Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme inhibitor (ACEi) / Angiotensin Receptor Blocker (ARB) withdrawal in advanced renal disease;

The STOP-ACEi Trial

STOP-ACEi TRIAL PROTOCOL: VERSION 3.0, 14th May 2014

Sponsor:	**Hull and East Yorkshire Hospitals NHS Trust (Ref. No.: R1578)**
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	Hull and East Yorkshire Hospitals NHS Trust
Coordinating Centre:	**Birmingham Clinical Trials Unit (BCTU)**
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MRC Medical Research Council

NHS National Institute for Health Research

Efficacy and Mechanism Evaluation Programme

Birmingham Clinical Trials Unit

Hull and East Yorkshire Hospitals NHS Trust

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STOP-ACEi Trial Office

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Safety Reporting

Fax SAE Forms to: 0121 415 9135

This protocol describes the STOP-ACEi trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the STOP-ACEi trial. The trial will be conducted in accordance with the protocol and Good Clinical Practice (GCP). Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Chief Investigator and Sponsor and Statistician Signatures

The Chief Investigator and the Sponsor have discussed this protocol. The Investigators agree to perform the investigations and to abide by this protocol.

The Investigator agrees to conduct the trial in compliance with the approved protocol, Good Clinical Practice (GCP), the UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition; as amended) and other regulatory requirements as amended.

Chief investigator

Professor Sunil Bhandari
Hull and East Yorkshire
Hospitals NHS Trust

Signature _____ Date _____

Sponsor Representative

James Illingworth
Hull and East Yorkshire
Hospitals NHS Trust

Signature _____ Date _____

Trial Statistician

Natalie Ives
BCTU
University of Birmingham

Signature _____ Date _____

Principal Investigator Signature Page

Principal Investigator:

I have read and agree to the protocol, as detailed in this document. I agree to adhere to the protocol as outlined and agree that any suggested changes to the protocol must be approved by the Trial Steering Committee prior to seeking approval from the Main Research Ethics Committee (MREC) and/or Regulatory Authority.

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, local regulations (as applicable) and the trial protocol and I agree to conduct the trial according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial.

Principal investigator

<insert PI name>

Signature	Date

Name of Institution

<insert PI institution>

The Principal Investigator should sign this page and return a copy to the STOP-ACEi Trial Office.

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List of Abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitor
ACR	Albumin:Creatinine Ratio
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
AR	Adverse Reaction
BCP	Biochemical Profile
BCTU	Birmingham Clinical Trials Unit
BMI	Body Mass Index
BNF	British national formulary
BP	Blood Pressure
CI	Chief Investigator
CKD	Chronic Kidney Disease
CCRN	Comprehensive Clinical Research Network
CLRN	Comprehensive Local Research Network
CRF	Case Report Form
CRP	C-Reactive Protein
CSG	Clinical Study Group
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DIBD	Development International Birth Date
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ESA	Erythropoietin Stimulating Agent
ESRD	End Stage Renal Disease
EudraCT No.	European Union Drug Regulating Authorities Clinical
FBC	Full blood count
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GP	General Practitioner
Hb	Haemoglobin
ICF	Informed Consent Form
IMP	Investigational Medicinal Product

ISRCTN	International Standard Randomised Control Trial Number
KDQOL-SF	Kidney disease quality of life short form
KRC	Kidney Research Consortium
LVEF	Left ventricular ejection fraction
MAP	Mean Arterial Pressure
MCH	Mean Cell Haemoglobin
MCV	Mean Cell Volume
MDRD	Modification of Diet in Renal Disease
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical research council
MRD	Minimum Relevant Difference
MREC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
NICE	National Institute for Health and Care Excellence
PCR	Protein:Creatinine Ratio
PI	Principal Investigator
PIS	Participant Information Sheet
NT-proBNP	N Terminal Pro-B-type Natriuretic peptide/Pro Brain Natriuretic Peptide
RAS	Renin-Angiotensin System
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Summary & Trial Schema

Title	**Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme inhibitor (ACEi) / Angiotensin Receptor Blocker (ARB) withdrawal in advanced renal disease; The STOP-ACEi trial**
Short title/ Acronym	**STOP-ACEi**
Type of trial	Randomised Controlled Trial
Trial design	An investigator led multi-centre open-label, randomised controlled clinical trial of 410 participants with advanced (stage 4 or 5) progressive Chronic Kidney Disease (CKD) receiving either ACEi or ARBs or a combination of both.
Trial Treatment	Control arm: Continue ACEi or ARB or combination of both Experimental arm: Discontinue ACEi or ARB or combination of both
Primary Objective	To test the hypothesis that stopping ACEi or ARB treatment or a combination of both, compared with continuing on these treatments, improves or stabilises renal function in patients with progressive stage 4 or 5 CKD based on assessment of renal function using the Modification of Diet in Renal Disease (MDRD) 4-variable estimated Glomerular Filtration Rate (eGFR) at 3 years follow-up
Secondary Objectives	To test whether in each of the randomised groups: **Clinical outcomes:** • Cystatin-C levels differ; • Blood pressure control is the same; • The number of participants starting renal replacement therapy or sustaining a >50% decline in eGFR differs; • There is a difference in the time taken to reach end stage renal disease (ESRD) or need for renal replacement therapy; • Hospitalisation rates from any cause are different; • Participant quality of life and wellbeing (measured using the KDQOL-SF™ v1.3 questionnaire) differs;

	• Participant physical function (measured using the 6-minute walk test) differs; • That withdrawal of these treatments does not cause excess harm (e.g. increased cardiovascular events such as heart failure, hypertension, myocardial infarction, stroke) and is not associated with an increase in adverse effects; • Participant survival in each group is similar; **Mechanistic Outcomes:** • There is a change in urine protein excretion; • Discontinuation of ACEi/ARB affects haemoglobin concentration; • Discontinuation of ACEi/ARB affects the requirement for erythropoiesis stimulating agents (ESA).
Accrual period	24 months
Trial duration per participant	36 months
Estimated total trial duration	72 months (6 years; 6 months set-up, 24 months recruitment, 36 months follow-up, 6 months analysis and write-up)
Planned trial sites	UK multi-site
Total number of participants planned	410
Main inclusion/exclusion criteria	**Inclusion criteria** • Aged ≥18 years (male or female); • CKD stage 4 or 5 (eGFR <30mls/minute using the MDRD equation) and must not have received a kidney transplant or be on dialysis therapy; • Progressive deterioration in renal function (fall in eGFR of >2ml/min/year over previous 24 months) as measured by linear regression analysis. A simple excel spread sheet for calculation of this will be provided to all sites. **A minimum of 3 measurements of eGFR over the previous 24 months are required to identify a >2ml/min/year fall. The last eGFR must be within three months of randomisation.**

	• Treatment with either an ACEi or ARB or a combination of both for >6 months with at least 25% of the maximum recommended daily dose on the day of consent; • Resting blood pressure (BP) ≤160/90 mmHg when measured in accordance with British Hypertension Society guidelines in clinic or home blood pressure readings within the previous month or a 24h ambulatory blood pressure measurement within the last 3 months are acceptable. • At least 3 months of specialist renal follow-up at the time of entry into the trial; • Written, signed informed consent to the trial. **Exclusion criteria** • Aged <18 years; • Uncontrolled hypertension (>160/90mmHg) or requirement for 5 or more agents to control BP; • Undergoing dialysis therapy; • Previous kidney transplant; • Any condition which, in the opinion of the investigator, makes the participant unsuitable for trial entry due to prognosis/terminal illness with a projected survival of less than 12 months; • History of myocardial infarction or stroke in preceding 3 months; • Participation in an interventional research study in preceding 6 weeks; • Pregnancy, confirmed by positive pregnancy test, or breastfeeding; • Inability to provide informed consent (e.g. due to cognitive impairment); • Immune mediated renal disease requiring disease specific treatment; • Known drug or alcohol abuse; • Inability to comply with the trial schedule and follow-up.

LAY SUMMARY

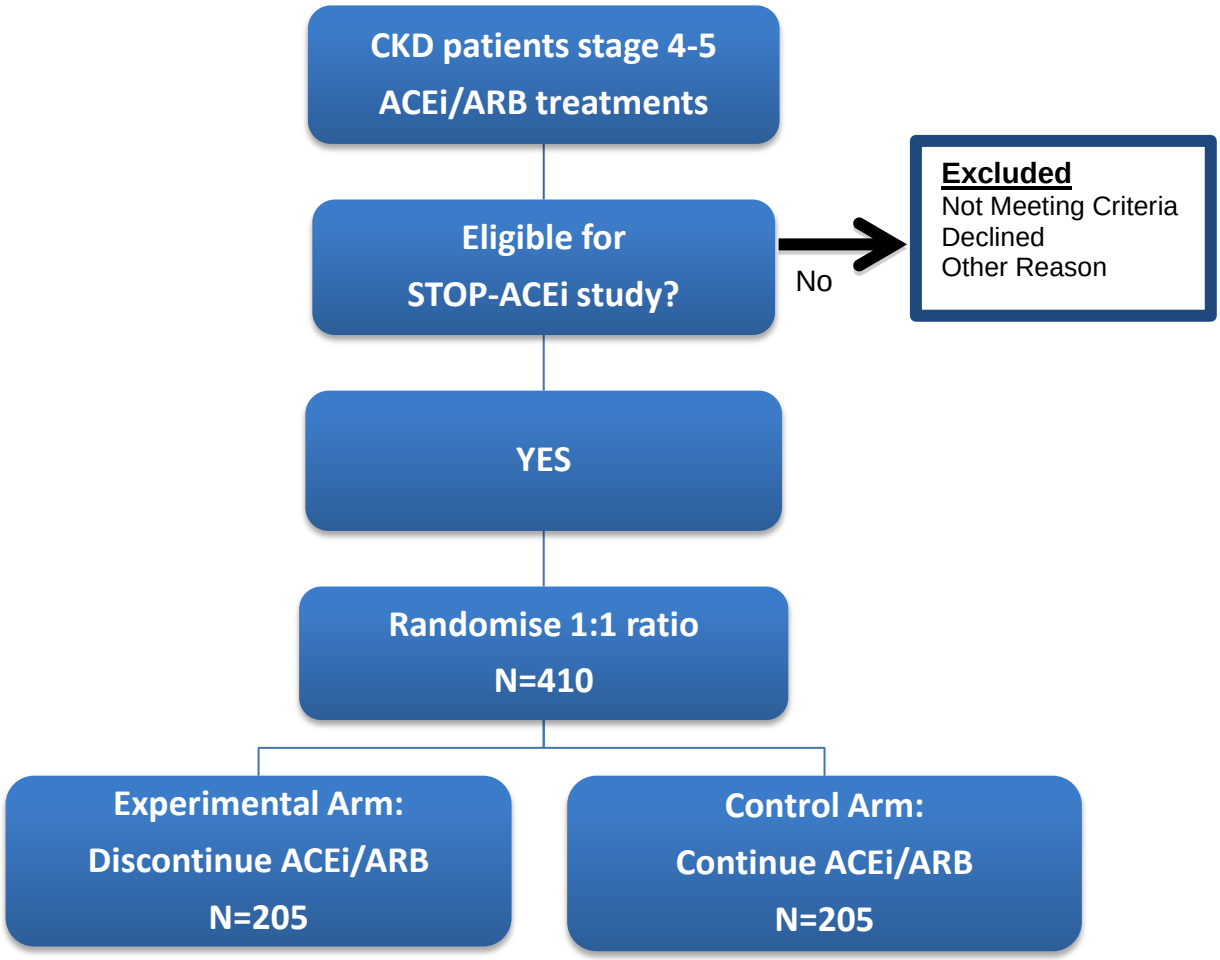
Chronic kidney disease (CKD) affects 1 in 10 adults in the UK and describes progressive loss of function of the kidneys over a period of months or years regardless of the original kidney disease. CKD can have serious implications for those affected including a risk of CKD progressing to complete kidney failure so that the affected person requires replacement of kidney function by dialysis treatment or kidney transplantation. Kidney disease is expensive with a high proportion of the health-care budget spent on people with CKD; the cost of dialysis treatment alone is ~£30,000/year. Patient quality of life can be poor, with dialysis leading to early death. Treating high blood pressure (BP) is the most important intervention that can slow progression of CKD to total kidney failure. Some people with CKD gain additional protection from drugs called Angiotensin Converting Enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARBs). These drugs treat high BP but also slow CKD progression by changing the pressure in the kidney. This may also influence hormone pathways that contribute to the decline of kidney function.

Recent research suggests that in some people with advanced CKD (stage 4 or 5) who are progressing to complete kidney failure and are receiving treatment with an ACEi and/ or ARB, stopping these drugs leads to stabilisation and improvement of kidney function and decreases or delays the need for dialysis treatment. This indicates that in some patients the very tablets that are being used to protect the kidneys may be contributing to a harmful decline in their function by some currently unknown mechanism.

To date, the research on this is observational and to confirm the association between stopping these drugs and stabilisation of kidney function requires a study to compare the outcomes of a group of people who have had these drugs stopped with a group who continue on the drug. This is called a randomised controlled trial (RCT). In the **STOP-ACEi** trial we will randomly allocate suitable participants (by chance) to either continue or to stop their ACEi/ARB treatment and then to follow-up these participants for 3 years. This study is needed before this treatment strategy can be put into routine clinical practice. In addition we will look at other effects of stopping these drugs such as effects on heart attacks, strokes and participant quality of life.

1.1 Trial Schema for the STOP-ACEi Study

2 years recruitment



3 years follow-up

Each patient followed-up for 3 years at 3-monthly intervals with routine bloods – eGFR, FBC, BCP, CRP (annually), urine for PCR, BP, documentation of ESA dose, adverse events, compliance and changes in medication

Annual QOL questionnaire, weight and BMI, 6-minute walk test, ECG, and bloods for cystatin C, NT-proBNP, ACE and renin levels and biomarkers

Analysis

Interim analysis of efficacy and safety carried out for Data Monitoring and Ethics Committee (DMEC)

Final analysis once the last randomised participant completes 3 years follow-up

2. Introduction

2.1 Background

Although many different diseases may damage the kidneys, most result in a progressive decline in kidney function over and above that expected with normal aging and may eventually lead to “end-stage” renal disease (ESRD) when dialysis (or kidney transplantation) is needed to preserve health and prolong life. The progressive nature of kidney damage and the limited ability of the kidneys to regenerate is a major challenge for healthcare professionals caring for such patients, given the limited therapeutic strategies available to preserve kidney function.

Chronic kidney disease (CKD) stages 3-5 affects 1 in 10 adults in the UK and describes progressive scarring of the kidneys with time regardless of the original disease. CKD can have serious implications for those affected and is associated with a high prevalence of cardiovascular disease and high economic cost [1]. Advanced CKD (stage 4 or 5) is associated with an increased relative risk of death of around 2.5 fold and a relative risk of kidney failure, as defined by a requirement for dialysis treatment, of up to 50-fold of that of age-matched individuals with normal kidney function [2-5]. Furthermore, the presence of advanced CKD has a major negative impact on a range of other outcomes including quality of life [6, 7].

CKD is expensive with a high proportion of the health-care budget spent on these people; the cost of dialysis treatment alone is ~£30,000/year and survival rates on dialysis are poor with an annual mortality of 20-28%. Patient quality of life can also be poor, with dialysis leading to early death and there is a substantial increase in hospitalisations [1, 6]. The management of people requiring dialysis currently consumes 3% of the total NHS budget [7]. Clearly, there are huge potential benefits associated with slowing the progression of CKD to ESRD for patients, their families and for the healthcare systems in which they are managed. Treating high blood pressure (BP) is the most important intervention that can slow progression of CKD. Some people with CKD gain additional protection from angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs).

However, recent research suggests that in some people with advanced CKD (stage 4 or 5) who are progressing to complete kidney failure and are receiving treatment with an ACEi or ARB, stopping these drugs leads to stabilisation or improvement of kidney function and decreases or delays the need for dialysis treatment [25]. To date, the research on this is observational and to confirm the association between stopping these drugs and stabilisation

of kidney function requires a randomised controlled trial to compare the outcomes of a group of people who have had these drugs stopped with a group who continue on the drugs.

The trial population will be patients with advanced progressive CKD (stage 4 or 5) being treated with ACEi or ARBs or a combination of both.

2.2 Preclinical data

To date, irrespective of the underlying cause of CKD, attention has focussed on control of BP (hypertension is an almost universal complication of CKD) and minimisation of urinary protein excretion (a potential co-factor in progressive CKD) by using agents that block the renin-angiotensin system (RAS) and reduce intra-glomerular pressure over and above the effect on BP. Initial studies by Lewis and others demonstrated that ACEi and ARBs reduced the doubling time of creatinine in patients with type I and type II diabetes over a 3 year period [8-10]. Further studies have shown that ACEi and ARBs reduced the progression of renal disease in non-diabetic patients [11-15]. Data from the HOPE, LIFE and ALLHAT studies have confirmed the benefit of ACEi use in mild CKD [16-18]. Ruggenenti et al. in an analysis of 322 patients with non-diabetic CKD at varying stages of disease randomly assigned to either ramipril or conventional treatment, found that the renoprotective effects were maximised when ACEi therapy was started earlier in the course of the disease (i.e. GFR>50ml/min/1.73m^2), but suggested that therapy should be offered to all patients with CKD, even those with a GFR between 10 and 30 ml/min/1.73m^2 [19]. In 2006, Hou et al. examined 422 patients with non-diabetic CKD and placed them into one of two groups based upon their baseline serum creatinine levels. Patients in group one (serum creatinine between 133 and 265µmol/L) received 20mg of benazepril per day and patients in group two (serum creatinine between 274 and 442µmol/L) were randomised to 20mg of benazepril per day or placebo and then followed for 3.4 years [13]. The authors reported a significant 43% decrease in the composite end point of doubling of serum creatinine level, ESRD, or death in the benazepril group compared to placebo. In 2006, a Cochrane Review explored the use of ACEi and ARBs in preventing the progression of kidney disease in the diabetic patient population [20]. The review included 49 studies with 12,067 diabetic patients at all stages of kidney disease. It included studies that compared ACEi or ARBs to placebo and studies that directly compared ACEi and ARBs. The authors found that both ACEi and ARBs improved renal outcomes (ESRD, including doubling of creatinine, prevention of progression of micro- to macroalbuminuria, remission of micro- to normoalbuminuria) [20]. Further, when compared to placebo, use of ACEi at maximum tolerated doses appeared to prevent death in patients with diabetic kidney disease (relative risk (RR) 0.78; 95% confidence interval 0.61 to 0.98). These mortality data were not found with ARBs. The authors however cautioned against the conclusion that ACEi and ARBs prevent the progression of CKD and suggested that the

beneficial initial effect seen may be due simply to their anti-proteinuric effects, that there was little robust evidence of benefit in advanced CKD and that the conclusions were based mainly on composite end points.

These studies suggesting that these agents are renoprotective in patients with CKD have formed the basis of guidelines which recommend the use of ACEi/ARBs in patients with proteinuria and/or diabetes, and have been transposed to apply to advanced CKD. However, the rigor of some of these studies, which have failed to dissociate the renoprotective effects that are specific for ACEi/ARBs from their anti-hypertensive effect are now being questioned by many nephrologists.

A detailed assessment of the published data from the REIN study indicated a limited effect of ACE inhibition on glomerular filtration rate (GFR) progression despite a large difference in composite end points including doubling of serum creatinine [11, 19]. This may relate, in part, to the effects of ACEi on reducing glomerular capillary pressure and increasing glomerular blood flow through efferent arteriole vasodilatation, thus leading to a reduction in filtration fraction and hence proteinuria. Consequently, ACE inhibition should lead to increased peritubular circulation secondary to improved efferent arteriolar blood flow. However, the increase in peritubular capillary flow may affect proximal tubular transport of proteins and creatinine via effects on the organic cationic transporters leading to an increased tubular creatinine secretion and fall in serum creatinine and hence an apparent rise in GFR [21]. Indeed the mechanism and clinical effects in advanced CKD are unknown. Renoprotection from ACEi/ARB may in fact be lost in more advanced disease where significant ischaemic nephropathy is present. This hypothesis is supported by reports in both diabetic and non-diabetic patients with CKD indicating that ACEi/ARBs may actually accelerate renal progression [22-23]; and in more advanced CKD the intrarenal haemodynamic effects of ACEi/ARBs may decrease the time to renal replacement therapy. Furthermore, combined ACEi/ARB treatment has been shown in one large study to worsen renal outcomes in patients at high cardiovascular risk [24].

A recent land mark observational study by one of the co-applicants (El Nahas) demonstrated that ACEi/ARB withdrawal in 52 patients with advanced CKD led to an overall mean increase in eGFR of 10ml/min/1.73m^2 over 12 months, and an increase or stabilisation in eGFR in all but 4 patients. A modest change in blood pressure was also observed, with no increase in cardiovascular events [25]. Further evidence of the problems associated with ACEi/ARBs in these patients emanates from data from a retrospective cohort study which evaluated risk factors for adverse drug events and found factors such as hyperkalaemia and renal impairment as indications for discontinuation of the medication [26]. In this study of 2,225

out-patients administered ACEi, 19% of the initial group discontinued ACEi therapy due to adverse events. The close interaction of the kidney and the heart is critical to survival. Indeed the huge array of traditional and renal specific risk factors leads to a complex area of study and the risk factors for poor cardiovascular disease outcomes in the general population and in early CKD are associated with better outcomes in advanced CKD [27, 28]. Furthermore, cardiovascular events are more common in dialysis than pre-dialysis patients suggesting the increased importance of avoiding dialysis therapy, which accelerates cardiovascular risk. There are no studies assessing the benefits of ACEi/ARB therapy in cardiovascular risk reduction in advanced non-dialysis CKD. Several randomised controlled studies in dialysis patients have shown increased cardiovascular events with use of ACEi [29, 30]. No studies have adequately addressed the use of eGFR or measured or calculated GFR as a primary endpoint. Secondary analysis of the data generated from this study may help guide the design of future studies in this area.

2.3 Rationale and risks/benefits

Trial evidence on the effectiveness and safety of ACEi/ARB discontinuation in advanced CKD is lacking; this is reflected in current guidelines which provide no specific instructions regarding ACEi/ARB in relationship to the severity of CKD [31]. The study by El Nahas et al. [25] suggests that withdrawal of ACEi/ARBs in advanced CKD may be beneficial. Thus, the proposed randomised controlled trial logically follows on from the observations of El Nahas et al. in patients with CKD stage 4 or 5 (pre-dialysis) to address this issue further and fill the gap in knowledge. The results of this trial will provide evidence as to whether discontinuation of ACEi/ARB is beneficial to renal function (improvement/stabilisation) and improving other important parameters including laboratory (hyperkalaemia, anaemia) and clinical outcomes including hospitalisation rates, physical function and quality of life without causing an increase in cardiovascular events, for which evidence is currently lacking. It will clarify whether the benefits of this intervention (withdrawal of ACEi/ARB) out-weigh the risks. Data, based on calculated (estimated) GFR, will provide robust evidence to direct future guidelines and design a large randomised controlled trial (RCT) with a hard end point (death). The results of such a trial could potentially lead to substantial health gains by avoiding or delaying dialysis and an ultimate goal of better patient and dialysis free survival if we show that there is an increase in eGFR (with no detrimental effects on cardiovascular endpoints).

HYPOTHESIS: Does a strategy of discontinuing ACEi or ARBs or combination of both in patients with advanced (stage 4 or 5) progressive CKD lead to the stabilisation of or improvement in renal function over a 3 year follow-up period, provided good blood pressure control is maintained with other agents, compared to a strategy of continuing ACEi and / or ARB?

Renal replacement therapy with dialysis remains an expensive and undesirable therapeutic option for patients with CKD. Median survival on dialysis is only 3.5 years and is associated with poor quality of life [32]. Kidney transplantation, although associated with better clinical outcomes and quality of life, remains a scarce commodity and is not an option for many patients with ESRD, where co-morbidity precludes transplantation, including the large numbers of older patients (≥65 years old) who make up the majority with advanced CKD. There are few data on the effect of discontinuing ACEi/ARB on the cardiovascular event rate in this population (see above). Indeed no increased cardiovascular risk was noted in an observational cohort study from El Nahas et al. However the potential risk of increased cardiovascular events for participants will be carefully assessed throughout the trial using a detailed monitoring strategy, as outlined below. If the results of the trial show a benefit for ACEi/ARB withdrawal, it could have a huge impact on patients, their families and health services, by reducing or delaying the need for dialysis and kidney transplantation.

2.4 Assessment and management of risk

The current trial is a clinical evaluation designed to assess whether discontinuation of commonly used medications (ACEi or ARB or combination of both) in patients with advanced renal disease applied to all age groups is better than continuation of such therapy in a group of people who have an accelerated decline in kidney function with associated poor outcomes, high morbidity and high healthcare cost.

The trial will be overseen by a Data Monitoring and Ethics Committee (DMEC) to ensure that participants are not exposed to inappropriate risks. Information on participant safety data, adverse events, serious adverse events, treatment efficacy data, logistics (participant accrual rates) and quality assurance information (data-entry errors) will be provided to the DMEC. The trial has equipoise as; in patients with advanced CKD there are theoretical reasons why ACEi/ARB may be useful, useless or harmful. In practice, some clinicians withdraw these agents in patients with advanced CKD, but others do not. It is important for care of patients that controversy and debate evolves into evidence-based guidelines.

The assessment and management of risk is detailed in the separate **STOP-ACEi** Risk Assessment document. An on-going evaluation of risk will continue throughout the recruitment period.

3. Trial Design

STOP-ACEi is an investigator led multi-centre open-label, randomised controlled clinical trial of 410 participants aged 18 years or over with advanced (stage 4 or 5) progressive CKD receiving either ACEi or ARBs or a combination of both.

Participants will be recruited from renal units in the UK (the UK Kidney Research Consortium (KRC) CKD Clinical Study Group (CSG) has indications of interest in participation in this trial from over 30 units). Hull, Leicester, Sheffield and Birmingham are the main units and it is anticipated that 10-20 units will take part.

All standard measures will be assessed at three monthly intervals from baseline to 3 years in the standard follow-up clinic consistent with the recommendation of the National Institute for Health and Care Excellence (NICE) CKD guideline for routine clinical practice. All patients are reviewed on a regular basis at out-patient clinic visits every 3 months, thus all assessments are timed to fit in with routine clinic follow-up visits. Ideally, visits will be performed every 3 months, but a window of ±2 weeks is permitted for each visit. Participants will also have a telephone follow-up between the first and second visit at 4-6 weeks from randomisation to check for any medication changes or adverse events.

The participant will be randomised to either the control arm: continuation of ACEi or ARB or combination of both, or the experimental arm: discontinuation of ACEi or ARB or combination of both. Throughout the study, participants will be encouraged to ask questions and will be reminded that they can withdraw at any time without their clinical care being affected.

The number of attendances and tests performed will not be significantly altered by trial participation (Section 7.4 Assessment Schedule). Routine bloods to assess haemoglobin, C-reactive protein (CRP) and kidney function (eGFR and serum creatinine) will be measured, as is normal practice.

Routine Tests performed at each 3 monthly visit include:

- Full Blood Count (FBC) – includes haemoglobin (Hb), mean cell volume (MCV), mean cell haemoglobin (MCH) and platelet counts
- Biochemical profile (BCP) (includes serum creatinine, serum sodium, potassium, bicarbonate, calcium, phosphate, alkaline phosphatase, albumin, total protein, alanine transferase and eGFR)
- Urinary protein:creatinine ratio (PCR). Quantification of proteinuria will be carried out by measurement of the PCR in an early morning spot urine sample using standard laboratory techniques. It will also be acceptable to use albumin:creatinine ratio (ACR)

to measure proteinuria where this is standard local practice. Any ACR measurements will be converted to PCR for trial analysis.

- C Reactive Protein (CRP) analysis (annually)

A number of tests are required in addition to those completed at routine clinics, these include:

- cystatin C annually
- N Terminal Pro-B-type natriuretic peptide (NT-proBNP) analysed and recorded annually
- ACE and renin levels will be measured at baseline and annually to the end of the trial to examine for potential non-adherence, but acknowledging their limitations. Samples will be taken for all participants and a sample will be analysed from each arm of the trial.

In addition, urine and serum samples taken at baseline and at one and 3 years will be stored at Hull and East Yorkshire Hospitals NHS Trust for possible future biomarker analysis. Samples will be held for analysis and verification of research data for up to one year following declaration of the end of the trial. An application will be made for ethical approval of any continued storage of samples after this point, for use in further research projects. Otherwise the tissue will be destroyed in accordance with the HTA Code of Practice.

A 12 lead electrocardiogram (ECG) will be performed annually (this is not routinely carried out unless clinically indicated). The ECG will be reported and signed by the investigator as normal, abnormal but not clinically significant, or abnormal and clinically significant.

While an echocardiogram (echo) is not required for the trial, data available for any echo performed as part of clinical care will be recorded. Data will be recorded for any echo performed in the 12 months before the baseline visit and at any stage during trial participation.

Change in Quality of Life will be determined using the KDQOL-SF™ v1.3 questionnaire (not a routine test). This questionnaire will be carried out at baseline, and at 1, 2 and 3 years post randomisation. The KDQOL-SF™ v1.3 instrument includes the SF-36™ and is validated in CKD patients.

Physical function will be measured using the 6–minute walk test at baseline, 1, 2 and 3 years post randomisation (not a routine test). The 6-minute walk test is a low-cost and valid measure of exercise tolerance. Participants are instructed to walk for 6 minutes up and down a 20 metre long level corridor as quickly as possible. Performance is quantified by the total distance walked.

For both groups, the primary end-point is at the end of the 3-year follow-up period, when renal function and secondary end points will be analysed. At this point, the period of defined intervention will cease and participant treatment beyond this will be decided solely on clinical grounds. Conventional additional therapies will be adjusted as deemed necessary for best clinical practice. For the purposes of the trial, participants will not be considered to be on trial treatment after their 3 year follow-up assessment.

Data on demographics (date of birth, gender, ethnicity, smoking status, alcohol intake, weight & height, body mass index (BMI), primary aetiology of CKD) will be collected and recorded. A detailed disease history including cardiovascular co-morbidity, anti-hypertensive medications and list of all other concomitant medications will be taken at the baseline visit. In addition, the dose of erythropoietin stimulating agent (ESA) drug will be recorded at each three monthly visit. Clinic BP (average of three readings) will be recorded at each visit, adopting standard practice for its measurement. Home readings are acceptable but will be stated in the medical notes. The BP used in management will be used for study purposes.

For the purpose of the trial, urine and blood samples will be taken at baseline and at 3 monthly time points until the end of the trial at 3 years post randomisation (standard tests in clinics based on NICE guidelines); See *Table 1*.

Participants will be reviewed every three months as per normal practice. All data will be collected on case report forms (CRFs) and recorded on a secure database at the Birmingham Clinical Trials Unit (BCTU). This will be updated after each participant visit.

4. Trial Objectives

4.1 Hypothesis

Does a strategy of discontinuing ACEi or ARBs or a combination of both in patients with advanced (stage 4 or 5) progressive CKD lead to the stabilisation of or improvement in renal function over a 3 year follow-up period, provided good BP control is maintained with other agents, compared to a strategy of continuing ACEi and / or ARB.

4.2 Primary aim

- To test the hypothesis that stopping ACEi or ARB treatment or a combination of both, compared with continuing on these treatments, improves or stabilises renal function in patients with progressive stage 4 or 5 CKD based on assessment of renal function using the MDRD 4-variable eGFR at 3 years.

4.3 Secondary aims

To test whether in each of the randomised groups:

Clinical Outcomes

- Cystatin-C levels differ;
- Blood pressure control is the same;
- The number of participants starting renal replacement therapy or sustaining a >50% decline in eGFR differs;
- There is a difference in the time taken to reach ESRD or need for renal replacement therapy;
- Hospitalisation rates from any cause are different;
- Participant quality of life and wellbeing (measured using the KDQOL-SF™ v1.3 questionnaire) differ;
- Participant physical function (measured using the 6-minute walk test) differs;
- That withdrawal of these treatments does not cause excess harm (e.g. increased cardiovascular events such as heart failure, hypertension, myocardial infarction, stroke) and is not associated with an increase in adverse effects;
- Participant survival in each group is similar;

Mechanistic Outcomes

- There is a change in urine protein excretion;
- Discontinuation of ACEi/ARB affects haemoglobin concentration;
- Discontinuation of ACEi/ARB affects the requirement for ESAs.

4.4 Primary Outcome Measure

- Renal function measured using MDRD 4-variable eGFR at 3 years

4.5 Secondary Clinical Outcome Measures

- Cystatin-C;
- BP;
- Number of participants starting renal replacement therapy or sustaining a >50% decline in eGFR;
- Time taken to reach ESRD or need for renal replacement therapy;
- Hospitalisation rates from any cause;
- Participant quality of life and wellbeing (measured using the KDQOL-SF™ v1.3 questionnaire);
- Participant physical function (measured using the 6-minute walk test);

- That withdrawal of these treatments does not cause excess harm (e.g. increased cardiovascular events such as heart failure, hypertension, myocardial infarction, stroke) and is not associated with an increase in adverse effects;
- Mortality.

4.6 Secondary Mechanistic Outcome Measures:

- Urine protein excretion;
- Haemoglobin concentration;
- Dose of ESA.

5. Selection of Participants

Participants who potentially fulfil the inclusion criteria for this trial must have their eligibility confirmed by medically qualified personnel with access to and a full understanding of the potential participant's medical history. Eligibility should be assessed and documented by medically qualified personnel.

Four hundred and ten patients aged 18 years or over with progressive CKD (stage 4 or 5) will be enrolled. Each patient must meet all of the inclusion criteria, and none of the exclusion criteria, at entry to the trial. Patients who meet the entry criteria may be recruited by the investigator or any medically qualified member of the local trial team who has delegated responsibility for trial recruitment.

5.1 Inclusion criteria

- Aged ≥18 years (male or female);
- CKD stage 4 or 5 (eGFR <30mls/minute using the MDRD equation) and must not have received a kidney transplant or be on dialysis therapy;
- Progressive deterioration in renal function (fall in eGFR of >2ml/min/year over previous 24 months) as measured by linear regression analysis*;
- Treatment with either an ACEi or ARB or a combination of both for >6 months with at least 25% of the maximum recommended daily dose on the day of consent;
- Resting BP≤160/90mmHg when measured in accordance with British Hypertension Society guidelines in clinic or recent home blood pressure reading within the previous month or a 24h ambulatory blood pressure measurement within the last 3 months are acceptable;
- At least 3 months of specialist renal follow-up at the time of entry into the trial;
- Written, signed informed consent to the trial.

*There will be a requirement of a minimum of 3 measurements of eGFR to identify a >2ml/min fall over one year to enter the trial. The loss in eGFR will be expressed 'per year' so that over 12 months there must be a total loss of at least 2ml/min, but over 24 months there must be a total loss of at least 4ml/min, and so on. The last eGFR must be within three months of randomisation. We recognise the limitations of eGFR due to intra- and inter-patient variability in serum creatinine. Based on a reported intra-individual variation for serum creatinine of 4.3% and intra-laboratory variation of 3.0%, a variation of 13% can be considered 'real' with 95% probability. The power function in the MDRD equation has a component of variability that puts this up to 14.4% in eGFR between 2 tests. Hence a minimum of 3 eGFRs over one year or 6 over two years would be required to accurately identify a decline of >2ml/min/year in people with an eGFR <30ml/min. This will optimise the eGFR slope against time. This will be calculated using an excel spreadsheet which will allow entry of the previous creatinine measurements or eGFR values with automatic generation of a slope and rate of GFR loss. This program will be provided to all Principal Investigators (PIs) participating in the trial. The measurements of eGFR are inserted into the table with the date of the measurements and this generates the linear line with automatic calculation of the change in GFR.

5.2 Exclusion criteria

- Aged <18 years;
- Uncontrolled hypertension (>160/90mmHg) or requirement for 5 or more agents to control BP;
- Undergoing dialysis therapy;
- Previous kidney transplant;
- Any condition which, in the opinion of the investigator, makes the participant unsuitable for trial entry due to prognosis/terminal illness with a projected survival of less than 12 months;
- History of myocardial infarction or stroke in preceding 3 months;
- Participation in an interventional research study in preceding 6 weeks;
- Pregnancy confirmed by positive pregnancy test or breastfeeding;
- Inability to provide informed consent (e.g. due to cognitive impairment);
- Immune mediated renal disease requiring disease specific treatment.
- Known drug or alcohol abuse
- Inability to comply with the trial schedule and follow-up

6. Recruitment

A flowchart of the recruitment process is shown in the Trial Schema (**Section 1.1**) together with the treatment and follow-up schedule. Section 7 gives more detailed information.

410 participants will be recruited from 10-20 UK centres. The four main centres will be Hull, Leicester, Sheffield and Birmingham. Recruitment will be from secondary care from CKD clinics. Potential participants will be identified by the research team at each of the recruiting centres.

A database search of Leicester General Hospital has identified over 200 eligible patients and these clinics care for only a proportion of available patients that may be eligible for this trial. Likewise there are 710 patients under follow-up in CKD clinics at the Queen Elizabeth Hospital Birmingham with CKD stage 4 or 5, of which at least 60% have a rate of decline of >2 ml/min/year with a prevalent use of ACEi/ARB of 70%. This leaves >200 eligible patients. Similar data exists from Prof Bhandari and Prof El Nahas from clinics throughout Hull and Sheffield. Other centres will follow a similar process.

7. Trial Procedures and Schedule of Assessments

7.1 Screening procedures

Eligibility will be assessed against the inclusion and exclusion criteria and participants will then be identified as described below.

Currently, patients with CKD under the care of a nephrologist are reviewed every 3 months in a hospital out-patient clinic. Reflecting the secondary care basis of the proposed research, potential participants in secondary care will be identified by the research team at each of the recruiting centres (e.g. from medical records, clinical records, individual renal unit databases or other local registries) and will be invited to participate by letter. In some cases the research nurse or participant's responsible clinician may introduce the study to the participant before providing them with the invitation letter and participant information sheet.

Members of the site staff will screen for potential eligible trial participants using the inclusion/exclusion criteria. Patients who fulfil the inclusion criteria will have their eligibility assessed by medically qualified personnel with access to and a full understanding of their medical history. Eligible patients will be approached by sending a letter and a copy of the participant information sheet (PIS) 1 to 2 weeks before their next 3-monthly clinic assessment. This will allow sufficient time for potential participants to consider the information provided and discuss the trial with their family and friends and decide whether to

take part. At the clinic appointment, they will be approached by an appropriately trained and medically qualified member of the clinical team regarding entering the **STOP-ACEi** trial. This individual will discuss the trial with them in detail and give a comprehensive verbal explanation of the trial (explaining both the investigational and standard treatment options and highlighting any possible benefits or risks relating to participation). Time for questions throughout the discussion will be given and any questions adequately addressed. Informed consent will then be sought from the participants who agree to enter the study. After informed consent is given, a final confirmation of eligibility will be performed. We have submitted the trial for adoption by the Comprehensive Clinical Research Network (CCRN) and the Comprehensive Local Research Networks (CLRNs) will assist with subject identification and the recruitment process. Details of all patients approached about the trial should be recorded on the **STOP-ACEi** Screening Log.

7.2 Informed consent procedure

Potential participants will initially be provided with a PIS (i.e. the current Main Research Ethics Committee (MREC) approved version which should be on appropriately headed paper) and a covering letter explaining the trial to them and inviting them to participate in the trial. This will be sent to them 1-2 weeks before their next clinic attendance. They will have time to consider the trial and decide whether or not they wish to take part, and to discuss the trial with their family and friends if they would like to. At their next clinic appointment, potential participants will have plenty of time to discuss the trial further and to have any questions that they may have about the trial answered. The nature and requirements of the trial will be carefully explained. The investigator, or designated medically qualified personnel, will explain that there is no obligation for a potential participant to enter the trial, that trial entry is entirely voluntary, and that it is up to the potential participant to decide whether or not they would like to join. It will also be explained that they can withdraw at any time during the trial, without having to give a reason and that their decision will not affect the standard of care they receive. Any reasons for non-participation will be recorded if the information is volunteered. The participant and responsible clinician will sign the informed consent form and the responsible clinician will perform a final confirmation of eligibility.

At the appointment (baseline assessment), the research nurse will go through the randomisation form including the eligibility checklist. Assuming the patient is eligible they will be asked to sign a separate consent form and will be randomised into the study. Informed consent will be obtained before any trial-related procedures are undertaken. A copy of the signed informed consent form will be given to the participant. The original signed form will be retained at the study site in the Investigator Site File and a copy placed in the medical notes. A copy will also be sent to the **STOP-ACEi** Trial Office.

This study will include optional consent to allow future linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. CPRD, THIN, QResearch), secondary care data (Hospital Episode Statistics; HES) and mortality data from the Office of National Statistics (ONS) through The Health and Social Care Information Centre and other central UK NHS bodies. The consent will also allow access to other new central UK NHS databases that will appear in the future. This will allow us to extend the follow-up of patients in the trial and collect long-term outcome and health resource usage data without needing further contact with the study participants. This is important as it will link a trial of a treatment that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data, but which will not be collected during the follow-up period of the trial.

With the participant's prior consent, their General Practitioner (GP) will also be informed. A GP Letter for Treatment Continuation or Treatment Discontinuation is provided for this purpose.

If new safety information results in significant changes in the risk/benefit assessment, the consent form and PIS will be reviewed and updated as necessary. Participants will be re-consented if appropriate.

7.3 Randomisation procedures

After all eligibility criteria have been confirmed and informed consent has been received, the participants can be randomised into the **STOP-ACEi** trial. Participants will be randomised individually into the trial in a one-to one ratio to either **continue with their ACEi and/or ARB treatment (control arm) or to discontinue their ACEi and/or ARB treatment (experimental arm)**. Randomisation will be provided by a computer generated programme at the Birmingham Clinical Trials Unit (BCTU), using a minimisation algorithm to ensure balance between the arms with regard to important clinical variables. The minimisation variables will be diabetes (Type 1 diabetes, Type 2 diabetes (including insulin-treated Type 2 diabetes) or non-diabetic), BP (mean arterial pressure (MAP) measured as {[2 x diastolic] + systolic}/3; <100 or ≥100), age (<65 years or ≥ 65 years), proteinuria (PCR <100 or ≥100), and lastly eGFR measurement (<15 ml/min or ≥ 15ml/min).

7.3.1 Telephone and online randomisation

Participants can be randomised into the trial via a secure 24 hour internet based registered service (**https://www.trials.bham.ac.uk/stopacei**) or by a telephone call (telephone number **0800 953 0274**) to the BCTU. Telephone randomisation is available Monday-Friday, 09:00-

17:00. For the secure internet randomisation, each site and each researcher will be provided with a unique log-in username and password in order to access the online system. Online randomisation is available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance and occasional network problems.

Randomisation Notepads will be provided to investigators and should be completed and used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Notepad must be answered before a Trial Number can be given. If data items are missing, randomisation will be suspended, but can be resumed once the information is available. Only when all eligibility criteria and baseline data items have been provided will a Trial Number be allocated. A confirmatory email will be sent to the local Principal Investigator and the named research nurse with a copy sent to the Chief Investigator.

Investigators will keep their own study file log which links patients with their allocated trial number in the **STOP-ACEi** Patient Recruitment and Identification Log. The Investigator must maintain documents not for submission to the Trials Office (e.g. **STOP-ACEi** Patient Recruitment and Identification Logs and **STOP-ACEi** Screening Logs) in strict confidence.

The participant's GP should be notified that they are in **STOP-ACEi** trial, using the appropriate GP Letter for Treatment Continuation or for Treatment Discontinuation.

7.3.2 Back-up randomisation

If the internet based randomisation service is unavailable for an extended period of time, a back-up paper randomisation will also be available at the BCTU. The randomisation list will be produced using a random length block design. In this instance, investigators should ring the BCTU randomisation service (telephone number **0800 953 0274**).

7.4 Assessment schedule

Please see **Table 1** for the Schedule of Assessments.

7.4.1 Baseline and Follow-up Visits

Demographic data (date of birth, gender, ethnicity, smoking status, alcohol intake, weight & height, BMI, primary aetiology of CKD) will be collected and recorded at the baseline visit. A detailed disease history including cardiovascular co-morbidity, anti-hypertensive medications and list of other concomitant medications will also be taken. Changes to antihypertensive and other concomitant medications will be recorded at each 3-monthly visit. In addition, BP,

eGFR and the dose of ESA drug will be recorded at each 3-monthly visit. Blood and urine samples will be obtained for clinical laboratory testing; six minute walk test and questionnaires will be performed (see Section 3). A 12 lead ECG will be performed annually. The ECG will be reported and signed by the investigator as normal, abnormal but not clinically significant, or abnormal and clinically significant. Adverse events and compliance with the treatment allocation will be documented at each 3-monthy visit. Participants will also have a telephone follow-up between the first and second visit at 4-6 weeks from randomisation to check for any medication changes or adverse events.

Between the 3-monthly visits, patients should be monitored and managed in accordance with local practice for follow-up of any change of therapy. Any changes in medication or visits to a GP practice or hospital should be noted on the Patient Diary and recorded on the CRF at the next clinic visit.

While an echocardiogram (echo) is not required for the trial, data available for any echo performed as part of clinical care will be recorded. Data will be recorded for any echo performed in the 12 months before the baseline visit and at any stage during trial participation.

7.4.2 Investigational Samples for Trial

For the purpose of the trial, urine and blood samples will be taken at baseline and at 3 monthly time points until the end of the trial at 3 years post randomisation (standard tests in clinics based on NICE guidelines). All tests will be recorded for the purpose of the trial.

7.4.3 Tests to be performed

Clinic BP (average of three readings) will be recorded at each visit, adopting standard practice for its measurement. Home readings are acceptable but will be stated in the medical notes. The BP used in management will be used for study purposes.

Routine bloods to assess haemoglobin, C-reactive protein (CRP) and kidney function (eGFR and serum creatinine) will be measured, as is normal practice.

Routine Tests performed at each visit 3 monthly include:

- FBC – includes Hb, MCV, MCH and platelet counts
- BCP (includes serum creatinine, serum sodium, potassium, bicarbonate, calcium, phosphate, alkaline phosphatase, albumin, total protein, alanine transferase and eGFR)

- Urinary PCR. Quantification of proteinuria will be carried out by measurement of the PCR in an early morning spot urine sample using standard laboratory techniques. It will also be acceptable to use albumin:creatinine ratio (ACR) to measure proteinuria where this is standard local practice. Any ACR measurements will be converted to PCR for trial analysis.
- CRP analysis (annually)

A number of tests are required in addition to those completed at routine clinics, these include:

- cystatin C annually
- NT-proBNP analysed and recorded annually
- ACE and renin levels will be measured at baseline and annually to the end of the trial to examine for potential non-adherence, but acknowledging their limitations. Samples will be taken for all participants and a sample will be analysed from each arm of the trial.

The collection of any additional samples beyond standard practice will be at the responsible clinician's discretion. In addition, urine and serum samples taken at baseline and at one and 3 years will be stored at Hull and East Yorkshire Hospitals NHS Trust for possible future biomarker analysis. Samples will be held for analysis and verification of research data for up to one year following declaration of the end of the trial. An application will be made for ethical approval of any continued storage of samples, after this point, for use in further research projects. Otherwise the tissue will be destroyed in accordance with the HTA Code of Practice.

Physical function will be measured using the 6-minute walk test at baseline, 1, 2 and 3 years post randomisation. The 6-minute walk test is a low-cost and valid measure of exercise tolerance. Participants are instructed to walk for 6 minutes up and down a 20 metre long level corridor as quickly as possible. Performance is quantified by the total distance walked.

7.4.4 Questionnaires

Change in Quality of Life will be determined using the KDQOL-SF™ v1.3 questionnaire. This questionnaire will be carried out at baseline, and at 1, 2, and 3 years post randomisation. The KDQOL-SF™ v1.3 instrument includes the SF-36™ and is validated in CKD patients.

A **STOP-ACEi** Participant Diary will also be provided for participants to record any changes to ongoing treatment, acute illnesses and other issues. Participants will use this diary to record any intercurrent illness and or consultations with healthcare professionals (GP, nurse, hospital A+E departments etc.), along with details of changes in medicines prescribed or

purchased over the counter. Information from diaries reported by participants to consultants should be recorded in the medical record and on the trial CRFs.

Participants will be reviewed as per normal practice every three months. All data will be collected and recorded on a secure database at the BCTU. This will be updated after each participant visit.

Table 1: Schedule of assessments

Trial visit number		**1**	**Phone call**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit/month (± 2 weeks)	**Screening**	**Baseline**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**
Inclusion and exclusion criteria	Y	Y													
Informed consent		Y													
Randomisation and trial number allocation		Y													
Demographics: Date of birth, gender, ethnicity		Y													
Medical history including cardiovascular co-morbidity		Y													
Aetiology of CKD		Y													
Smoking status		Y													
Alcohol intake		Y													
Height		Y													
Weight		Y					Y				Y				Y
BMI		Y					Y				Y				Y
Blood pressure		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Record ESA dose		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Record data from cardiac echo †		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Changes to anti-hypertensive medication ‡		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Changes to other Concomitant Medications ‡		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance with the trial treatment allocation		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Adverse event documentation			Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Routine tests															
eGFR and BCP*		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
FBC**		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Trial visit number		**1**	**Phone call**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit/month (± 2 weeks)	**Screening**	**Baseline**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**
Urinary PCR or ACR by early morning spot urine		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
CRP		Y					Y				Y				Y
Additional tests															
Six minute walk test		Y					Y				Y				Y
KDQOL-SF™ v1.3 Questionnaire		Y					Y				Y				Y
12 Lead ECG		Y					Y				Y				Y
Cystatin-C		Y					Y				Y				Y
NT-proBNP		Y					Y				Y				Y
ACE and renin levels		Y					Y				Y				Y
Serum and urine samples for biomarker analysis ***		Y					Y								Y

† If a cardiac echo has been carried out as part of clinical care in the 12 months before the baseline visit or at any stage during trial participation, we would like to record this data

‡ Changes since last visit.

* Biochemical profile to include serum creatinine, serum sodium, potassium, bicarbonate, calcium, phosphate, alkaline phosphatase, albumin, total protein and alanine transferase

** Full blood count to include Hb, MCV, MCH and platelets.

*** This is optional. If for any reason the participant is unwilling to provide blood or urine samples for biomarker analysis, this will not preclude them taking part in the study.

7.5 Withdrawal

Participants are free to withdraw from participation in the **STOP-ACEi** trial at any time upon request or be withdrawn from the trial by the investigator if considered in the best interest of the participant. Participants who withdraw will continue to be managed according to standard best clinical practice.

Full details of the reason(s) for withdrawal should be recorded on the CRFs if healthcare professional-initiated, otherwise a simple statement reflecting participant preference will suffice. Participants who withdraw from trial treatment but continue with on-going follow-up and data collection should be followed-up in accordance with the trial protocol.

7.6 Trial Duration

Participant recruitment will proceed for 24 months or less if the necessary numbers are recruited sooner. The trial intervention will be for 36 months, and therefore the trial will be completed 60 months after commencement of recruitment, or 66 months after the start of the project, allowing 6 months to obtain regulatory approvals. Six months will be required at the end of the trial for data cleaning and analysis and for write up of the results before the project ends 72 months after its commencement.

8. Trial Procedures

8.1 Treatment of Participants

8.1.1 Experimental Arm

These participants will discontinue ACEi and/or ARB treatment (as detailed above). ACEi and/or ARB treatment will be discontinued from the point of randomisation onwards. If a participant is due to take an ACEi/ARB on the morning of the randomisation visit (i.e. before randomisation), this should be taken as normal. In order to compensate for the loss of anti-hypertensive activity, additional antihypertensive treatment will be commenced. Any antihypertensives used in routine clinical practice are permitted to control blood pressure throughout trial participation, but excluding ACEi or ARBs, except as a last resort. Any of the following alternative antihypertensives can be prescribed: calcium channel blockers, alpha- and beta-adrenoreceptor antagonists, hydralazine, minoxidil and thiazides. It is acceptable to use aldosterone receptor antagonists (e.g. spironolactone) in the experimental arm. The normal contraindications and safety precautions for use of these treatments should be adhered to, as per routine care. We recommend that the Renal Pharmacy Handbook is consulted in combination with the British National Formulary due to the complex prescribing needs of patients with Chronic Kidney Disease. In all cases, it is best to commence treatment at low doses and then increase to a therapeutic level. The choice of anti-hypertensive will depend on other treatment being taken by the participant and will be at the discretion of the responsible clinician.

8.1.2 Control Arm

These participants will continue on ‘standard’ care and will continue with their ACEi and/or ARB treatment. The choice and dose of ACEi and/or ARB will be at the discretion of the responsible clinician.

8.1.3 Both treatment groups

In both groups, BP will be controlled in participants in the trial to the target pressure outlined by the NICE Hypertension guideline (clinical guideline number 127) and NICE CKD guideline (clinical guideline number 73). The standard BP target will be used (≤140/85mmHg). Currently it remains unknown if there is an optimal BP for delaying renal progression and it is not clear whether there is any advantage to hypertension control using RAS blockade or BP reduction. ACEi/ARB can be used if the clinical status of the participant requires this at any time in the trial and this will be closely monitored with the potential for the DMEC to close the trial should there be significant dilution of the trial arms. All participants will remain in the study, irrespective of inability to control BP, as this may occur in normal clinical practice, but all efforts will be made to optimise BP and any treatment given will be recorded at the follow-up visit.

The monitoring of BP will be consistent with the NICE CKD guideline. As detailed home readings and 24 hour ambulatory BP readings are acceptable for the trial at baseline. Home readings or clinic BP readings are also acceptable a follow-up visits. An optimal BP of ≤140/85 mmHg (MAP ≤ 100) will be targeted if possible.

Between the 3-monthly visits, patients should be monitored and managed in accordance with local practice for follow-up of any change of therapy. Any changes in medication or visits to a GP practice or hospital should be noted on the Patient Diary and recorded on the CRF at the next clinic visit.

Measurement of ACE and renin levels at baseline and at 1, 2 and 3 years will be carried out as a measure of adherence, in addition to review of serum potassium concentrations which are measured as part of the routine biochemical profile taken 3 monthly.

Throughout the trial, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care to participants. A record of medication changes will be recorded in the CRF at each follow-up visit. In addition, the dose of ESA prescribed will be recorded.

Participants in both groups will continue to receive the best evidence-based medical management with other anti-hypertensive agents in order to maintain good BP control, as per routine clinical practice.

9. Investigational Medicinal Products (IMPs)

9.1 Name and description of IMPs

Participants will be randomised to the control arm: continuation of ACEi or ARB or combination of both or the experimental arm: discontinuation of ACEi or ARB or combination of both.

The following medications are the currently available ACEi and ARBs as detailed in the British National Formulary (BNF) and will be discontinued in those participants randomised to the experimental arm of the **STOP–ACEi** trial.

ARBs
Candesartan
Irbesartan
Telmisartan
Eprosartan
Losartan
Olmesartan
Valsartan
Azilsartan

ACEi
Lisinopril
Enalapril Maleate
Ramipril
Captopril
Cilazopril
Fosinopril Sodium
Moexipril Hydrochloride
Perindopril Erbumine
Perindopril Arginine
Quinapril
Trandolapril
Imidapril Hydrochloride

9.2 Summary of findings from non-clinical studies

ACE inhibitors were developed as therapeutic agents targeted for the treatment of hypertension. Since the initial application of these agents, several additional clinical indications have been identified including use in diabetes mellitus and heart failure and disorders of proteinuria. In animal models of hypertension, the efficacy of ARBs is equivalent to the efficacy of ACE inhibitors. In animal models that reflect complications of hypertension, such as kidney dysfunction, cardiac and vascular hypertrophy and stroke, ARBs and ACE inhibitors are also equally effective. These studies have demonstrated the beneficial effects of controlling BP, potentially preventing target organ damage in animal models of diabetes mellitus and the capacity to cause cardiac remodelling in cardiac injury models. However, in models of advanced renal disease there is little clinical data. Animal models of chronic renal disease and use of ACEi/ARBs have suggested that their renoprotective effects result primarily from inhibition of Ang II-mediated stimulation of angiotensin subtype 1 receptors. Previous data in Munich Wistar Fromter (MWF) rats, an experimental model for progressive kidney disease, have shown that the structural lesions associated with progressive kidney

disease are modified by the introduction of ACE inhibition therapy. The addition of ACEi led to a reduction in glomerulosclerosis and increase in glomerular mass suggesting regeneration of glomerular tissue. Indeed this has led to a normalisation of proteinuria and stabilised the serum creatinine in these models. However data in models of advanced renal disease are lacking due, in part, to the lack of proper animal models for chronic progressive renal disease and in vitro systems by which the effects of drugs could be tested with fairly established clinical relevance.

9.3 Summary of findings from clinical studies

Initial studies by Lewis, Ruggenenti and others have demonstrated that ACEi and ARBs reduced the doubling time of creatinine in patients with type I and type II diabetes and non-diabetic patients [8-19]. In 2006, Hou et al. added further weight to these findings with a significant 43% decrease in the composite end point of doubling of serum creatinine level, ESRD, or death [13]. A subsequent Cochrane Review explored the use of ACEi and ARBs in preventing the progression of kidney disease in the diabetic patient population and found that both ACEi and ARBs improved renal outcomes (ESRD, including doubling of creatinine, prevention of progression of micro- to macroalbuminuria, remission of micro- to normoalbuminuria) [20]. The authors however cautioned that there was little robust evidence of benefit in advanced CKD and that the conclusions were based mainly on composite end points. These studies suggesting that these agents are renoprotective in patients with CKD have formed the basis of guidelines which recommend the use of ACEi/ARBs in patients with proteinuria and/or diabetes, and have been transposed to apply to advanced CKD. However, the rigor of some of these studies, which have failed to dissociate the renoprotective effects that are specific for ACEi/ARBs from their anti-hypertensive effect are now being questioned by many nephrologists.

The Ramipril Efficacy in Nephropathy (REIN) Study was a large, multi-centre study that showed conclusive results. However, the REIN Study showed a limited beneficial effect of ACE inhibitors in reducing the progression of glomerular filtration rate despite a large difference in doubling of serum creatinine [19]. Some studies suggested that the beneficial effect of ACE inhibitors was mediated by other factors in addition to their antihypertensive effect. Most of the trials enrolled patients with a variety of non-diabetic kidney diseases, and subgroup analyses from some trials suggested a greater beneficial effect in patients with glomerular diseases, as compared with non-glomerular diseases. Renoprotection from ACEi/ARB may in fact be lost in more advanced disease where significant ischaemic nephropathy is present. This hypothesis is supported by reports in both diabetic and non-diabetic patients with CKD indicating that ACEi/ARBs may actually accelerate renal progression [22-23]; and in more advanced CKD the intrarenal haemodynamic effects of

ACEi/ARBs may decrease the time to renal replacement therapy. Furthermore, combined ACEi/ARB treatment has been shown in one large study to worsen renal outcomes in patients at high cardiovascular risk [24].

Trial evidence on the effectiveness and safety of ACEi/ARB discontinuation in advanced CKD is lacking; this is reflected in current guidelines which provide no specific instructions regarding ACEi/ARB in relationship to the severity of CKD [31].

The close interaction of the kidney and the heart is critical to survival. Cardiovascular events are more common in dialysis than pre-dialysis patients suggesting the increased importance of avoiding dialysis therapy, which accelerates cardiovascular risk. There are no studies assessing the benefits of ACEi/ARB therapy in cardiovascular risk reduction in advanced non-dialysis CKD. Several randomised controlled studies in dialysis patients have shown increased cardiovascular events with use of ACEi [29, 30].

The land mark observational study by El Nahas et al. has demonstrated that ACEi/ARB withdrawal in 52 patients with advanced CKD led to an overall mean increase in eGFR of 10ml/min/1.73m^2 over 12 months, and an increase or stabilisation in eGFR in all but 4 patients. A modest change in blood pressure was also observed, with no increase in cardiovascular events [25].

The results of **STOP-ACEi** will provide evidence as to whether discontinuation of ACEi/ARB is beneficial to renal function (improvement/stabilisation) and improving other important parameters including laboratory (hyperkalaemia, anaemia) and clinical outcomes including hospitalisation rates, physical function and quality of life without causing an increase in cardiovascular events, for which evidence is currently lacking. It will clarify whether the benefits of this intervention (withdrawal of ACEi/ARB) out-weigh the risks.

9.4 Summary of known and potential risks and benefits

ACEi and ARBs are medication primarily used to treat hypertension and congestive heart failure in addition to preventing kidney function decline in certain groups. The main benefit is lowering BP which also prevents a number of more serious secondary issues. The drawbacks of continuing therapy include minor things such as skin rashes, dizziness, altered taste sensation, headaches and a dry cough but also potentially deterioration in renal function and liver dysfunction. Other less common adverse effects of ACEi include sinusitis, rhinitis, dyspepsia, diarrhoea or constipation, myalgia and hyperkalaemia.

Renal replacement therapy with dialysis remains an expensive and undesirable therapeutic option for patients with CKD. Median survival on dialysis is only 3.5 years and is associated

with poor quality of life [32]. Data from Beddhu et al. who used propensity scores in a multivariate model in Dialysis Morbidity and Mortality Study Wave 2 patients showed that each 5-ml/min fall in MDRD GFR was associated with an increased hazard of death in a multivariable Cox model (hazard ratio [HR] 1.14; P = 0.002) [33]. There are few data on the effect of discontinuing ACEi/ARB on the cardiovascular event rate in this population (see above). Indeed no increased cardiovascular risk was noted in an observational cohort study from El Nahas et al. However, the potential risk of increased cardiovascular events for participants will be carefully assessed throughout the study using a detailed monitoring strategy, as outlined below. If the results of the study show a benefit for ACEi/ARB withdrawal, it could have a huge impact on patients, their families and health services, by reducing or delaying the need for dialysis and kidney transplantation.

The Reference Document for the trial is the current Summary of Product Characteristics (SmPC) for each of the ACEi/ARBs. Total worldwide exposure to ACEi/ARB is extensive. The most frequently reported adverse drug reactions include a dry cough, constipation and rashes. Hypersensitivity or anaphylactoid reactions occur very rarely and may lead to angioedema. Contraindications to the use of the IMP include known hypersensitivity to the drugs and those detailed in the BNF.

9.5 Route and administration and dosage

In the control arm (continuation of ACEi/ARB) drugs will be taken orally. The dose and choice of drug will be decided by the responsible clinician and will be titrated to achieve the target BP of ≤140/85 mmHg where possible. The responsible clinician can use any other antihypertensive medication for optimal patient care, as well as the ACEi/ARB, to achieve target BP in those cases which remain difficult to control and the clinician decides it is required.

9.6 Dosages, dose modifications and method of administration

In the control arm the dosage, given orally will be titrated according to BP to aim to achieve a BP of ≤140/85 mmHg where possible and according to the responsible clinician for optimal patient care.

In the experimental arm (discontinuation of ACEi/ARB), the responsible clinician can use any other antihypertensive medication as they see fit to achieve the BP target. Choice and dose of antihypertensive medication will be left with the responsible clinician. Any antihypertensives used in routine clinical practice are permitted to control blood pressure throughout trial participation, but excluding agents that inhibit the renin-angiotensin-aldosterone system, except as a last resort. Any of the following alternative antihypertensives

can be prescribed: calcium channel blockers, alpha- and beta-adrenoreceptor antagonists, hydralazine, minoxidil and thiazides. The normal contraindications and safety precautions for use of these treatments should be adhered to, as per routine care. We recommend that the Renal Pharmacy Handbook is consulted in combination with the British National Formulary due to the complex prescribing needs of patients with Chronic Kidney Disease. In all cases, it is best to commence treatment at low doses and then increase to a therapeutic level. The choice of anti-hypertensive will depend on other treatment being taken by the participant and will be at the discretion of the responsible clinician.

9.7 Source and labelling of IMPs

Participants will be randomised to the control arm: continuation of ACEi or ARB or combination of both, or the experimental arm: discontinuation of ACEi or ARB or combination of both. There will be no IMP to source or label in the experimental arm. Participants randomised to the control arm will continue ACEi or ARB or combination of both as prescribed in routine clinical practice and at the discretion of their responsible clinician. Participating hospital pharmacies will be responsible for the continued supply of medication for participants in the control arm throughout the trial as per routine local clinical practice. The medication will be commercial stock in standard packaging. As the medication is a continuation of the participant's standard treatment from the local pharmacy's own stock it will not be labelled as an IMP. Participants will be issued with a letter detailing instructions, and local and trial contact and reference details.

Regulation 46 of The Medicines for Human Use (Clinical Trial) Regulations 2004 allows for a particular situation where specific trial labelling is not required. This applies to trials of marketed products being (a) used within the terms of their marketing authorisation, (b) dispensed to a subject in accordance with a prescription given by an authorised health care professional and (c) labelled in accordance with the regulations that apply to dispensed relevant medicinal products. IMPs in the **STOP-ACEi** trial are marketed products being used within the terms of their marketing authorisation. They will be dispensed to the participant in accordance with a prescription given by an authorised health care professional (the participant's responsible clinician) and will be labelled in accordance with the regulations that apply to dispensed relevant medical products. The medication will be commercial stock in standard packaging. Therefore specific trial labelling is not required.

The IMP to be used in the **STOP-ACEi** trial can be labelled with a standard pharmacy dispensing label under the exemption described above and participants issued with trial information cards. This will be clearly documented in the submission in support of the Clinical Trials Authorisation (CTA) application.

9.8 Assessment of compliance

Compliance with the randomised treatment allocation will be evaluated at each clinic assessment and recorded on the CRFs.

10. Pharmacovigilance

Definitions of different types of adverse event (AE) are listed in *Table 2*. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the participant (this should be documented in the source data) with reference to the most recent updated SmPC for the IMP and expected events from IMP discontinuation as listed in Section 10.1.

Standard definitions are outlined in *Table 2*.

Table 2: Standard AE definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death; • is life-threatening; • requires hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability or incapacity; or

	• consists of a congenital anomaly or birth defect
Unexpected Adverse Reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorisation, in the SmPC for that product; (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question: (c) or clearly defined in this protocol
SUSAR	Suspected Unexpected Serious Adverse Reaction

10.1 Recording and assessment of adverse events

The last IMP administration or discontinuation for trial purposes will be on the date of the participant's final assessment at 3 years post trial entry. The participant will not be considered to be on trial treatment after this point. Treatment of the participant after the 3 year trial period is completely at the discretion of the responsible clinician. All adverse events will be reportable to the **STOP-ACEi** Trial Office up until the participant's final assessment at 3 years.

Adverse events will be recorded in the medical records and CRFs. Most AE/ARs that occur in this trial, whether they are serious or not, will be 'expected'.

Refer to *Table 3* for definition of expectedness.

Table 3: Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP) or discontinuation of the IMP clearly defined in this protocol
Unexpected	An adverse event which is not consistent with the information about

	the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP) or discontinuation of the IMP clearly defined in this protocol

Adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

The assessment of relationship of adverse events to the administration or discontinuation of the IMP is a clinical decision based on all available information at the time. The following categories as outlined in *Table 4* will be used to define the causality of the adverse event.

Table 4: Categorisation of causality

Category	Definition
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration or discontinuation of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events)
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration or discontinuation of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments)
Not related	There is no evidence of any causal relationship

The reference document to be used to assess expectedness against the IMP is the SmPC for that IMP. The SmPCs for each IMP can be accessed via the electronic Medicines Compendium (eMC) which contains up to date, easily accessible information about medicines licensed for use in the UK http://www.medicines.org.uk/emc/

Events that may possibly be expected from discontinuation of ACEi or ARB or combination of both are:

1. Hypertension
2. Hypokalaemia
3. Increased peripheral oedema
4. Gout
5. Change in urinary proteinuria
6. Weight gain
7. Increase in breathlessness

Cardiovascular events such as myocardial infarction (MI), stroke and heart failure could potentially be expected from ACEi/ARB withdrawal but may equally be expected from progression of the patient's CKD. It is more likely that cardiovascular events occurring within the first 3 months of ACEi/ARB withdrawal could be related to ACEi/ARB withdrawal and cardiovascular events occurring after 3 months of ACEi/ARB withdrawal are related to the patient's disease progression. This should be considered by the responsible clinician when assessing the relatedness and expectedness of any cardiovascular events that occur in patients who have discontinued ACEi/ARB treatment.

All cardiovascular events will be reported as AEs, ARs, SAEs, SARs, or SUSARs, as appropriate. The DMEC will closely monitor the incidence of all SAEs, including cardiovascular events across the whole trial population throughout the trial. Trial evidence of ACEi/ARB superiority in reducing cardiovascular risk when compared with other antihypertensive drugs, such as diuretics or calcium channel blockers, is lacking. Indeed the other ancillary mechanisms (reduction in angiotensin II–mediated vasoconstriction, thrombosis, salt/water retention, oxidative stress and inflammation, and promotion of vascular remodelling and restructuring) have not been shown to add significantly to the reduction of cardiovascular risk in patients with diabetes or non-diabetes. Indeed a recent meta-analysis of all studies published online on 3rd October 2013 in the British Medical Journal has confirmed that there is no difference in ACEi versus non ACEi therapy in cardiovascular events. "There is little evidence from these overviews to support the preferential choice of particular drug classes for the prevention of cardiovascular events in chronic kidney disease" [34]. It is an objective of the **STOP-ACEi** trial to assess whether discontinuing ACEi/ARBs does not cause excess harm (e.g. increased cardiovascular events) and does not cause adverse effects.

The **STOP-ACEi** Trial protocol will be used as the reference document to assess disease related and/or procedural expected events.

10.2 Non-serious adverse events / adverse reactions

Refer to Table 2 for definitions

All such events, whether expected or not, should be recorded in the participant's hospital notes and on the relevant CRF and sent to the **STOP-ACEi** Trial Office.

10.3 Serious Adverse Events

Refer to Table 2 for definitions

All SAEs will be recorded in the hospital notes and should be reported to the **STOP-ACEi** Trial Office on a SAE Form. The completed form should be faxed to the **STOP-ACEi** Trial Office on **0121 415 9135**, as soon as possible and within 24 hours of becoming aware of the event. The Principal Investigator should be able to respond to any related queries raised by the **STOP-ACEi** Trial Office as soon as possible.

10.3.1 Expected SAEs NOT to be reported on a SAE Form

Expected SAEs are those listed in the current SmPC for the trial IMPs and Section 10.1 and can be excluded from the expedited reporting outlined in Section 10.4, for example if they are expected to occur on a regular basis and offer no further new information to the safety profile. These events should continue to be recorded in the source data and relevant CRFs.

In addition, events **NOT** considered to be SAEs are hospitalisations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and has not worsened

Note: Death from any cause should be reported on an SAE Form and returned to the **STOP-ACEi** Trial Office.

10.4 SUSARs

Refer to Table 2 for definitions

SAEs classed by the local investigator as both suspected to be related to the trial IMP or discontinuation of the IMP and unexpected are categorised as SUSARs, and are always subject to expedited reporting. An SAE Form should be completed, and faxed to the **STOP-**

ACEi Trial Office within 24 hours of the research staff at the site becoming aware of the event.

The Chief Investigator (or nominated individual) will undertake urgent review of all such SAEs and may request further information immediately from the clinical team at site. The Chief Investigator will not overrule the causality, expectedness or seriousness assessment given by the local investigator but may add additional comment on these.

SUSARs will be notified to the MHRA and MREC by the **STOP-ACEi** Trial Office. SUSARs that are fatal or life-threatening will be notified to the MHRA and REC within 7 days after the **STOP-ACEi** Trial Office has been notified. Other SUSARs will be reported to the main REC and MHRA within 15 days after the Trial Office has been notified.

10.5 Development Safety Update Reports

The **STOP-ACEi** Trial Office will provide the MREC and the Medicines and Healthcare products Regulatory Agency (MHRA) with Development Safety Update Reports (DSURs). The reports will be submitted within 60 days of the anniversary date of the MHRA clinical trial authorisation (Developmental International Birth Date (DIBD)) of the trial each year until the trial is declared ended.

10.6 Annual progress reports

An annual progress report will be submitted to the MREC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

10.7 Pregnancy

Participants will be asked to inform members of their research team at the site of any pregnancies (i.e. of female participants or female partners of male participants) which occur during the trial participation period. All pregnancies will be recorded on the CRF and followed up for outcome, any outcome meeting the definition of an AE/SAE will be reported to the **STOP-ACEi** Trial Office on the relevant CRF and SAE form, as necessary. It is unlikely that pregnancies will occur in this patient group due to the severity of CKD, but if a pregnancy does occur the patient will be counselled by her responsible clinician in regards to the risks to the participant, the participant's renal function and the foetus. ACEi and ARB medications should be discontinued in pregnancy in addition to other potential medications. The responsible clinician will adjust all medication as required for the pregnancy to continue if desired. The patient will be monitored throughout this.

10.8 Reporting urgent safety measures

If any urgent safety measures are taken by a Principal Investigator they shall immediately and in any event no later than 24 hours from time of the measures being taken, inform the BCTU by fax (0121 415 9135). If any urgent safety measures are taken the Principal Investigator/BCTU/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the MREC of the measures taken and the circumstances giving rise to those measures. BCTU shall inform the Sponsor of any urgent safety measures taken, or that they are informed of, within 24 hours of being informed of the event.

10.9 Notification of Serious Breaches of GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

The BCTU on behalf of the Sponsor shall notify the MREC and MHRA in writing of any serious breach of:

(a) the conditions and principles of GCP in connection with the trial; or

(b) the protocol relating to the trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

11. Data Management and Quality Assurance

11.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The CRFs, other than the SAE Form, will not bear the participant’s name. The participant’s initials, date of birth and trial identification number, will be used for identification.

11.2 Data collection

A CRF is required and should be completed for each individual subject. The completed original CRFs are the sole property of the sponsor and should not be made available in any

form to third parties except for authorised representatives or appropriate regulatory authorities without written permission from the sponsor.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The **STOP-ACEi** Trial Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

The CRFs will comprise of (but NOT limited to) the following Forms (*Table 5*):

Table 5: Data Collection Forms

Form Name	Schedule for submission
Randomisation Notepad	Collected at randomisation
Baseline and follow-up CRFs	As soon as possible after each follow-up assessment time point
Serious Adverse Event Form	Faxed within 24hrs of research staff at site becoming aware of event

11.3 Data handling and analysis

CRFs can be entered online at http://www.trials.bham.ac.uk/stopacei. Authorised staff at sites will require an individual secure login username and password to access this online data entry system. Paper CRFs must be completed, signed/dated and returned to the **STOP-ACEi** Trial Office by the Investigator or an authorised member of the site research team (as delegated on the **STOP-ACEi** Trial Signature & Delegation Log) within the timeframe listed above.

Entries on the CRF should be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. All missing and ambiguous data will be queried. All sections are to be completed.

Investigators will keep their own study file logs which link patients with anonymised CRFs. The Investigator must maintain documents not for submission to the Trials Office (e.g.

STOP-ACEi Patient Recruitment and Identification Logs and **STOP-ACEi** Screening Logs) in strict confidence.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate. The investigator has ultimate responsibility for the collection and reporting of all clinical safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely, enduring and available when required. The CRFs must be signed by the investigator or an authorised staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs source documents must be dated, initialled and explained and should not obscure the original entry.

In most cases the source documents are the subject's medical records. In these cases, data collected on the CRFs must match the data in the medical records.

CRFs may be amended by the **STOP-ACEi** Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

11.4 End of Trial

The end of the **STOP-ACEi** trial will be defined as when the final participant recruited reaches the 3 year follow-up time-point.

11.5 Direct Access to Source Data

The investigator(s)/institution(s) will permit trial-related monitoring, audits and REC review and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion and will consent to provide access to their medical notes.

12. Archiving

Archiving will be authorised by the BCTU on behalf of the Sponsor following submission of the end of trial report.

Principal Investigators are responsible for the secure archiving of essential trial documents for their site, according to the local policy at that site. All essential documents will be archived for a minimum of 5 years after completion of trial.

Destruction of essential documents will require authorisation from the BCTU on behalf of the Sponsor.

13. Statistical Considerations

13.1 Outcome Measures

13.1.1 Primary outcome measure

- Renal function measured using MDRD 4-variable eGFR at 3 years

13.1.2 Secondary outcome measures

- Cystatin-C;
- BP;
- Number of participants starting renal replacement therapy or sustaining a >50% decline in eGFR;
- Time taken to reach ESRD or need for renal replacement therapy;
- Hospitalisation rates from any cause;
- Participant quality of life and wellbeing (measured using the KDQOL-SF™ v1.3 questionnaire);
- Participant physical function (measured using the 6-minute walk test);
- That withdrawal of these treatments does not cause excess harm (e.g. increased cardiovascular events such as heart failure, hypertension, myocardial infarction, stroke) and is not associated with an increase in adverse effects;
- Mortality.

13.1.3 Secondary Mechanistic Outcome Measures:

- Urine protein excretion;
- Haemoglobin concentration;
- Dose of ESA.

13.2 Sample size and recruitment

13.2.1 Sample size calculation

Limited data was available upon which to calculate the sample size for the **STOP-ACEi** trial. One observational study by Ahmed et al., provided data on eGFR in 52 patients with

advanced CKD in the 12 months prior to stopping ACEi/ARB treatment, at the point of stopping ACEi/ARB and 12 months after stopping (see *Table 6* below) [25]. This data was used for the basis of the sample size calculation.

Table 6:

Mean ± Std.Err (Std.Dev)	12 months before ACEi/ARB stopped	When ACE'/ARB was stopped	12 months after ACEi/ARB was stopped
eGFR (ml/min/1.73m^2)	22.9 ± 1.4 (10.1)	16.38 ± 1 (7.2)	26.6 ± 2.2 (15.9)

To err on the side of caution, the largest standard deviation above was used to estimate the variability for the eGFR (i.e. a SD of 16 ml/min/1.73m^2) for the sample size calculation. To detect a minimum relevant difference (MRD) between groups of 5 ml/min/1.73m^2 (i.e. effect size of 0.31) with 80% power and alpha=0.05, a total of 410 participants (205 per group) will need to be recruited (this includes allowance for 20% dropout). These figures are based on a 2-sample T-test.

As part of the interim analyses presented to the DMEC, a review of the sample size assumptions regarding the variability of the eGFR will be included, by calculating the mean and standard deviation for the eGFR at baseline for all participants randomised at that point into **STOP-ACEi**. If the assumptions do not hold, then the sample size may be re-calculated based on these data.

13.3 Statistical analysis

A separate Statistical Analysis Plan for the **STOP-ACEi** trial provides a detailed description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those who are randomised to discontinue ACEi/ARB therapy and those randomised to continue with ACEi/ARB therapy. All analyses will be based on the intention to treat principle, with all patients analysed in the arms to which they were allocated irrespective of compliance with the randomised allocated treatment, and all patients will be included in the analyses. For all tests, summary statistics (e.g. mean differences, relative risks) will be reported and 95% confidence intervals will be constructed where appropriate. For all analyses, a p-value <0.05 will be considered statistically significant and there will be no adjustment for multiple testing.

13.3.1 Primary outcome analysis

The primary endpoint for this trial is assessment of renal function (using MDRD 4-variable eGFR) between the two treatment groups at 3 years.

The primary outcome is the continuous measure eGFR at 3 years. These data will be summarised using means and standard deviations, with differences in means and 95% confidence intervals reported. The two groups will be compared at 3 years using both a 2-sample T-test and ANCOVA to adjust for baseline scores. Longitudinal plots of the data over time will also be constructed for visual presentation of the data. As a secondary analysis, a repeated measures analysis, including a treatment by time cross-term, will be carried out on all data across the entire 3 years of follow-up.

It is anticipated that the randomisation strategy will be successful, so the primary analysis can be conducted using an un-adjusted analysis. However, there may be a need for further regression analysis to control for the effects of confounding variables.

13.3.2 Secondary outcome analysis

The secondary endpoints for the trial include both continuous and categorical data items.

Continuous endpoints (e.g. BP, quality of life):

Any secondary endpoints that are continuous in nature will be analysed in the same way as the primary outcome.

Categorical (dichotomous) endpoints (e.g. hospitalisation rates):

For dichotomous secondary endpoints, the proportion of participants and percentages will be compared between arms using a chi-squared test. Relative risks and 95% confidence intervals will be calculated. Logistic regression may be used to allow for covariates in the model.

Time to Event endpoints (e.g. time to ESRD, mortality):

These endpoints will be compared between treatment arms by using survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons. It is anticipated that the randomisation strategy will be successful, so the primary analysis can be conducted using a simple log-rank test. In the event that important covariates are unbalanced between groups, a secondary analysis will be carried out using a

Cox proportional hazards or an extended Cox model to account for any differences. Treatment effects will be expressed as hazard ratios with 95% confidence intervals.

13.3.3 Missing data and sensitivity analyses

Primary analysis will concentrate on available data only, with no attempt made to impute missing data. Where appropriate, sensitivity analyses will be carried out to examine the possible impact of missing data on the results (full details of this is in the Statistical Analysis Plan).

13.3.4 Subgroup analyses

The minimisation variables in the randomisation process will be diabetes (Type 1 diabetes, Type 2 diabetes (including insulin-treated Type 2 diabetes), non-diabetic), BP (mean arterial pressure (MAP) measured as {[2 x diastolic] + systolic}/3; <100 or ≥100), age (<65 years or ≥ 65 years), proteinuria (PCR <100 or ≥ 100), and eGFR measurement (<15 ml/min or ≥ 15ml/min).

Several a *priori* subgroup analyses are planned with respect to the above minimisation variables for both primary and secondary outcomes. Given the well-known dangers of subgroup analyses, these analyses will be treated as hypothesis-generating. Subgroup analyses will employ a test of interaction to explore whether there is evidence that the treatment effects differ across subgroups. Any other analyses that are not pre-specified will be deemed post hoc and the limitations related to this form of analysis will be acknowledged in any subsequent publication.

13.4 Interim analyses

Interim analysis of the data with respect to adverse events and serious adverse events will be performed every 3-4 months and sent to the DMEC. A full efficacy and safety analysis report will be reviewed by the DMEC on an annual basis or more frequently if required by the DMEC or Trial Management Committee. The DMEC will outline and agree the stopping rules for the trial which will be documented in the DMEC charter. It is likely that the Haybittle-Peto boundary will be used. This states that if an interim analysis shows a probability of less than 0.001 that the treatments are different, then the trial should be stopped early. This Haybittle-Peto approach will be used as stopping guide, alongside data on important secondary endpoints and all other relevant evidence. A DMEC report and charter outlining the terms of reference (including information on stopping rules) will be agreed with the DMEC. The report will specify which endpoints are to be included in the reports to the Trial Steering Committee.

13.5 Final analysis

The final analysis for the **STOP-ACEi** trial will occur once the last randomised participant completes the 3 years follow-up.

14. Ethics and Regulatory Requirements

The BCTU, on behalf of the sponsor, will ensure that the trial protocol, PIS, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and the MREC, prior to any participant recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval (Clinical Trial Authorisation) prior to implementation.

Before a site can enrol participants into the trial, the Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

Within 90 days after the end of the trial, the BCTU, on behalf of the sponsor, will ensure that the MREC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The Chief Investigator will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and MREC within one year after the end of the trial.

15. Monitoring Requirement for the Trial

Monitoring of this trial will be to ensure compliance with GCP. A risk proportionate approach to the initiation, management and monitoring of the trial will be adopted (as per the MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products) and outlined in the trial-specific risk assessment/monitoring plan.

16. Finance

The National Institute for Health Research (NIHR) and the Medical Research Council (MRC) Efficacy and Mechanism Evaluation (EME) Programme (11/30/07) is funding this trial with Comprehensive Clinical Research Network (CCRN) support. Therefore no individual per patient payments will be made to NHS Trusts, Investigators or participants. Excess cost for the study remains part of NHS costs while study investigations outside routine care and not covered by the CLRN will be funded. These include cystatin C, ACE and renin levels and NT-proBNP. The CCRN will provide funding for research nurse support.

17. Indemnity

As it is not an industry-sponsored trial, ABPI guidelines on indemnity do not apply and there are no special arrangements for compensation for any non-negligent harm suffered by patients as a result of participating in the study. The normal NHS indemnity liability arrangements for clinician initiated research will, therefore, operate – see NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996. It should be noted, however, that negligent liability remains the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for their patients.

This is an NHS-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the Trust R&D department. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

18. Dissemination and Publication

The Chief Investigator will coordinate dissemination of data from this trial. All publications and presentations, including abstracts, relating to the main trial will be authorised by the **STOP-ACEi** Trial Management Group. The results of the analysis will be published in the name of the **STOP-ACEi** Collaborative Group in a peer reviewed journal (provided that this does not conflict with the journal's policy). All contributors to the trial will be listed, with their contribution identified. If requested, trial participants will be sent a summary of the final results of the trial, which will contain a reference to the full paper.

All publications using data from this trial to undertake original analyses will be submitted to the Trial Management Group for review before release. To safeguard the scientific integrity of

the trial, data from this trial will not be presented in public before the main results are published without the prior consent of the Trial Management Group.

19. Statement of Compliance

The **STOP-ACEi** trial will be conducted in compliance with the approved protocol, GCP, the Research Governance Framework and the applicable regulatory requirements.

20. References

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