardiovascular outcomes in patients with stage 3b chronic kidney disease.
Lay Title	A potential new treatment for kidney disease
Internal ref. no.	RH/BARACK D/0003
Clinical Phase	III
Trial Design	Prospective Randomised Open Blinded Endpoint (PROBE)
Trial Participants	Patients meeting the criteria for a diagnosis of CKD stage 3b (eGFR 30-44 ml/min/1.73m^2) according to NICE guidelines. Due to the higher than anticipated measurement error/fluctuations, the range was extended to 30-50 ml/min/1.73m^2 following the initial recruitment period.
Planned Sample Size	2910 participants will be randomised 1:1 to receive either routine care or the aldosterone receptor antagonist spironolactone 25mg OD on top of routine care.
Follow-up duration	3 years (excluding long-term follow-up)
Planned Trial Period	52 months (excluding long term mortality follow-up)
Primary Objective To determine the effect of aldosterone receptor antagonism on mortality and cardiovascular outcomes (onset or progression of cardiovascular disease) in	**Primary Endpoint**. Time from randomisation until the first occurring of death, first onset or hospitalisation for heart disease (coronary heart disease, arrhythmia, new onset/first recorded atrial fibrillation, sudden death, failed sudden death), stroke, or heart failure. Primary endpoints will be adjudicated by an independent endpoints committee blinded to treatment

patients with stage 3b CKD.	arm.
Secondary Objectives To determine the effect of ARA in patients on: Measures of cardiovascular haemodynamics Left ventricular function Decline in renal function Treatment costs and benefits Incidence of TIA To determine the safety of ARA in patients with stage 3b CKD.	**Secondary Endpoints** • Change in carotid-femoral pulse wave velocity from baseline to final visit – intensively phenotyped group. • Change in blood pressure annually and at final visit • Rates of hypotension (<100mmHg systolic or >20 mmHg systolic drop on standing) • Mean change in ambulatory blood pressure from randomisation to final visit (measured in mmHg) – intensively phenotyped group. • Changes in BNP. • Change in ACR • Changes in eGFR • Change in health status on EQ-5D-5L, ICECAP-A and Qol VAS • Cost effectiveness analysis • Transient Ischaemic Attack – as defined by the American Heart Association (2009) • Rates of adverse events ○ Rates of hyperkalaemia
Investigational Medicinal Products	Spironolactone

Form	Tablet
Dose	25mg OD
Route	Oral

2 ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials & Research Governance, University of Oxford
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DVS	Data Verification Site
eCR	Electronic Clinical Records
GCP	Good Clinical Practice
GP	General Practitioner
ICER	Incremental Cost Effectiveness Ratio
ICMJE	International Committee of Medical Journal Editors
ID	Identification
ITT	Intention to Treat
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health Research
PCCTU	Primary Care Clinical Trials Unit

PI	Principal Investigator
PROBE	Prospective Randomised Open Blinded Endpoint
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDD	Study Data Documents
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSC	Trial Steering Committee

Medical Abbreviations

ACE	Angiotensin Converting Enzyme
ACR	Albumin Creatinine Ratio
ARA	Aldosterone Receptor Antagonist
ARB	Angiotensin II Receptor Blockers
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes Mellitus
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate

ESRF	End stage Renal Failure
HbA1c	Glycated Haemoglobin
HRQL	Health Related Quality of Life
ICECAP-A	ICEpop CAPability measure for Adults
KDQOL-SF	Kidney Disease Quality of Life – Short Form Questionnaire
LDL	Low-density Lipoprotein
LV	Left ventricular
LVH	Left ventricular hypertrophy
LVSD	Left Ventricular Systolic Dysfunction
MDRD	Modification of Diet in Renal Disease
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NSAID	Non-steroidal Anti-inflammatory Drug
ONS	Office for National Statistics
PWV	Pulse Wave Velocity
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RAAS	Renin-angiotensin-aldosterone System
TIA	Transient Ischaemic Attack
VAS	Visual Analagure Scale

3 BACKGROUND AND RATIONALE

3.1 Background

Chronic kidney disease (CKD) is increasingly common, affecting around 10% of the entire population, associated with an age-related decline in renal function that is accelerated in hypertension, diabetes mellitus, obesity and primary renal disorders. While this high (and rising) prevalence is in part due to the ageing population, it is also a result of increases in hypertension and diabetes mellitus as well as a variety of primary renal disorders. CKD is defined and categorised in to 5 stages using glomerular filtration rate (GFR) as well as evidence of renal damage (imaging or proteinuria) in the early stages. The largest group, with over 50% of cases, is CKD stage 3, defined as a GFR of 30 to 59 ml/min/1.73m^2. Population studies have used the four variable Modification of Diet in Renal Disease (MDRD) formula to determine estimated GFR (eGFR) [1]. In patients aged 65 or over, up to 35% have an eGFR of less than 60 mls/min/1.73m^2 [2]. CKD prevalence appears to be increasing, rising from 10% to 13% over the last decade in one large cohort in the United States [3].

CKD and risk of cardiovascular disease

CKD is a major cause of increased mortality and morbidity through increased vascular events and progression to end stage renal failure (ESRF) [4]. These increased events result in CKD having high cost to healthcare systems, with the dialysis required in ESRF benchmarked as at the maximum acceptable cost effectiveness threshold for an intervention by most healthcare systems. However, the most important component of CKD in terms of mortality and morbidity is cardiovascular disease (CVD) [5]. There is a graded inverse relationship between cardiovascular risk and eGFR, independent of age, sex and other risk factors [6-9] or for creatinine [10]. While the cardiovascular risk of end-stage CKD is extreme, in public health terms the burden resides in early stage (CKD stages 1-3) disease, which is more prevalent, affecting around 40% of those over 70 years. When added to conventional risk factors, renal markers substantially improve risk stratification and CKD is therefore an important and under-recognised risk factor for CVD in the general population [11].

Although the risks of myocardial infarction and other manifestations of coronary artery disease are increased in CKD, the pattern of CVD is atypical, with a much greater incidence of heart failure and sudden cardiac death than in the general CVD population [12-14]. The

main pathological features in CKD that appear to determine this particular cardiovascular risk phenotype are:

1) Left ventricular hypertrophy and fibrosis accompanied by both systolic and diastolic dysfunction: there is a very high prevalence of left ventricular hypertrophy (LVH) in CKD, often accompanied by magnetic resonance imaging evidence of fibrosis, with LVH in over 30% of patients in stage 2 CKD (eGFR 20-29) and Stage 3 CKD (eGFR 30-59) and in 80% of patients at the start of renal replacement therapy [15-17]. Importantly, the increase in LV mass is a strong independent predictor of mortality in CKD (as in non-CKD states) and regression of LVH is associated with improved cardiac outcome.
2) Arterial wall thickening, stiffening and calcification (atherosclerosis). Large conduit arteries buffer the changes in pressure resulting from intermittent ventricular ejection. Stiffening of the arteries (loss of arterial compliance) leads to increased systolic and pulse pressure, and the resultant increase in afterload is a major cause of LVH and its progression over time [18-20]. Prospective studies have demonstrated that measures of aortic stiffness, such as aortic pulse wave velocity (PWV), and augmentation of central aortic pressure by early wave reflections (AIx), are strong independent predictors of all-cause and cardiovascular mortality in patients on dialysis [21, 22] and lowering aortic PWV, mainly by use of an ACE-inhibitor, is associated with an improved survival in dialysis patients [23]. In the latter study, the reduction in aortic PWV was associated with a parallel reduction in mean arterial and pulse pressure in survivors. In contrast, in those dying from cardiovascular events neither pulse pressure nor aortic PWV were significantly modified by ACE inhibition, although mean arterial pressure (the usual measure in clinical practice) was lowered to the same extent as in survivors. All these data suggest that arterial stiffness is not merely a marker of arterial damage but a potentially reversible factor contributing to mortality.

Therefore, although patients with CKD also suffer typical patterns of cardiovascular disease (coronary and peripheral artery atherosclerosis), the excess rates of cardiovascular events in CKD appear to relate more to vascular wall and ventricular changes then to atherosclerosis. The causes of atherosclerosis and LVH in CKD are complex but it is likely that as renal

function declines, the onset of sodium overload combined with hypertension, chronic anaemia, oxidative stress and activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system all contribute to this development of atherosclerosis, myocardial hypertrophy and fibrosis. Furthermore, many of these factors cause vascular endothelial dysfunction which as well as leading to atherosclerotic disease is a major functional component of arterial stiffening [16]. It is the early development of arterial stiffening, causing loss of arterial compliance, increased afterload and exposure of end organs to high phasic pressures, which is thought to be a key factor in the causation of left ventricular hypertrophy and small vessel damage in the brain and kidney [15].

Given this particular vascular pathophysiology, it is unsurprising that conventional cardiovascular risk factors are less predictive of outcomes in CKD than in the general population, [24] and much less predictive than eGFR and protein excretion [6, 9, 25], even after controlling for variables such as blood pressure [17]. Furthermore, interventions to reduce the increased cardiovascular risk in CKD have proved disappointing, with only limited evidence for traditional therapies in terms of cardiovascular outcomes. For example, the SHARP (Study of Heart and Renal Protection) trial [26] aimed to assess the safety and efficacy of reducing LDL cholesterol in more than 9000 patients with chronic kidney disease with a low dose of a statin (simvastatin 20 mg daily). The trial showed that lowering of LDL cholesterol safely reduced the risk of major atherosclerotic events in patients with CKD. However, the reduction in non-fatal myocardial infarction or coronary death was not significant. There are also limited therapeutic options for the prevention of further renal functional decline. Presently, the only interventions shown to reduce or prevent renal function decline for most patients with CKD is avoidance of renal damage (e.g. treating infections and avoiding NSAIDs in at-risk people), and effective treatment of risk factors, namely hypertension and diabetes mellitus (DM). In addition, drugs acting on the RAAS system offer modest additional benefits to blood pressure (BP) lowering alone in patients with diabetic nephropathy with proteinuria [27].

Better treatment options to provide protection from vascular events or delay progression of CKD are therefore urgently needed, especially given the increasing burden of the disease. Desirable clinical outcomes for any new therapies would be effective and safe reduction of

cardiovascular events and premature death and/or delay in progression of renal decline. The most important target CKD population for such preventive interventions are those with CKD stage 3b (eGFR 30-44 ml/min/1.73m^2), since this has high prevalence at 3%, represents progressive renal disease, and is associated with a 12 fold increase in cardiovascular disease (CVD), compared to those with eGFR above 60. In contrast, relative cardiovascular risk is 2 fold in CKD 3a (eGFR 45-59), though the prevalence is nearer 15% [6]. Important new candidates for potential cardio-protection in CKD are drugs that act on the aldosterone pathway of the RAA system.

Role of aldosterone in cardiovascular disease

Blockade of RAAS with Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) has shown mortality benefit in patients with chronic heart failure and in those with, or at high risk of, coronary artery disease [27-29]. The benefits are attributed to prevention of the multiple adverse effects of angiotensin II.

Aldosterone may also be an important mediator of cardiac and vascular damage in many disease states. Mineralocorticoid receptors are present in many tissues, including the brain, heart and blood vessels as well as the kidney and there is aldosterone production within these tissues [30]. These receptors may also be activated by circulating glucocorticoids in the presence of oxidative stress [31]. Local mineralocorticoid receptor activation by aldosterone leads to numerous pathological effects on the cardiovascular system including endothelial injury, inflammation, oxidative stress and fibrosis in the heart and vasculature, as well as the development of hypertension and autonomic dysfunction [30, 32, 33].

Rationale for ARA intervention to reduce cardiovascular events: In animal models, chronic aldosterone infusion and sodium loading results in myocardial fibrosis and ventricular hypertrophy in rats, while treatment with ARAs prevents aortic and myocardial fibrosis even in the absence of blood pressure lowering [33, 34]. In aldosterone treated stroke-prone hypertensive rats, spironolactone exerts a strong protective effect against the development of nephrosclerotic and cerebrovascular lesions [35]. In humans, studies have shown that primary aldosteronism is associated with a greater LV mass and higher risk of adverse cardiovascular events than control hypertensive populations and in patients after myocardial

infarction, plasma aldosterone concentration within the normal range predicts an adverse prognosis [36-38]. A recent study of subjects undergoing coronary angiography confirmed an independent association of plasma aldosterone levels with total and cardiovascular mortality [39].

Importantly, there are reliable and large studies that show that targeting aldosterone improves outcomes in established cardiovascular disease. In heart failure, a human disease state that like CKD is characterised by sodium overload and high levels of aldosterone production, the addition of the ARA spironolactone (RALES) in severe heart failure [40], or eplerenone (EPHESUS) [41] in post infarction heart failure and in mild to moderate chronic heart failure (EMPHASIS) [42], to standard therapy including ACE inhibition, reduced mortality by 30%, which therefore has a greater impact on mortality than both ACE inhibitors and beta-blockers. Further, treatment with ARAs in addition to ACE inhibitors prevents adverse LV remodelling after myocardial infarction and effectively reduces LVH in drug resistant hypertension [43]. The mechanisms of action of aldosterone include up-regulation of AT1 receptors and direct effects on fibroblast collagen synthesis as well as decreased matrix metallo-proteinase secretion [30]. An anti-fibrotic effect of ARA therapy may also be important. After myocardial infarction circulating markers of collagen turnover and fibrosis were reduced by ARA therapy [43] and in the RALES study myocardial collagen turnover was significantly reduced by spironolactone, and the fall in the marker of this index was related to the mortality benefit [44].

Role of aldosterone and potential for ARA in progression of renal disease

Angiotensin Converting Enzyme inhibitors *(*ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) appear superior to other blood pressure (BP) lowering drugs in slowing the progression of CKD, though the effect may be marginal [27]. These agents are therefore widely recommended in international guidelines as 'Reno-protection' for CKD patients, especially those with proteinuria or diabetes mellitus.

Renal specialists have avoided use of ARA drugs because of perceived risk of azotaemia and hyperkalaemia, though similar restrictions were applied to ACE inhibitors until outcome data were reported. There are, however, accumulating data on combined treatment with

ACE and ARAs to improve renal function in patients with CKD [45]. Animal experiments have shown that aldosterone can mediate renal injury and that ARAs, such as eplerenone, effectively reduce this [46-48]. Importantly, ARAs are similarly effective in low aldosterone models of CKD probably reflecting the importance of local (paracrine) aldosterone synthesis. [49] In humans, small studies have reported that adding ARAs to ACE inhibitors or ARBs reduces proteinuria and may slow progression of renal disease [50, 51]. From a safety perspective, even oligoanuric haemodialysis patients can tolerate spironolactone in low doses [52].

Diagnosis of CKD

The current UK standard estimating equation for GFR, Modification of Diet in Renal Disease study (MDRD) [53], results in an underestimation bias for higher levels of renal function. The more recent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [54] has been validated in general populations (excluding very elderly persons) [55, 56], as well as in different ethnic groups with appropriate equation modification (as per MDRD [57, 58]) and has shown greater accuracy. The MDRD equation has some utility in cardiac risk prediction [59, 60] but CKD-EPI based CKD staging improves risk prediction [61, 62] and this may influence policy in the United States with plans to switch to CKD-EPI for GFR reporting [63]. Evidence for the optimal GFR estimation method in primary care populations has not been systematically summarised. BARACK D will measure CKD using both criteria and will provide important new comparator data to inform this debate.

3.2 Rationale for Current Trial

CKD is common and increasing in prevalence. Cardiovascular disease is a major cause of morbidity and death in CKD, though of a different phenotype to the general CVD population. Currently, few therapies have proved effective in modifying the increased CVD risk or the rate of renal decline in CKD. There are accumulating data that aldosterone receptor blockers (ARAs) may offer cardio-protection and delay renal impairment in patients with the CV phenotype in CKD. The use of ARA in CKD has therefore been increasingly advocated and even termed the ‘renal aspirin’ [64]. To date, however, no large study of ARAs with renal or CVD outcomes is underway.

There are recent data that indicate beneficial effects of ARA therapy on surrogate markers for cardiovascular disease risk in patients with CKD, i.e. not just in those with established advanced cardiovascular disease, such as heart failure. This is important because there are presently limited therapeutic options to reduce overall cardiovascular risk in CKD, with modest effects of LDL reduction shown in the recent SHARP study [26] and sub-studies of large ACE inhibitor and statin trials only suggesting limited cardiovascular benefits in patients with early stage CKD [11, 28].

The Birmingham CRIB-2 study, in which two of the co-applicants to BARACK D were involved (Ferro & Townend), recently showed that spironolactone provided significant beneficial effects on validated intermediate cardiovascular end points of prognostic value, including LV mass and arterial stiffness [65]. In a placebo controlled double blind trial 112 patients with stage 2 and 3 CKD with good blood pressure control on established treatment with ACE inhibitors or ARBs were treated in an active run-in phase with spironolactone 25 mg once daily and then randomised to continue spironolactone or to receive a matching placebo. LV mass (cardiac magnetic resonance) and arterial stiffness (augmentation index, and aortic distensibility using MR imaging) were measured before run in and after 40 weeks of treatment. Compared with placebo, the use of spironolactone resulted in highly significant reductions in LV mass and arterial stiffness (pulse wave velocity, augmentation index and aortic distensibility), improved myocardial diastolic function and collagen turnover [65]. These clinical findings were attributed to a reduction in arterial and myocardial inflammation and fibrosis but may also be a function of the considerable human and animal evidence base that aldosterone receptor antagonism improves endothelial dependent vasodilatation and vascular nitric oxide bioactivity [66]. Further recent data have shown that ARA therapy in early CKD prevented progression of carotid intima-media thickness in haemodialysis patients [67]. These recent clinical data on the effect of ARA on intermediate vascular outcomes have resulted in calls for definitive trials [68 , 69]. In a recent review, the RALES Chief Investigator Bertram Pitt was cautiously optimistic that use of an ARA '…will reduce the mortality and morbidity associated with CKD, as well as prevent its progression to end-stage renal disease with all of its health-care and health-cost consequences" [68].

ARA therapy might therefore be an effective candidate for improved cardiovascular outcomes, through the prevention of aldosterone mediated vascular endothelial dysfunction as well as widespread cardiovascular inflammation, fibrosis, hypertrophy. Since spironolactone is well recognised as an effective anti-hypertensive agent for patients with hypertension, even when this is resistant to other drugs [70], the intensive phenotyping of blood pressure, LV function and arterial stiffness in BARACK D will enable modelling of the extent to which any positive results may be explained by any blood pressure differences between study arms. The 25mg dose of spironolactone used in BARACK D, and most clinical trials in which it has been involved, is similar to that used in hypertension and heart failure cases which are states characterised by excess cardiovascular risk and with a high probability of co-morbid CKD.

4 OBJECTIVES

Primary Objective	**Primary Endpoint**
To determine the effect of aldosterone receptor antagonism on mortality and cardiovascular outcomes (onset or progression of cardiovascular disease) in patients with stage 3b CKD.	Time from randomisation until the first occurring of death, first onset or hospitalisation for heart disease (coronary heart disease, arrhythmia, new onset/first recorded atrial fibrillation, sudden death, failed sudden death), stroke, or heart failure. Primary endpoint will be adjudicated by and independent endpoints committee blinded to treatment arm.
Secondary Objectives	**Secondary Endpoints**
To determine the effect of ARA in patients on measures of cardiovascular haemodynamics	• Change in blood pressure annually and at final visit • Rates of hypotension (<100mmHg systolic or >20 mmHg systolic drop on standing)
Left ventricular function	• Changes in BNP
Decline in renal function	• Change in ACR • Changes in eGFR
Treatment costs and benefits	• Change in health status on EQ-5D-5L • Cost effectiveness analysis
Incidence of TIA	• Transient Ischaemic Attack – as defined by the

	American Heart Association (2009)
To determine the safety of ARA in patients with stage 3b CKD	• Rates of adverse events ○ Rates of hyperkalaemia
Intensively Phenotyped Group Secondary Objectives	**Intensively Phenotyped Group Secondary Endpoints**
To determine the effect of ARA in patients on measures of cardiovascular haemodynamics	• Mean change in ambulatory blood pressure from randomisation to final visit (measured in mmHg) • Change in carotid-femoral pulse wave velocity from baseline to final visit

5 TRIAL DESIGN

5.1 Summary of Trial Design

A PROBE trial: Eligible patients, from a minimum of 120 practices recruited by 6 NIHR School for Primary Care Research departments and collaborating renal specialist groups, with previously recorded blood test results suggesting CKD stage 3b will be invited to take part in the study and randomised between the ARA spironolactone 25mg OD on top of routine care versus routine care. Blood pressure in both groups will be titrated (monitored and adjusted accordingly) by the physicians against NICE guideline standards and routine checks of electrolytes undertaken. Primary outcome will be time to changes in cardiovascular events.

A subgroup of participants will form the intensively phenotyped group in whom 24hr blood pressure and arterial stiffness will be monitored in detail to enable modelling of the extent to which positive results may be explained by any blood pressure differences between study arms. The secondary endpoints marked “intensively phenotyped group” in section 4 will determine the effect of ARA on 24h BP and PWV and on CKD 3b.

An internal pilot will be conducted which, in addition to testing study procedures and documentation, will test our assumptions regarding:

i) practice uptake of the invitation to participate
ii) rates of eligible CKD patients in practice populations on existing disease registers
iii) the response rates to patient invitations

iv) the rates of consent at baseline visits.

These early recruitment data will be used after 4 months to determine whether any changes are needed to overall recruitment strategy in the other centres eg whether numbers of practice sites need to be supplemented.

5.2 Primary and Secondary Endpoints/Outcome Measures

As listed in section 4.

5.3 Trial Participants

5.3.1 Overall Description of Trial Participants

Patients identified by their GPs or physicians who have been diagnosed with CKD stage 3b (eGFR 30-44 ml/min/1.73m^2 but widened to 30-50 ml/min/1.73m^2 following initial recruitement to encompass larger than anticipated measurement error/fluctuations) based on their recent blood tests. Patients declining to participate will be asked for consent to review their records for comparative data.

5.3.2 Inclusion Criteria

Participants must fulfil either the **Search 1** or **Search 2** criteria and all of the following:

Search 1

- Evidence of stage 3b CKD using the MDRD equation. This includes patients on the CKD register undergoing annual monitoring who have had two or more recent blood samples in the 30-50 ml/min/1.73m^2 range in the preceding 24 months, with a minimum of 6 weeks between tests
    - Where only one test has been performed in the preceding 24 months and is in the 3b range, the patient will be invited to attend the baseline visit at least 6 weeks from the initial test, the eGFR result from this can be taken as the second confirmatory test. Physicians will also be reminded that standard care suggests a second confirmatory test.

Search 2

- Patients with eGFR results in the preceding 24 months with a reading of25-29 ml/min/1.73m^2
- Participant is willing and able to give informed consent for participation in the study.

- Male or Female, aged 18 years or above.
- Able (in the recruiting physicians opinion) and willing to comply with all study requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study.
- Willing to provide contact details to the Research Team (encompassing recruitment centre and practice staff), for use at any time should the need arise, on trial related matters.
- If the participant is a female of child-bearing potential, they are willing to ensure effective contraception during the trial period.

5.3.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Female participants who is pregnant, lactating or planning pregnancy during the course of the study.
- Type 1 diabetes mellitus
- Terminal disease or felt otherwise unsuitable by their physician.
- Chronic heart failure clinical diagnosis or known LVSD with EF<40%.
- Recent myocardial infarction (within 6 months).
- Active cancer with less than 1 year life expectancy or in palliative care.
- Alcohol or drug abuse.
    - Suspected or known current hazardous or harmful drinking, as defined by an alcohol intake of greater than 42 units every week.
    - Suspected or known current substance misuse.
- Most recent potassium result >5.5 mmol/L, where not thought to be spurious, or previous raised potassium needing a reduced dose of ACEI/ARB or intolerance to spironolactone..
- eGFR >60 ml/min/1.73m^2 in the last 6 months and no identifiable reason for a temporary reduction in eGFR.
- Serum potassium at baseline over 5 mmol/L.
- Documented Addisonian crisis and/or on fludrocortisone.

- Documented symptomatic hypotension or baseline systolic blood pressure under 100mmHg.
- Recent acute kidney injury or admission for renal failure.
- ACR > 70 mg/mmol.
- Prescription of medications with known harmful interactions with spironolactone as documented in the British National Formulary including tacrolimus, lithium and cyclosporine.
- Any other significant disease or disorder which, in the opinion of the recruiting physician, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

5.4 Expenses and Benefits

All Participants will be reimbursed receipted, reasonable travel expenses.

5.5 Study Procedures

See Appendix B for details of study visits and procedures.

5.5.1 Screening and Eligibility Assessment

Potential subjects will be identified by searching routine electronic clinical records (eCRs) for patients with biochemical evidence of CKD stage 3b (eGFR 30-44 ml/min/1.73m^2 but widened to 30-50 ml/min/1.73m^2 following initial recruitement to encompass larger than anticipated measurement error/fluctuations) identified from one blood test in the last two years. The GP practice/renal specialist group will then send out an invitation letter inviting the patients to attend a baseline assessment and eligibility visit. A reply slip, pre-paid envelope and alternative contact details (e.g. e-mail address and phone number) will be provided for expressions of interest. Further to this through the invitation letter patients will be informed of an intention to carry out out phone calls within two weeks of the initial mail out. In order to prevent patients receiving unwanted phone calls they will be given opportunity to opt out of receiving this call via a phone number, postal reply slip in a prepaid envelope, or email. These calls will have dual purpose, being facilitated by a member of the research team; firstly to identify any concerns, anxieties, or questions the patients may have, as patients may not have been told they have "Chronic Kidney Disease" in consultation previously, and may have been given an alternative description for example "renal impairment", by their

physician. Secondly this will act as reminder call to patients giving them the opportunity to seek any further information they require with regard to the study, and will allow them to express interest in the study if they so wish. Approximately two weeks after the initial mail out a reminder letter will be sent to non-responders (including patients who have not been contactable by phone), along with, in a sub group, a feedback form for negative responders to complete should they wish.

A further search will be performed, again for the preceding 24 months, to identify patients with one reading in the eGFR range 25-29 ml/min/1.73m^2 (with no eGFR >60 ml/min/1.73m^2 in the last 6 months). Patients identified from these searches will be invited to a screening visit, using the same strategy as described above and, if found to be within the 30-50 ml/min/1.73m^2 range, asked to attend the baseline visit a minimum of 6 weeks later. If the patient's eGFR at this visit is not in the 30-50 ml/min/1.73m^{2}range but still within the wider range (25-29 ml/min/1.73m^2) the patient will be asked to return 3 months later for a repeat screening visit. This process will repeat throughout the recruitment period for as long as the patient is willing. The initial screening visit will consist of an informed consent procedure and a single renal profile blood test to encompass potassium levels and eGFR.

Initial calculations showed that, for the average practice, 180 patients are likely to meet Stage 3b CKD criteria. Assuming that around 80% of these patients are eligible and at least 50% of these are willing to take part (based on our experience recruiting to heart failure studies which have a similar age distribution as patients with CKD), then 72 patients may be recruited per practice, requiring 37 practices in total, but increased to 60 to allow for poor recruiting practices, or 15 practices per Townsend quartile of deprivation. To improve the representativeness of the trial population, the number of practices per recruiting centre will be increased to 20 with the intention of reducing these numbers by 50% and giving 30 practices per Townsend quartile of deprivation.

Following analysis of the initial patient recruitment data, 20 practices having mailed-out, the number of practices recruited by the 6 main NSPCR hubs was increased to a minimum of 300, to be initiated in a phased manner.

5.5.2 Informed Consent

Informed consent will be taken according to the PC-CTU Standard Operating Procedure (TM SOP7) “Obtaining Informed Consent”. A Patient Information Leaflet will be given by the Research Team to the patient following identification as a potential participant. This leaflet describes the purpose of the study, explains in detail what is required of participants, discusses potential risks and benefits, and provides contact details for the Research Team. The patient will be given adequate time to consider participation and read the leaflet, consulting with family or friends or any other independent advisors if needed, before seeing the Research Team for the first study consultation. At the baseline assessment informed consent will be taken, by a suitably qualified member of the Research Team, who will have received training in Good Clinical Practice and will be authorised to take consent by the Chief Investigator, delegated through the Principal Investigators where applicable. The Consent Form will be signed and dated both by the patient and the member of the Research Team taking consent. No study related procedures will take place prior to the signing of the Consent Form. It is clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give a reason for withdrawal. If the patient requires more time to make a decision on participation then a further consultation will be arranged. Participants will be asked to consent to being contacted by the Research Team in the event they fail to return for any of the trial follow-up. Consented participants will be asked to complete a Contact Details Form which includes all of their relevant contact details and indication as to their preferred method of contact by the Research Team. A copy of the signed Consent Form will be given to the participant and a further copy will be sent with the Contact Details Form to the Research Team. One copy of the consent will remain in the patient’s records at the GP practice/specialist renal group.

Consent will be taken to allow relevant sections of patient medical notes and data collected during the study may to be looked at by responsible individuals from the University of Oxford and collaborating partners, regulatory authorities (including the MHRA) and the NHS trust, where it is relevant to taking part in the trial.

Patients declining to participate will be asked if they are willing to provide separate written consent to review their records for comparative data. Data will be manually recorded in a separate CRF and transferred to the trial database.

5.5.3 Baseline Assessments

Potentially eligible patients will be invited to attend a baseline clinic at a trial practice where the trial will be explained. Informed consent will be obtained and baseline assessments performed.

A subset of patients will form the intensively phenotyped group who will undergo additional trial procedures as described below and in the procedure schedule (Appendix B). The intensive phenotyping of 24hr blood pressure and arterial stiffness in BARACK D will enable modelling of the extent to which any positive results may be explained by any blood pressure differences between study arms.

Following consent, all patients will have the following information taken and investigations performed at the initial visit:

- Age
- Gender
- Self-assigned ethnicity
- Residential postcode
- Clinical history
- Past medical history
- Current medication
- Smoking status
- Physical examination
- Weight
- Height
- Waist circumference (using validated method)
- Office BP measurement using a British Hypertension Society validated automated device after 5 minutes rest

- Venepuncture for routine haematology and biochemistry including renal function (including eGFR calculated using MDRD and CKD-EPI formulae, hepatic and bone profiles, full blood count, fasting blood sugar, HbA1c, lipids, and, where local labs allow, BNP). Tests will be performed by a suitably qualified member of the Research Team (e.g. G.P. or research/practice nurse). Where appropriate to the Department of Health guidelines (e.g. routine tests) funding will be provided by the CLRN. Any outstanding costs will be met by the funder. Where transport and local coordination allows (initially involving specific practices within the Oxford recruitment area) an additional blood sample will be taken and stored for future genetic and protein testing.
- Urinalysis using albumin:creatinine ratio (ACR). Where transport and local coordination allows (initially involving specific practices within the Oxford recruitment area) an additional urine sample will be taken and stored for future testing.
- 12 lead electrocardiograph – where practice equipment availability allows
- Quality of life questionnaires (EQ-5D-5L and KDQOL-SF questionnaire)
- Issue diary card to monitor side effects of trial medication
- Pregnancy tests will be performed on women of childbearing potential, if deemed necessary, at the discretion of the physician

In the intensively phenotyped group only:

- 24 hour ambulatory blood pressure estimation
- Pulse wave velocity measured with added cardiovascular software, using a validated applanation tonometry device [44]

Following the baseline visit, as with all laboratory analyses returned to the GP practice/specialist renal group under routine care as the same mechanisms will be utilised, blood results (which are normally returned within 1 working day) will be reviewed as soon as practically possible and no later than 72hrs after receipt, and the reports signed by the recruiting physician, or delegate (for example the patients own GP) who will record the results in the CRF including information on whether they are normal, abnormal but not clinically significant, or abnormal AND clinically significant. In the latter case the eligibility of the participants will be reviewed. The patients' General Practitioner (GP) will be referred to, in order to confirm eligibility, if:

- BP ≥ 180/110mmHg

- ACR ≥ 70 mg/mmol: to refer to GP to consider referral to nephrology specialist if patients have not been reviewed by nephrologist in the past 5 years since the diagnosis.
- ACR= 30-69 mg/mmol and BP ≥ 140/90 mmHg and NOT on either angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB): to refer to GP to consider for ACEI/ARB. Patients will be re-invited to participate in BARACK-D study after they have been on ACEI/ARB for at least 6 weeks.
- ACR= 30-69 mg/mmol with haematuria: to refer to GP for review.

Once eligibility is confirmed, the physician will randomise the patient (by accessing Sortition to obtain the randomisation code), produce the necessary prescription (in some instances through the patients own GP depending on standard practice mechanisms), if applicable, and issue to the patient where necessary, and book an appointment for the patient to return for the next visit after taking spironolactone for 7 days or 7 days following randomisation where assigned to the routine care arm.

5.5.4 Randomisation and Codebreaking

Block Randomisation with randomly varying block size will be performed in line with PC-CTU SOP ST05 “Randomisation and Blinding Procedures” and will be via the internet. Before recruitment commences the statistician in close conjunction with the trial management team conducts full validation and user testing the system to ensure the settings meets all the requirements specified in the randomisation specification document and approves it ‘going live’. The PC-CTU trial team, in conjunction with the PC-CTU trial statistician will be responsible for generating the randomisation schedule. The trial statistician ensures that the production of the randomisation schedule uses a reproducible process. Where appropriate, the randomisation schedule is checked and the outcome is documented at regular points throughout the trial by the statistician or designee to ensure that it has been followed. We will stratify by Practice ensuring a balance of the two arms within each practice. Patients will be randomised to treatment with spironolactone 25 mg once daily prescribed on top of routine care or to continue with routine care alone.

Randomisation will be performed using Sortition, PC-CTU’s in-house online randomisation system. It supports multiple studies and sites, a range of randomisation algorithms (simple,

block, stratified and minimised), unbalanced allocation ratios, blind or open trials, email notifications and site package statistics (for blind trials). It is secure, provides full audit logs and has been validated at algorithm and interface levels.

BARACK D is a PROBE trial where neither the patients nor physicians are blinded to the trial treatment but the primary endpoints will be assessed by an independent endpoint committee who are blinded to the treatment arm.

5.6 Subsequent assessments

Subsequent assessment will continue for both treatment arms for a further 36 months with follow up visits at weeks 1, 2, 4, 12, 26, and then every 13 weeks to 156 weeks. Windows either side of the visits will be two days for V1 and V2, 4 days at V3 and V4, 7 days for V5 and two weeks thereafter (all calculated from date of randomisation). Patients will also be flagged with ONS for long term follow up of mortality, with initial assessment at 5 years. Measurements at each follow-up visit will vary according to the schedule in Appendix B but will consist of a combination of:

- Office BP measurement, using a validated automated device;
- Venupuncture for creatinine & electrolyte levels;
- eGFR (MDRD and CKD-EPI estimations);
- Monitoring for side effects.
- Additional bloods for fasting blood sugar and HbA1c, BNP (where local labs allow), lipids,full blood count and samples for future analysis;
- QoL questionnaires;
- Issue of drug monitoring diary card.
- Urinalysis using albumin: creatinine ratio.
- Home blood pressure measurement recorded on diary card.

Additionally, in the intensive phenotyping sub-group:

- Pulse wave velocity and other arterial wall measurements;
- Ambulatory BP measurements.

Patients will also be supplied with a validated home blood pressure monitoring machine, along with an additional diary card and an instruction sheet, for 1 week every 6 months to document their self-assessed blood pressures. They will take 2 readings twice daily, i.e. 2 each morning and 2 each evening over the week. The readings for the first two days will be discarded and the mean of the remaining readings taken as the home blood pressure level.

Physicians will be strongly encouraged to manage blood pressure according to NICE CKD guidelines (2008): Blood Pressure Targets: CKD and ACR <70 mg/mmol: systolic blood pressure target of <140 mmHg (target range 120–139 mmHg) and diastolic blood pressure target <90 mmHg. Choice of antihypertensive agents: ACE inhibitors/ARBs if not already prescribed will be offered to people with hypertension and ACR ≥30 mg/mmol. We estimate that around two thirds of patients in BARACK D will be additionally taking an ACE inhibitor or ARB. The remainder, (people with CKD and hypertension and ACR <30 mg/mmol) will be offered a choice of antihypertensive treatment according to the NICE guidance on hypertension (NICE clinical guideline CG127 or its update) to prevent or ameliorate progression of CKD.

5.7 Definition of End of Trial

The end of trial will be defined as the date of the last visit for the last participant for the initial 3 year follow-up period. The trial will have an independent TSC and DMEC who will assess the study feasibility as the trial progresses and will have 'stop rule' authority to advise early termination of the trial in the event of safety concerns or futility either through poor recruitment, lack of events, or lack of any treatment effect. These 'stop rules' will be defined fully by the DMEC using the data from the internal pilot. A formal futility and feasibility analysis will be performed at 12 months by the DMEC to assess recruitment and retention which will determine whether criteria for the trial to proceed have been met.

5.8 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time in line with the following criteria:

1. Withdrawal from treatment (follow-up continued)
2. Complete withdrawal from trial excluding notes review (without participant involvement)

3. Complete withdrawal

In addition, the recruiting physician may discontinue a participant from the study treatment at any time if it is considered necessary for any reason including the following general rules:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation as judged by the trial physician
- Significant non-compliance with treatment regimen or study requirements
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Lost to follow up

In all cases, where possible, follow-up and inclusion in the intention-to-treat analysis, will continue.

Safety monitoring will include the following discontinuation rules:

Hyperkalaemia: In RALES, incidence of serious hyperkalaemia was 2% although patients with a creatinine of > 221 were excluded [17]. In EPHESUS, eplerenone caused a K^+ > 5.5 mmol/L in 10% of patients with a GFR of < 70 ml/min [30]. In CRIB-2 [22], during the open label run in only 1 patient was withdrawn due to hyperkalemia (K^+>6.5) and 6 had a K^+ of >5.5 mmol/L requiring dose reduction to alternate days. During the double blind phase only 2 patients on ARA and 2 on placebo had a K^+ of >5.5 mmol/L. For BARACK D, serum K^+ and creatinine will be checked at all visits. Patients will stop trial medication if systemically unwell due to intercurrent infection, diarrhoea or need for surgical intervention for any reason. Study drug will be re-started one week after the recruiting physician is satisfied recovery has taken place; serum K^+ and creatinine will be rechecked at weeks 1 and 2 following resumption. The protocol below will be followed in the event of hyperkalaemia:

- Serum potassium below 5.4 mmol/L, no action;
- Between 5.5-5.9, reduce dose to 25mg alternate days;
- 6.0-6.4 stop study drug and restart after 7 days on alternate days and if remains over 6.0 withdraw patient from trial treatment;
- >6.5 appropriate management and withdraw patient from trial treatment.

Deterioration of renal disease: If there is a deterioration of 20% in eGFR between vists then withdraw the patient from trial treatment and refer to specialist care;
Hypotension: If there is >20 mmHg systolic postural drop in blood pressure with symptoms during the trial and/or the systolic blood pressure drops to below 100 mmHg then the trial medication will be discontinued;

If withdrawn from the trial, the reason for withdrawal will be recorded on the trial withdrawal form and if due to an adverse event, the Research Team will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

5.9 Source Data

Source documents will include:

- Primary care electronic and paper records/outputs
- Reports from laboratory investigations
- Hospital correspondence
- Records of 24 hour ambulatory and home BP measurements
- Patient questionnaires
- Patient diary cards
- The CRF itself where there is no other written or electronic record of data

Clinical trial data is collected by the PC-CTU both electronically and in paper format, with a paper back-up for the data captured electronically. In this instance, supplementary data will be provided both electronically and in paper format. All Study Data Documents (SDDs) in paper format are date stamped upon receipt and tracked within a trial management database. A full pre-entry review ensures that all pages have been received, IDs are consistent and obvious errors/missing data are appropriately addressed prior to entry. All SDDs are double entered by two independent staff into the clinical database.

Data validation for all data entered into the clinical database, either manually or by electronic data capture from site, is achieved by programming study specific checks or through manual review of listing outputs. All discrepancies generated by electronic validation checks or

manual listings are reviewed by the Clinical Data manager. If clarification from a Research Site is required, the query is added to a Data Verification Site (DVS) Report, and subsequently issued. The Clinical Data Manager oversees the tracking of DVS reports until they are resolved, and application of any updates to the clinical database. Query status is tracked and monitored within the clinical database and feedback is provided regularly to the trial management team.

All documents will be stored safely in confidential conditions according to PC-CTU policies and SOPs. On all study-specific documents, other than the signed consent and contact details form, the participant will be referred to by the study participant number/code, not by name. Study documentation will be archived for a period of 5 years according to PC-CTU SOP TM24 “Archiving”.

Source data will be verified as appropriate by the PC-CTU Quality Manager or delegate using a risk based approach and will be defined in the monitoring plan.

5.10 Economic Analysis

A health economic analysis will be integrated into the trial.

Research Question: What is the cost-effectiveness of adding an ARA to usual care in CKD3b?

Data collection: The cost analysis will adopt an NHS perspective. Data on health care resource use will be collected from all trial patients, including all relevant hospital and GP consultations, medications, referrals, tests and equipment. Protocol-driven costs will be omitted. Where possible data on resource utilisation will be collected from electronic patient records, although it is likely that some resources will not be routinely documented in electronic format and data extraction from the medical notes will be supplemented by self-reported resource utilisation diaries filled out by the patients. Patients will be asked to complete the diaries for the period from weeks 0-12, 13-26 and every 13 weeks up to 152 weeks in which we will ask them to identify and record items relating to utilisation of any other relevant health care resources and patient burden, including time off work and foregone leisure and productivity time (i.e. absenteeism).

Where possible, we will value our items on health care resource utilisation using appropriate unit costs obtained from published sources, including the most recent version of Unit Costs of Health and Social Care and NHS Reference Costs. We will estimate unit costs which are not available from secondary sources using the approach used in the most recent version of Unit Costs of Health and Social Care.

Primary endpoint data will be collected within the trial. NICE recommends the use of preference-based health-related quality of life (HRQL) measures for the purpose of determining Quality Adjusted Life Years (QALYs) for economic evaluation. The use of quality-adjusted life years aims to capture the impact of disease progression and non-fatal events on quality of life in addition to any impact on survival. The EQ-5D-5L will be used to measure patient health-related QoL at baseline, 6 months, 12 months and annually thereafter. Patient's 5-dimension (mobility, self-care, usual activities, pain/discomfort, anxiety and depression) EQ-5D-5L health state classification at each trial time point will be converted into a utility score on a 0 to 1 scale where 0 is equivalent to dead, and 1, to perfect health. This conversion will be made using the new algorithm based on the UK value set currently being conducted by the Euroqol Group, if available at the time of analysis. If not available the current crosswalk algorithm provided by the EuroQol group and algorithm estimated by Dolan et al. derived from a survey of the UK population (n=3337) [71], will be used. Utility values in the tariff set range from no problems on any of the five dimensions in the EQ-5D-5L descriptive system (value=1.0) to severe or extreme problems across all five dimensions (value=−0.594) [71, 72]. The utility scores will be combined with within-trial survival data to estimate the quality adjusted life-years (QALY's) required for the cost-utility analysis.

Adding an ARA to usual care in the CKD3b population may improve the patient's overall quality of life which goes beyond health. The ICEpop CAPability measure for Adults (ICECAP-A), and Quality of Life Visual Analogue Scale (QoL VAS) will be used to measure CKD patient's overall quality of life, initially at baseline, 6 months, 12 months in a sub-population of the trial, and annually thereafter as funding permits. ICECAP-A is a self-reported measure of capability in adults (over 18 years). The measure covers attributes of wellbeing that were found to be important to adults in the UK. ICECAP-A comprises five attributes: settlement (feeling settled and secure), attachment (love, friendship and support),

control (independence), role (achievement and progress), and enjoyment (enjoyment and pleasure); and each factor has four response levels. Index values have been estimated using a best-worst scaling technique. QoL VAS is a vertical line from 0 to 100 with anchors of best and worst imaginable life for people to report their perceived quality of life today. Together with KDQOL-SF and EQ-5D, ICECAP-A and QoL VAS will provide a full picture of treatment effect on CKD, general health and overall quality of life.

Analysis:

Missing data:

The resource-use/cost and EQ-5D-5L data will be investigated to ascertain the extent of missing data and whether it is missing at random or not at random and/or censoring. If this amounts to more than 10% of the data collected missing at random, we will conduct multiple imputation using standard methods [73, 74].

Analysis of healthcare resource use, cost and EQ-5D-5L data

The focus of studying the healthcare resource use is to investigate how ARA plus routine care in CKD patients affects the health care costs. With the aim of the economic analysis to estimate how the costs of the intervention minus the difference in health care costs between the intervention and routine care group of patients balances against the health care benefits. A two-stage analysis of the healthcare resource use and their costs will be conducted. First the impact of the intervention on (1) all healthcare resource use/costs, (2) kidney disease specific healthcare resource use/costs, and (3) CVD related healthcare resources costs will be evaluated over the duration of the study (36-month period). Secondly, a regression framework that relates healthcare costs to baseline characteristics (age and gender), kidney disease stage, progression, other co-morbidities and CVD will be developed. The objective being to provide estimates of healthcare costs for different kidney disease stages and CVD events to inform the extrapolation model (see below). A similar regression framework approach will be used for the EQ-5D-5L tariff data at the different data collection time-points, again to inform the extrapolation model.

Within-trial cost-effectiveness analysis

The economic evaluation will compare the implementation of ARA plus routine care with routine care for CKD patients. We plan to conduct a within-trial economic analysis, then if the trial demonstrates clinical effectiveness, these within trial results will be used to extrapolate beyond the trial endpoint and model the likely life-time cost-effectiveness.

A within-trial cost-consequence analysis will initially be reported, describing all the important results relating to the health care resource use, costs and consequences of ARA plus routine care compared with routine care for CKD patients. Subsequently, a within-trial cost-effectiveness analysis will consider cost per additional primary endpoint (mortality and onset of CVD) averted, and a cost-utility analysis will determine cost per quality-adjusted life year (QALY) gained. The use of QALY's aims to capture the impact of disease progression and non-fatal events on health-related quality of life in addition to any impact on survival. Discounting at a rate of 3.5% will be applied. Results will be expressed in terms of incremental cost-effectiveness ratios (ICERs). Sensitivity analysis will test the robustness of the results. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings, to determine the impact of changes on results. Non-parametric bootstrapping and probabilistic sensitivity analysis will explore uncertainty in the confidence placed on the results of the economic analysis and cost effectiveness acceptability curves will be presented.

Lifetime cost-effectiveness analysis:

If trial results demonstrate clinical effectiveness, extrapolation beyond the trial period of 36 months will be undertaken using methods. The methods used will depend on the within trial data, but will either use parametric methods as set out by the NICE Decision Support Unit [74] or use a lifetime decision-model (developing a Markov model or adapting a CKD model that is currently being developed by researchers in HERC for the SHARP trial http://www.ctsu.ox.ac.uk/~sharp/) in order to determine the long-term cost-effectiveness of the intervention in terms of cost per QALY gained. This will be based on the individual patient data (using the results from the regression analyses outlined above) from the study and external data (where required). It will be carried out from an NHS and Personal Social Services perspective, to take into account health care costs and longer term social care costs of cardiovascular events and the impact on life expectancy, quality adjusted life expectancy. The model will be run over remaining patient lifetime, with costs and benefits

discounted at a rate of 3.5%. The lifetime cost-effectiveness analysis will be driven by the decision analytic model and the way treatment effects are propagated in the model. Extensive deterministic sensitivity analysis will be undertaken to assess the impact of changing the values of key parameters and will be used to explore the importance of modelling assumptions. Probabilistic sensitivity analyses will be conducted to deal with uncertainty in model parameters and cost-acceptability curves presented.

6 TREATMENT OF TRIAL PARTICIPANTS

6.1 Description of Study Treatment

Spironolactone has been selected as the trial ARA, to be used in the "Standard Care + Spironolactone" arm, since it has a large evidence base for effective treatment in hypertension and heart failure. There are considerable data from these trials on the drug's renal safety in high risk cardiovascular populations. Spironolactone is also the most cost effective ARA being available as a generic prescription. The modest cost of the prescriptions to the NHS will be treated as an excess treatment cost but this is not anticipated as likely to cause local barriers to recruitment.

Clinical trial labelling will not be required in accordance with Article 14 of the EU clinical trial directive.

6.2 Storage of Study Drug

Spironolactone 25mg will be prescribed on FP10 by the study recruiting physician using the physician's local pharmacies, processes and systems. As such, there will be no trial specific study treatment requirements. The trial treatment regime will be 25mg spironolactone once daily for the duration of the trial.

6.3 Compliance with Study Treatment

Study treatment compliance will be self-monitored throughout the trial using a medication monitoring diary card. For participants assigned to the spirolactone treatment arm, where appropriate, for example if compliance cannot be verified through patient report, prescription

uptake will also be verified by the patient's physician through database searches of prescription collection.

6.4 Accountability of the Study Drug

The study treatment will be prescribed on FP10 by the recruiting physician, or delegate (for example the patient's own GP, depending on standard practice mechanisms) and therefore no drug accountability processes will be necessary.

6.5 Concomitant Medication

If participants on the spironolactone arm develop medical conditions which require treatment with medications known to have harmful interactions with spironolactone as listed in the British National Formulary, then their prescription will be halted [75] but follow-up will continue.

6.6 Post-trial treatment

Throughout the trial the participant remains the responsibility of their GP practice/specialist renal group and therefore under normal care.

7 SAFETY REPORTING

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE or adverse reaction is any untoward medical occurrence in the participant administered the study medication which does not necessarily have to have a causal relationship with the study medication. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

7.1.2 Adverse Reaction (AR)

An adverse reaction is defined as an untoward and unintended response to the study medication. The phrase "responses to a medicinal product" means that a causal relationship

between the study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Causality of all cases will be judged by the site physician.

7.1.3 Serious Adverse Event (SAE)

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

- Results in death,
- Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events. NOTE: Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

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

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

7.1.4 Serious Adverse Reaction (SAR)

An adverse event that is both serious and, in the opinion of the reporting recruiting physician, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

7.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product).

7.1.6 Causality and Expectedness

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Definitely related: the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

Probably related: the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP.

Possibly related: although a relationship to the IMP cannot be completely ruled out, the natur of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Unrelated: where an event is not considered to be related to the IMP.

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the IMP.

7.2 Procedures for Recording Adverse Events

All site staff are appropriately trained in the procedures to follow and the forms to use by the PC-CTU prior to study initiation. Regular central monitoring for all studies and site monitoring, as determined by the trial specific risk assessment, will be used to ensure that all adverse events are identified and acted on appropriately.

All adverse events will be recorded at trial visits for the initial 6 months of follow-up by the member of the Research Team conducting that visit for the previous inter-visit period. Following this initial 6 month period, only the following AEs will be monitored by the member of the Research Team performing that visit in accordance with PC-CTU SOP TM19 "Pharmacovigilance":

- Enlargement of breasts in men and women
- Erectile dysfunction
- Irregular periods
- Vaginal bleeding after the menopause
- Deepening of the voice in women, change in the tone of voice in men
- Excessive hair growth
- Tiredness
- Palpitations
- Numbness and tingling

AEs considered related to the study medication as judged by a medically qualified member of the Research Team or the Sponsor will be followed until resolution or the event is considered stable, clinically insignificant or asymptomatic. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the recruiting physician's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment and, if treatment is withdrawn, the reason will be recorded. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

- The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.
- The relationship of AEs to the study medication will be assessed by a medically qualified member of the Research Team.

7.3 Reporting Procedures for Serious Adverse Events

7.3.1 Reporting

All SAEs occurring during the study, either observed by the recruiting physician or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF and forwarded by the site to PC-CTU, using the "PC-CTU SAE Report Form" following assessment for seriousness and relatedness by the site clinician. This form will be completed and faxed to the PC-CTU using the number quoted on the report form. The form should also be emailed to the PC-CTU using the email address quoted on the form. As a minimum, the following information will be recorded:

- Description
- Date of onset
- End date
- Severity
- Assessment of relatedness to study medication
- Other suspect drug or device
- Action taken.

Follow-up information should be provided as necessary.

SAEs must be reported to the PC-CTU within 24 hours of discovery or notification of the event. The PC-CTU will acknowledge receipt of the SAE Report Form using the PC-CTU 'SAE Form Receipt' document. This receipt will be emailed and faxed to the site physician. If the site physician does not receive a receipt within 24hrs of them sending the report (during office hours), they should re-send the SAE Report Form to the PC-CTU by email or fax and telephone ahead.

The documentation will be reviewed by the Quality Assurance Manager (or nominated person) and the 'SAE Checklist' will be completed and retained by the PC-CTU. Following the initial check of the report, any additional information will be requested, and the CI or their medically qualified designated representative will review and evaluate the report for seriousness, causality and expectedness, within three additional working days. In the event of a SUSAR the reporting timelines stated below will be followed. If there have been two

assessments of causality made, the site physician's assessment cannot be downgraded. Where there is a discrepancy the worst case assessment is used for reporting purposes.

The PC-CTU will also ensure that SAE reports are reviewed by the Data Monitoring and Ethics Committee (DMEC), at least twice during the study at face-to-face meetings. Further correspondence will take place at least quarterly.

Additional information, as it becomes available, will also be reported on the SAE Report Form (i.e. updating the original form) and returned to the PC-CTU by email or fax as above.The SAE Report Form will be filed in the Trial Master File according to PC-CTU SOP TM12 'Trial Master File', with copies filed in the patient's notes, the Case Record Form file and the Investigator Site File.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy will be recorded and followed up for congenital abnormalities or birth defects until the end of the trial at which point standard care will recommence.

Trial Managers complete regular reports reviewed by the senior members of the PC-CTU. One of the metrics contained within this reporting is the number of SAEs reported and the cumulative number of SAEs for each study. Any concerns identified will be immediately raised with the Chief Investigator and may be tabled for discussion at the regular PC-CTU Management Committee meetings or referred to the study's DMEC for review. The DMEC also monitors the frequency and pattern of events reported as part of its independent oversight of the trial.

7.4 SUSAR Reporting

In collaboration with the PC-CTU, CTRG and DMEC, the Trial Management group will report all SUSARs to the Competent Authorities (MHRA in the UK), the Research Ethics Committee concerned and Host NHS Trusts.

All SUSARs will be reported electronically to the MHRA within the timelines defined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) using the following e-SUSAR reporting link via the MHRA website: https://esusar.mhra.gov.uk/

To use the e-SUSAR link, a copy of the MHRA approval letter for a new trial should be sent to the Sponsor so that they can log the trial on to the e-SUSAR system that they maintain. The Sponsor will then send the CI, and anyone else that has been nominated, the log-in password and details for them to view the trial and report SUSARs directly on to the system.

A fatal or life-threatening SUSAR is reported as soon as possible to the MHRA, the competent authorities of any EEA State other than the United Kingdom in which the trial is being conducted, and the relevant Ethics Committee not later than 7 days after the Sponsor was first aware of the reaction. Any additional relevant information should be reported within 8 days of the initial report.

A SUSAR which is not fatal or life-threatening is reported as soon as possible and in any event not later than 15 days after the PC-CTU is first aware of the reaction.

The Trial Management group will also inform all members of the Research Team concerned of relevant information about SUSARs that could adversely affect the safety of participants.

Further details are available at https://esusar.mhra.gov.uk/about/

7.5 Data Monitoring and Ethics Committee

BARACK D will have a Data Monitoring and Ethics Committee, who will report to and advise the Trial Steering Committee who, in turn, will report to and advise the Trial Management group. Both the DMEC and TSC will have independent chairs and 'stop rule' authority to advise early termination of the trial in the event of safety concerns or futility wither through poor recruitment, lack of events, or lack of any treatment effect ('stop rules' to be defined by DMEC). All committees will convene regularly prior to, during, and following the trial. Together, the responsibilities of the committees are:

- To safeguard the safety, rights and well-being of the trial participants.
- To systematically monitor the trial data and review any analysis as outlined in the Statistical Analysis Plan or as requested by the TSC.

- To make recommendations to the TSC as to whether the trial is operating as expected or if there are any ethical or safety reasons why the trial should not continue.
- To consider data emerging from other related studies and its potential impact on the trial, if requested by the TSC.
- To pick up any trends, such as increases in un/expected events, and take appropriate action.
- To seek additional advice or information from investigators where required.
- To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment.

7.6 Developmental Safety Update Report

In addition to the expedited reporting above, the CI shall submit once a year, throughout the clinical trial within 60 days of the date of the anniversary of the CTA or on request, a Developmental Safety Update Report to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and sponsor in line with PC-CTU SOP TM19 “Pharmacovigilance”.

8 STATISTICS

8.1 Description of Statistical Methods

The primary analyses will be conducted on all randomised participants, applying the principle of intention-to-treat (ITT), as far as is practically possible, given any missing data. Specifically, the participants will be analysed in the groups to which they were allocated. The primary outcome will be analysed using Cox proportional-hazards method, adjusting for practices. Results will be presented as hazard ratios with 95% confidence intervals and associated two-sided P-values. To test the robustness of the result, a sensitivity analysis will be carried out, using the same method, adjusting the following pre-specified baseline prognostic factors: diastolic and/or systolic blood pressure above or below NICE target, type II diabetes and coronary artery disease.

Same approach will be repeated for individual components of the primary composite endpoint and all-cause mortality as secondary analyses. Analyses for other outcomes will be carried out using multiple log-binomial regression models for binary data and linear mixed effect model for continuous data collected over time.

Assumption of proportional hazards will be examined and if any of the assumptions were violated, a suitable alternative survival method will be considered. Similarly, alternative methods will be considered if any violation of assumptions is detected in any of the aforementioned methods for other outcomes.

Adverse effects will be tabulated according to randomised group assignments and the proportions will be compared using Fisher's exact test.

A full detailed analysis plan, including approach of handling missing data, subgroup analyses, and sensitivity analyses, and a plan for interim analysis will be prepared before the first interim analysis by a statistician who is independent from the study. All analyses will be performed by the trial statistician and validated by a separate statistician. A senior statistician will provide supervision to all statistical aspects in the trial.

8.2 The Number of Participants

A UK representative spread of practices will be achieved by stratifying practice postcode location into quartiles of Townsend Deprivation Score and selecting practices that agree to take part sequentially until each deprivation quartile practice target is reached. This strategy will most probably ensure that populations selected will also be representative for ethnicity but the sequential practice selection strategy will be examined after ten practices have been selected for each deprivation quartile to ensure practices serving high proportions of ethnic minorities are including in the final five places, if this has not already occurred in the earlier selections.

The estimate for the cardiovascular (CV) event rate (defined by hospitalisation for coronary heart disease, heart failure, ischemic stroke and peripheral arterial disease) and total mortality rate in patients with CKD 3b (eGFR 30-44 ml/min/1.73m^2) being 11.29 and 4.76 per

100 person years respectively gives a combined event rate of 16.05 per 100 person years [5]. In those with eGFR in the range 45-50 ml/min/1.73m^2, the event rate is conservatively estimated to be 0.667 times as high (10.7 events per 100 person years[76] and we assume half the participants will fall in this range giving an overall event rate of 13.4 events per 100 person years. To detect a 20% relative risk reduction in death or cardiovascular events within 3 years in the intervention group as compared with the control group (i.e. hazard ratio=0.8) with a two sided significance of 0.05, 1455 participants per arm are required seeking 90% power and assuming 10% drop out rate per year.

We have decided to power the trial conservatively on a 20% risk reduction since this proposed treatment effect is around half the risk reduction observed in the ARA mild heart failure trial (EMPHASIS). The estimated hazard ratio in the EMPHASIS eplerenone versus placebo mild heart failure trial (only mildly symptomatic patients were included) were 0.63 (CI 0.54-0.74, p<0.001) for the composite endpoint of death from CV causes or hospitalisation for heart failure at the median follow up of 21 months. The conservative upper CI for the treatment effect was 26% reduction. The placebo CV event rate in EMPHASIS trial was similar to observational data on CV events in CKD 3b patients [5].

8.3 The Level of Statistical Significance

5% significance level is used to calculate number of patients required for the trial.

8.4 Criteria for the Termination of the Trial.

A formal futility analysis will be performed at 12 months from first study recruitment with possible termination for safety or futility. “Stop rules” will be defined fully by the DMEC.

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

The missing at random assumption will be tested as far as is possible by analysing each baseline covariate in a regression model to determine which if any are associated with missingness.

All baseline covariates are expected to be observed. Baseline values will be summarised for those who did and did not complete follow up measurements to describe any characteristics related to missingness that are able to be observed.

We will be analysing our data using an intention to treat analysis. All randomised patients will be included in the analysis, assuming non-informative censoring for those withdrawn from the study or lost to follow-up for the primary analysis.

During statistical data review and analysis, any anomalies in the data will be investigated and discussed with the trial management team. The data investigation will be broad and flexible and focus on variability of the data, consistency, dispersion, outliers, inliers, relationships between variables and relationships over time. The statistical data review will be fully documented with all the output dated. If fraud is proved, fraudulent data will be removed from the analysis.

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

We do not anticipate any deviation from the statistical plan outlined above. However, provision for alternative methods and changes to analyses will be included in the statistical analysis plan as specified in the PC-CTU's SOP ST01.01 "Statistical Analysis Plan".

8.7 Inclusion in Analysis

We will be analysing our data using an intention to treat analysis. All randomised patients will be included in the analysis, assuming non-informative censoring for those withdrawn from the study or lost to follow-up for the primary analysis.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution (Oxford University BARACK D Research Team) and the regulatory authorities to permit trial-related monitoring, audits and inspections. Individual GP practices/specialist renal groups will be required to give access to those bodies described above and this will be outlined in the Site Agreement.

10 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and PC-CTU Standard Operating Procedures. The PC-CTU has in place procedures for assessing risk management for trials which will outline the monitoring required. The monitoring will be carried out by the PC-CTU Quality Assurance Manager or equivalent. The investigators and all trial related site staff will receive appropriate training in Good Clinical Practice and trial procedures.

Regular monitoring will be performed according to ICH GCP using a risk based approach. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents where possible. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The Study Monitor may also assess SAE's.,

The PC-CTU Trial Management Committee will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMC will be comprised of individuals responsible for the trial's day to day management (e.g the CI, trial manager, statistician, data manager) and will meet regularly throughout the course of the trial.

A Trial Steering Committee (TSC) will be convened to provide overall supervision of the trial and ensure its conduct is in accordance with the principles of GCP and the relevant regulations. The role of a Trial Steering Committee is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The Trial Steering Committee will agree the trial protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial. The TSC will consist of members who are independent of the investigators, in particular an independent chairperson.

An independent Data Monitoring and Ethics Committee (DMEC) will review the accruing trial and safety data to ensure trial site staff and participants are aware of any relevant safety information and to determine whether any reasons exist for the trial to be discontinued.

11 SERIOUS BREACHES

In line with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended 2006 and 2008), PC-CTU SOP TM25 “Related Deviations and Serious Breaches” contains a requirement for the notification of "serious breaches" to the MHRA within 7 days of the sponsor becoming aware of the breach.

A serious breach is defined as “a breach of the conditions and principles of Good Clinical Practice (GCP) in connection with the trail; or the trial protocol (as amended from time to time) which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial.

Possible serious breaches may be identified by members of the study team through various means including meetings, site monitoring and audit visits. Members of the team may also receive allegations of serious breach of GCP directly or indirectly from whistle blowers or complainants from within or outside the University. Information in written form will be retained and where communication is verbal, study staff will generate a written record. The possible breach will then be recorded and discussed with the relevant trial team members.

Information regarding possible serious breaches will be treated as confidential with details being released to staff on a need-to-know basis. All individuals interviewed during the investigation will be expected to respect this confidentiality. A specific folder will be created both electronically and within the TMF and will include all relevant documentation and copies of emails, referencing the addressee, the date and time of the email.

Once information has been received, the subsequent procedure will be followed:

- Data will be collated

- The study team, involving relevant staff e.g. QA manager, will review MHRA guidance to assess whether the event constitutes a serious breach. All relevant information and decisions made shall be recorded on the PC-CTU Serious Breaches Assessment Form.
- If, following assessment, the event is considered a serious breach, the CI will confirm the decision and contact CTRG. Day 1 as regards to the reporting timelines will be from the agreement of the characterisation between the CI and CTRG. The event will then be reported to the MHRA by the head of CTRG or delegate within seven days and provide follow-up to the CI and study team.
- PC-CTU staff will immediately review the related documentation and systems to assess the possible cause or systemic failure in order to inform an action plan.

A Corrective Action Preventative Action Plan will be drawn up by the study team in collaboration with CTRG.

12 ETHICS

12.1 Declaration of Helsinki

The Research Team will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki 1964 (and subsequent revisions).

12.2 ICH Guidelines for Good Clinical Practice

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

12.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), the Medicines and Healthcare Regulatory Authority (MHRA in the UK), the relevant NHS Research and Development Departments and host institution for written approval. The Research Team will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4 Participant Confidentiality

Ensuring patient confidentially is an established and robust process within the PC-CTU. All Staff adhere to the principles of Good Clinical Practice (GCP) and the Data Protection Act, 1998.

It is the PC-CTU's preferred procedure that patients will only be identified on study documents by use of a unique study ID which cannot be used to identify individual participants. Where this is not possible specific consent will be taken and participants contact details will be used, in order of their preference e.g. when necessary to make follow-up phone calls or emails. All study documents such as case report forms (CRFs) holding patient information are held securely with restricted access either electronically or in paper format.

CRFs and all other documents holding identifiers are anonymised as soon as possible with the process of management being outlined in detail within the ethics application and in trial specific procedures. The holding of patient identifiers is noted as a trial specific vulnerability in the risk assessment and the Chief Investigator (CI) is required to clearly outline how such risks will be managed, to minimise both likelihood and impact and how the success of the management will be monitored and assessed.

12.5 Other Ethical Considerations

We do not believe that there are any significant ethical issues related to this trial. Site staff will be fully trained in GCP according to their study role.

13 DATA HANDLING AND RECORD KEEPING

All Data Management functions will be performed in line with PC-CTU SOP DM1 "Data Management". A Data Management Plan (DMP) is in place for all PC-CTU studies outlining in detail the study specific procedures that are in place to ensure that high quality data are produced for statistical analysis. The DMP is reviewed and signed by all applicable parties including the Trial Manager and the Trial Statistician prior to the first patient being enrolled.

Clinical trial data is collected by the PC-CTU both electronically and in paper format. All Study Data Documents (SDDs) in paper format are date stamped upon receipt and tracked within a trial management database. A full pre-entry review ensures that all pages have been

received, IDs are consistent and obvious errors/missing data are appropriately addressed prior to entry. All SDDs are double entered by two independent staff into the clinical database.

Data validation for all data entered into the clinical database, either manually or by electronic data capture from site, is achieved by programming study specific checks or through manual review of listing outputs. All discrepancies generated by electronic validation checks or manual listings are reviewed by the Clinical Data manager. If clarification from a Research Site is required, the query is added to a Data Verification Site (DVS) Report, and subsequently issued. The Clinical Data Manager oversees the tracking of DVS reports until they are resolved, and application of any updates to the clinical database. Query status is tracked and monitored within the clinical database and feedback is provided regularly to the trial management team.

Prior to database lock, dataset review is undertaken by the Information System Manager and the Trial Statistician. All critical data items are 100% checked against original SDDs to ensure accuracy and an error rate is established across all fields to ensure a consistently accurate dataset.

An independent review of the quality of the data being produced by each PC-CTU trial is provided by its Data Monitoring and Ethics Committee throughout the study.

14 FINANCE AND INSURANCE

The trial is funded by the National Institute for Health Research Health Technology Assessment Programme.

14.1 Compensation for harm

Negligent Harm: Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the Research Sponsor will be covered by the University of Oxford. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

Non-Negligent Harm: Indemnity and/or compensation for harm arising specifically from an accidental injury, and occurring as a consequence of the Research Subjects' participation in the trial for which the University is the Research Sponsor will be covered by the University of Oxford.

15 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was Funded by the National Institute for Health Research Health Technology Assessment Programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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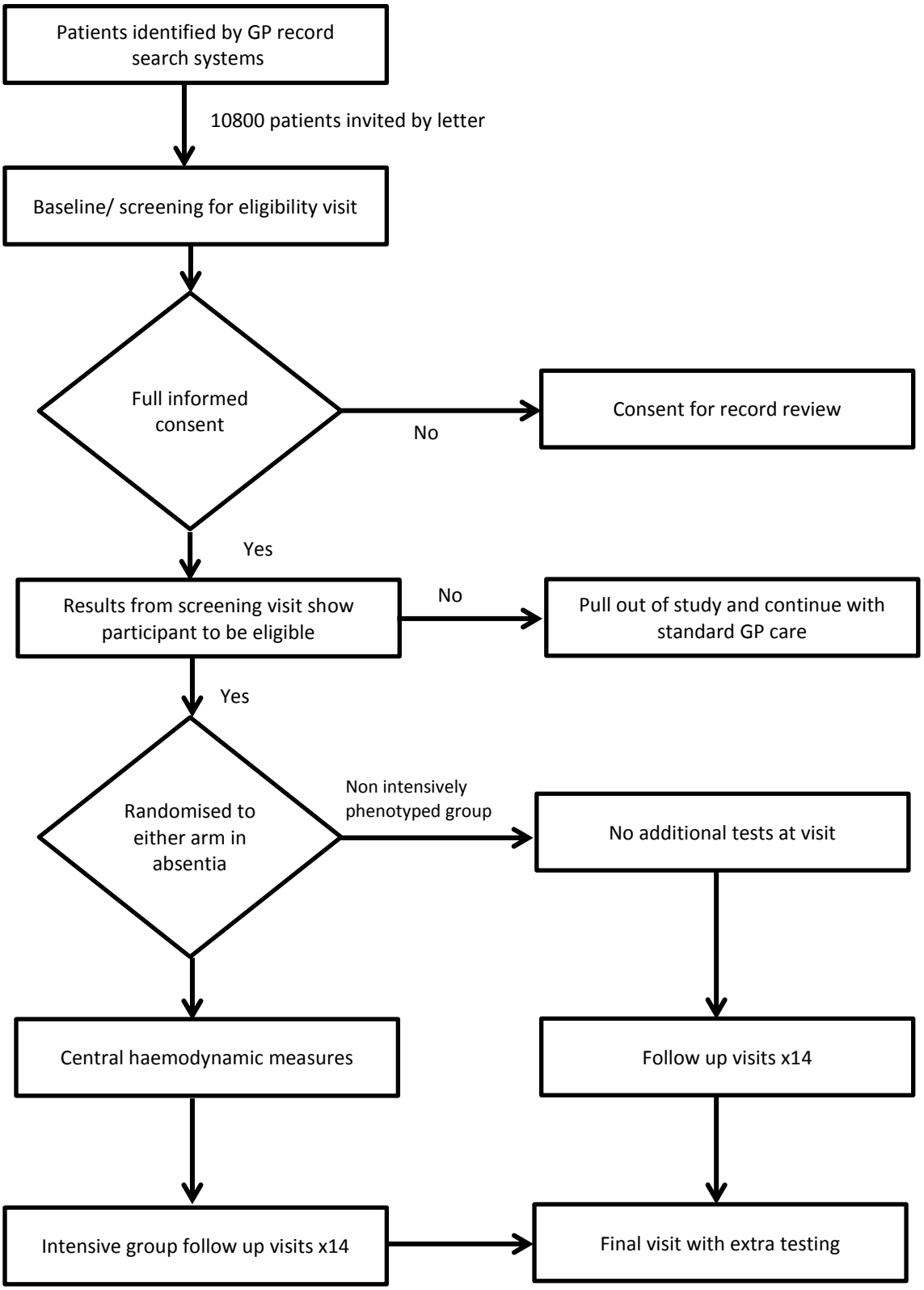
APPENDIX A: STUDY FLOW CHART



17 APPENDIX B: SCHEDULE OF PROCEDURES

		Treatment and Follow-up																
Week	S	B	0	1	2	4	12	26	39	52	65	78	91	104	117	130	143	156
Visit		V		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Valid informed consent	Renal profile screening visits where applicable + Informed consent	x	Randomisation *in absentia* and prescription produced once blood results received															
Full demographic details		x																
Medical history		x																x
Clinical history		x																
Concomitant medications		x					x	x		x		x		x		x		x
Weight, Height, Waist/Hip		x																x
Physical examination		x																
Office BP measurement		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Home BP measurement							x			x		x		x		x		x
KDQOL-SF questionnaire		x						x		x				x				x
QoL EQ-5D-5L questionnaire		x						x		x				x				x
ICECAP-A questionnaire		x						x		x				x				x
QoL VAS		x						x		x				x				x
Diary card (medication monitoring)		x					x	x		x		x		x		x		x
Diary card (Health Economics)		x					x	x	x	x	x	x	x	x	x	x	x	x
Adverse event monitoring		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine ACR		x																x
12 lead ECG		x																x
Blood Tests for:																		
Full blood count		x																x
Renal profile		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Liver function test and bone profile		x						x		x				x				x
Lipids		x						x		x				x				x
HbA1c		x						x		x				x				x
Fasting Blood sugar		x						x		x				x				x
BNP (where local labs allow)		x						x		x				x				x
Future analysis (where applicable)		x								x				x				x
Intensively Phenotyped Group Only																		
Pulse Wave Velocity		x						x		x				x				x
24h ambulatory BP estimation		x						x		x				x				x

For visit windows see section 5.6.