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 4.0, 25th April 2019

Sponsor:	Hull University Teaching Hospitals NHS Trust (Ref. No.: R1578)
Chief Investigator:	Professor Sunil Bhandari Hull University Teaching Hospitals NHS Trust
Coordinating Centre:	Birmingham Clinical Trials Unit (BCTU)
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UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

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STOP-ACEi Trial Office

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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, 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), General Data Protection Regulations 2018, the Trust Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care Research and other regulatory requirements as amended.

Chief investigator

Professor Sunil Bhandari
Hull University Teaching
Hospitals NHS Trust

Signature

01/05/2019

Date

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07/05/2019

Date

Trial Statistician

Natalie Ives
BCTU
University of Birmingham

Signature

26/04/2019

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

PI name and institution	Signature	Date

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
NYHA	New York Heart Association
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	95 months (6 months set-up, 47 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 BP readings within the previous month or a 24h ambulatory BP 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

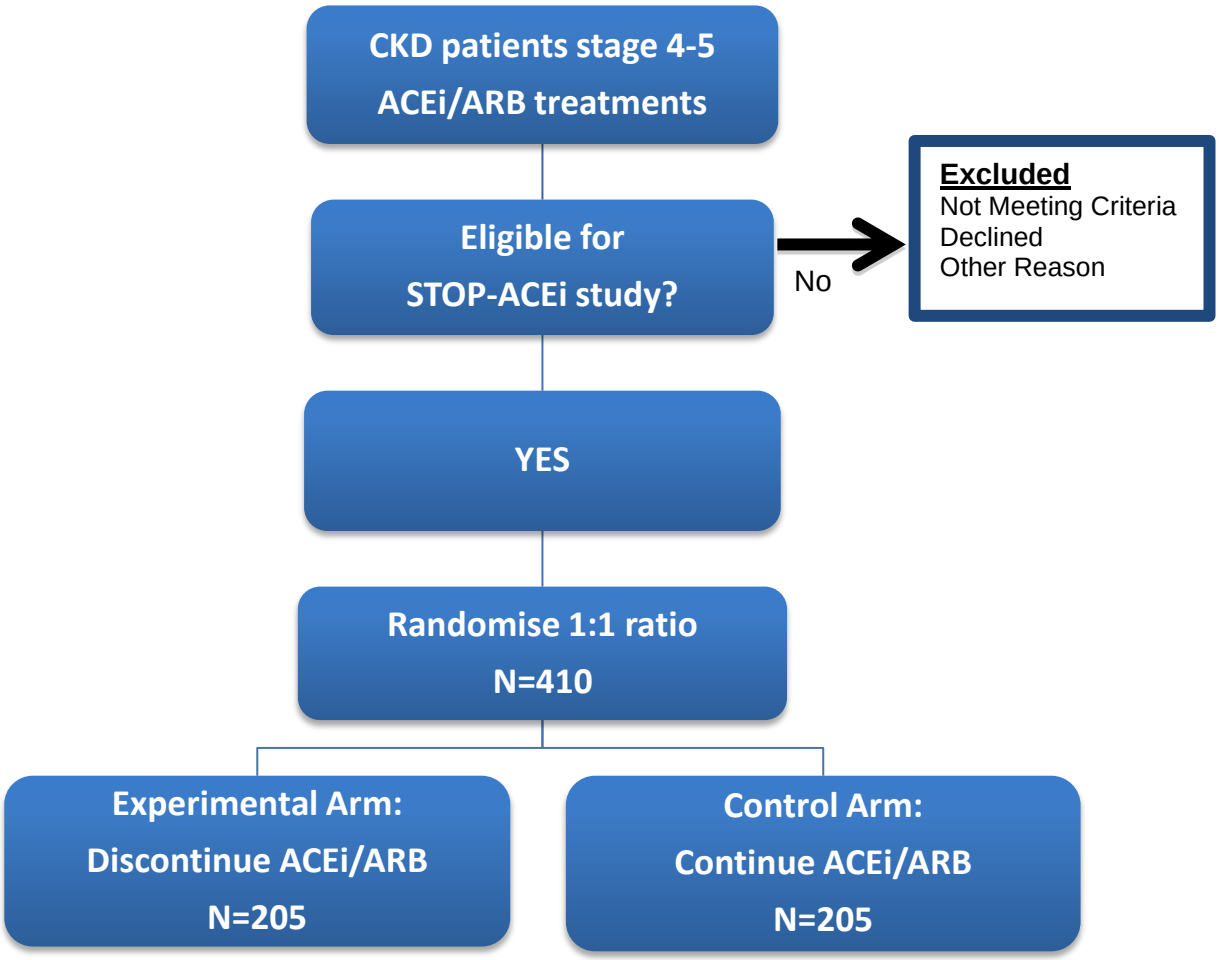
Chronic kidney disease (CKD) affects 1 in 10 adults in the UK and describes progressive loss of function of the kidneys over a period of months or years regardless of the original kidney disease. CKD can have serious implications for those affected including a risk of CKD progressing to complete kidney 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

4 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 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 BP 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 BP 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.

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;
- BP 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 BP reading within the previous month or a 24h ambulatory BP 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.

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. 410 participants will be recruited from 20-40 UK centres. The three main centres will be Hull, 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 the Queen Elizabeth Hospital Birmingham has identified 710 patients under follow-up in CKD clinics 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. 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. 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 (protein: creatinine ratio (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.

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 ±6 weeks is permitted for each visit. Therefore, the visit window permits collection of trial outcome data alongside routine clinical visits, in keeping with a pragmatic trial design. A visit should be attributed to the nearest trial visit due date. Where there have been multiple clinical visits within a trial visit window, the data nearest the trial visit due date should be used. Care should be taken to ensure collection of the research-specific assessments needed for trial outcome analysis at the annual time points wherever possible. 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 number of attendances and tests performed will not be significantly altered by trial participation.

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, eGFR and the dose of ESA drug will be recorded at each 3-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. 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 (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. 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 reported by the participant should be recorded in the source data and reported on the case report form (CRF) for 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. 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.

The following tests, which are required for trial outcome analysis, will be performed at each follow-up visit. Samples will be collected and tests performed in accordance with local practice, and the result reported on the trial CRF.

- Serum creatinine
- Haemoglobin
- Urinary PCR. Quantification of proteinuria will be carried out by measurement of the PCR 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. Where possible, an early morning sample should be used.

In addition, if the following tests are performed as part of routine clinical monitoring, they should be reported on the trial CRF. However, additional testing is not required if these tests are not clinically required:

- FBC – platelet count
- Biochemical Profile:
    - Sodium
    - Potassium
    - Bicarbonate
    - Calcium
    - Phosphate

  - Alkaline phosphatase
  - Albumin
  - Total protein
  - Alanine transferase
- C-reactive protein (CRP) analysis (at annual visits only)

A number of tests are required in addition to those completed at routine clinics. The samples will be taken and prepared at the local site, stored for transport in batches to the central lab, and analysed centrally. A source record should be made to document the taking of these sample and any issues with sample preparation/storage. Samples for these analyses will be taken at annual trial visits only.:

- Cystatin C
- NT-proBNP
- ACE and renin levels will be measured at baseline and annually to the end of the trial to examine for potential non-adherence with the randomised trial treatment allocation, 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 University Teaching 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 (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 level corridor/walkway 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.

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 (± 6 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 including assessment of NHYA class and Framingham criteria for participants with heart failure			Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Routine tests															
Tests required for trial outcome analysis: ● Serum creatinine ● Haemoglobin ● Urinary PCR or ACR by early morning spot urine where possible		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Report results of routine tests where these are performed for clinical care*		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
CRP. Report result where performed for clinical care.		Y					Y				Y				Y

Trial visit number		**1**	**Phone call**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit/month (± 6 weeks)	**Screening**	**Baseline**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**
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
Take and store serum and plasma samples required for trial outcome analysis (all participants):** ● Cystatin-C ● NT-proBNP ● 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.

* Where performed as part of clinical care, the following results should be reported on the CRF:
Biochemical profile - sodium, potassium, bicarbonate, calcium, phosphate, alkaline phosphatase, albumin, total protein and alanine transferase
Full blood count - platelets.

** See trial samples guide for details of sample preparation. Samples will be prepared and stored locally, then transported in batches to a central laboratory for analysis.

*** 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.

Many of the outcome measures for the STOP-ACEi trial are recorded as part of routine clinical monitoring for patients with advanced CKD. If a patient expresses a wish to withdraw from full trial follow-up, they should be asked if they would be happy to allow continued collection of data

from their clinical records for use in the trial, without further trial-specific follow-up. This is especially appropriate where a patient wants to withdraw due to the burden associated with the additional research assessments or due to worsening disease burden (e.g. at the point of commencing dialysis). This partial withdrawal will enable collection of as full a data set as possible for the trial and support an Intention to treat analysis, while reducing burden/inconvenience for the participant. For participants that opt for partial follow-up, treatment should revert to that clinically indicated; this may or may not include use of ACEi/ARBs. A clear record should be made in the patient's medical records so it is clear which aspects the patient has withdrawn from and what consent remains. It is accepted that the trial data set will be incomplete for those that have partially withdrawn since any research-specific assessments or tests not clinically indicated will not be performed, as per the scope of the patient's consent. However, the partial data collection is preferable to complete withdrawal. Generally, it is expected that the following outcome data will be available in the medical records for a participant that has partially withdrawn, though local practice may vary:

- Serum creatinine (to calculate renal function by MDRD 4-variable eGFR; primary outcome), where measured for clinical care
- BP, where measured for clinical care
- Commencement of renal replacement therapy, including the date
- Hospitalisations, though it is recognised this may be limited to hospitalisations at the Trust where the patient is seen for trial follow-up or those otherwise noted in the medial records
- Cardiovascular events and adverse effects, where recorded
- Mortality
- Urinary PCR or ACR, where measured for clinical care
- Haemoglobin, where measured for clinical care
- Dose of ESA, where recorded, e.g. in prescription records
- Treatment compliance data, where ACEi/ARB use is recorded, e.g. in prescription records

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. The treatment non-

compliance should be recorded in the source data (e.g. prescription records) and reported in the CRF.

7.6 Trial Duration

Participant recruitment will proceed for at least 24 months. 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 may be commenced. Any antihypertensives used in routine clinical practice are permitted to control BP 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 CKD. 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 at 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 reported by the participant should be recorded in the source data and reported on the CRF for 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. Medication changes will be recorded in the source data at each follow-up visit, and reported in the CRF. In addition, the dose of ESA prescribed will be recorded in the source data and reported in the CRF.

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.

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.

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 BP 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 medications 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 identified in section 10.6.1.

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 BP 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 CKD. 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 or primary care 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 by checking prescription records and enquiring with the participant. Compliance will be recorded in the source data and reported on the CRFs.

10. Pharmacovigilance

Definitions of different types of adverse event (AE) are listed in *Table 2*.

Table 2: Standard AE definitions

Term	Abbreviation	Definition
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction	AR	Any untoward and unintended responses to an IMP related to any dose administered.
Serious adverse event (SAE)	SAE	Any untoward medical occurrence or effect that: • results in death; • is life-threatening; • requires hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability or incapacity; • consists of a congenital anomaly or birth defect; or • is otherwise considered medically significant by the Investigator.

Serious Adverse Reaction	SAR	An Adverse Reaction which also meets the definition of a Serious Adverse Event.
Unexpected Adverse Reaction	UAR	An AR, the nature and severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or Summary of Product Characteristics (SmPC) for a licensed product. When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	**SUSAR**	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

10.1 Reporting requirements

The collection and reporting of AEs will be in accordance with the UK Clinical Trial Regulations and the requirements of the Medicines and Health care products Regulatory Agency (MHRA). Definitions of different types of AEs are listed in the table of abbreviations and definitions (Table 2).

The Investigator should document all AEs experienced by the trial participant in the source data and assess their seriousness. All SAE reports must be reviewed, signed and dated by the Principal Investigator within 7 days of site's awareness of the SAE.

10.2 Adverse Events Requiring Reporting in STOP-ACEi

For trial purposes, the adverse event reporting period will commence at the patient's consent and continue until 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.

The safety profile for the trial population and IMPs are well established so, although all AEs should be recorded in the source data, a strategy of targeted reporting of AEs will therefore not affect the safety of participants. The reporting of only the following subset of AEs (Table 3) via the CRFs, for the appropriate period, is consistent with aims of the trial.

Since the trial treatments are part of standard care for the trial population, AEs will be detected from routine clinical monitoring, e.g. from clinically indicated investigations, routine testing and patient-reported symptoms. An ECG will also be performed annually, which may be beyond standard clinical monitoring in some cases. Since it is of particular interest for the trial intervention, participants with heart failure should have additional assessment at trial visits to enable reporting of the New York Heart Association (NYHA) class and Framingham criteria on the CRF (see below for details). Beyond that, no additional trial-specific safety monitoring is required.

The NYHA class will be reported as one of the following:

- Class 1: Patients with no limitation of activities, they suffer no symptoms from ordinary activities.
- Class 2: Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
- Class 3: Patients with marked limitation of activity; they are comfortable only at rest.
- Class 4: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Positive diagnosis of heart failure by the Framingham criteria requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria. It is not necessary to perform additional tests but the criteria will be reported as ‘met’, ‘unmet’ or ‘not known’ on the CRF. For example, it is not necessary to perform a chest x-ray to detect radiographic cardiomegaly if one is not otherwise clinically indicated but, where cardiomegaly has been observed, it should be recorded in the source data (e.g. in medical records or clinical reports) and reported on the CRF. The major Framingham criteria are:

- Paroxysmal nocturnal dyspnoea
- Neck vein distention
- Rales
- Radiographic cardiomegaly
- Acute pulmonary oedema
- S3 gallop

- Increased central venous pressure (>16 cm H2O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to treatment

The minor Framingham criteria are:

- Bilateral ankle oedema
- Nocturnal cough
- Dyspnoea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Decrease in vital capacity by one third from maximum recorded
- Tachycardia (heart rate >120 beats/min.)

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 meta-analysis of all studies has confirmed 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.

Table 3: AEs to be reported in STOP-ACEi

Type of event	How to record in source data	How to report	Risk consideration
Out of range lab result	As per standard practice, e.g. on a lab report.	Targeted lab results only will be reported on the CRF (see section 7.4.3).	Deranged lab results are a feature of CKD, so additional monitoring or reporting beyond routine clinical care is unlikely to be informative. Lab values of significance for the intervention and trial population will be recorded on the CRF.
Non-serious AEs (other than out of range lab results). This would include new conditions/diagnoses and patient-reported symptoms.	As per standard practice, e.g. in medical records or clinical investigation reports.	At each follow-up visit, report on the CRF all AEs that have occurred since the previous trial visit. Most events are simply listed under the appropriate clinical category, e.g. pulmonary, gastrointestinal etc. Events of particular interest to the intervention or patient population are recorded in dedicated sections of the CRF. These include: • CKD progression • Cardiovascular events (hospitalisation for heart failure, myocardial infarction, stroke or cerebrovascular event). • For participants with heart failure, the NYHA classification, Framingham criteria and treatment details should be reported. In addition, the patient-completed KDQOL-SF™ contains symptom scales.	Since the trial IMPs are very well characterised and form part of standard treatment for the trial population, collection of non-serious AEs is unlikely to add to the safety profile of the treatments used. However, collection of AEs detected from routine clinical monitoring will help indicate whether the trial intervention is associated with increased adverse events, which is one of the trial secondary outcomes. Simple recording in accordance with routine clinical care and collection of AEs via the CRFs will adequately facilitate this.
SAEs	See section 10.3.		

10.3 Serious Adverse Event Reporting in STOP-ACEi

For all SAEs, the Investigator will do one of the following three procedures (Figure 1):

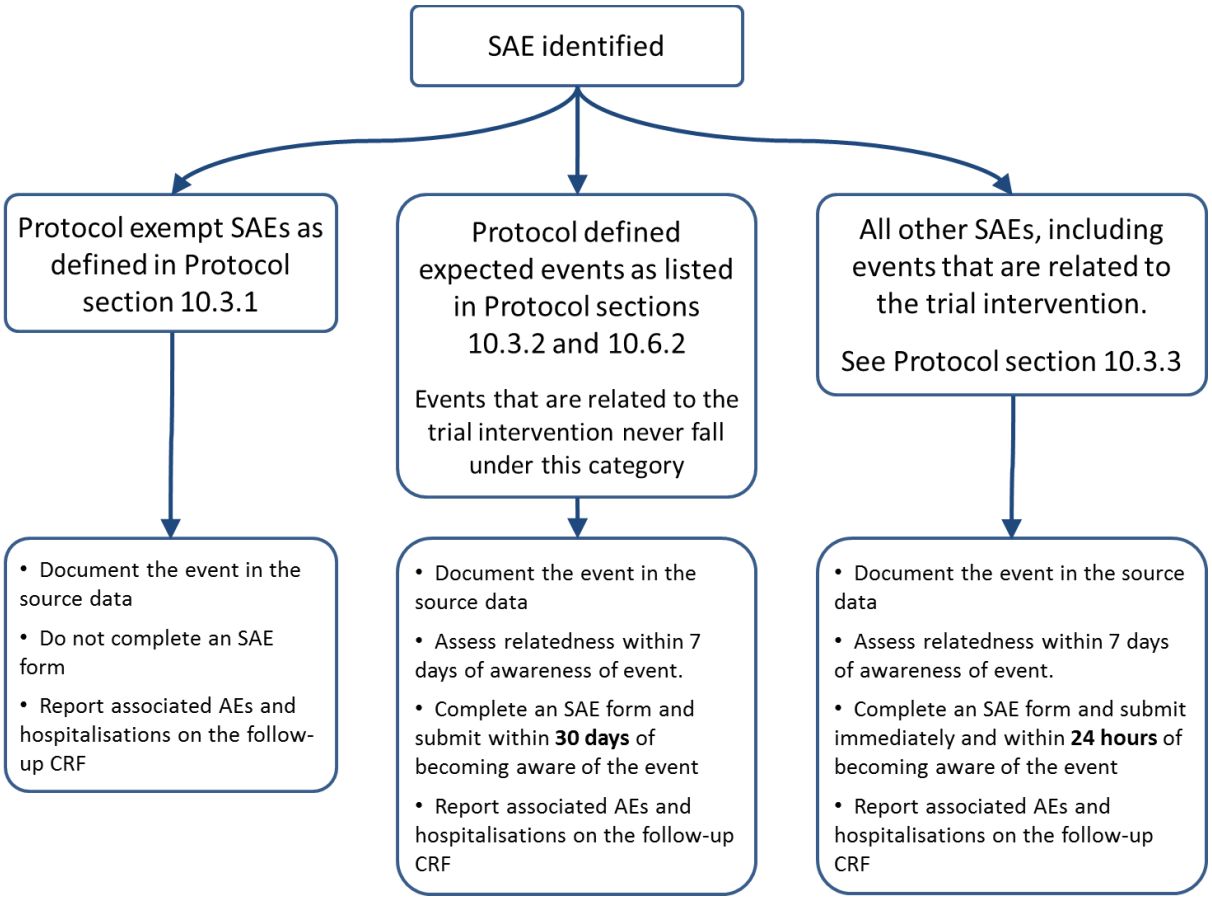
- record protocol-exempt SAEs, as defined in section 10.3.1, in the medical notes but such events do not require reporting to the sponsor/CTU on an SAE form.
- where the SAE does not require expedited (immediate) reporting, as defined in section 10.3.2, it should be reported to the trials office on an SAE report within 30 days of becoming aware of the event.

- where the event requires expedited reporting, as defined in section 10.3.3, it should be reported to the trials office immediately and within 24hrs of the Investigator becoming aware of the event.

All SAE reports must be reviewed, signed and dated by the Principal Investigator within 7 days of site's awareness of the SAE.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial treatment or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs in an expedited manner, regardless which department first becomes aware of the event.

Figure 1: Flowchart for reporting of SAEs in STOP-ACEi



10.3.1 Events not requiring reporting to the Sponsor/CTU on an SAE form

At whatever time they occur during an individual's participation in the trial, the following are "protocol exempt" SAEs.

- Pre-planned hospitalisation

- Hospital admissions lasting less than 24 hours

All events which meet the definition of serious must be recorded in the participant notes throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. However, any hospitalisations or associated AEs should still be reported on the CRF.

10.3.2 Events requiring non-expedited reporting to the Sponsor/CTU on the SAE form

The safety profiles of the trial IMPs are well established and they will be used in accordance with their existing licences. The study population typically have co-morbidities associated with older age and their advanced CKD including diabetes, hypertension, anaemia or cardiovascular disease. Many adverse events are anticipated due to the participants' clinical condition and the many associated clinical interventions including polypharmacy, which is widespread in the population. Causality is therefore difficult to determine from individual cases.

The events defined in the Protocol as "expected" (see Section 10.6.2) should be recorded by the trial team in the subject's notes and on the SAE form, but do not require expedited reporting (immediately on the Investigator becoming aware of the event) since the assessment of expectedness for individual events has been pre-defined.

Note that any events thought to be possibly, probably or definitely related to the trial intervention must always be reported immediately, and within 24hrs of the Investigator becoming aware of the event, irrespective of inclusion in this list. All SAE reports must be reviewed, signed and dated by the Principal Investigator within 7 days of site's awareness of the SAE.

10.3.3 Events that require expedited reporting to the Sponsor/CTU on the SAE form

All SAEs, except those listed in Sections 10.3.1, 10.3.2 and 10.6.2, occurring within the reporting period, should be reported to the trials office immediately and within 24hrs of the Investigator becoming aware of the event. All SAE reports must be reviewed, signed and dated by the Principal Investigator within 7 days of site's awareness of the SAE.

Events that are thought to be possibly, probably or definitely related should always be reported immediately and within 24hrs of the Investigator becoming aware of the event.

10.4 Reporting procedure

10.4.1 Reporting procedure for SAEs

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate(s)) should report the SAE to their own Trust in accordance with local practice, and to the BCTU trials office as described here.

To report an SAE to the BCTU trials office, the Investigator (or delegate(s)) must complete, date and sign the trial specific BCTU SAE form. The completed form, together with any other relevant, appropriately anonymised data should be faxed or scanned to the BCTU trials team using one of the numbers listed below, in accordance with the timelines given in section 10.3. Unless exempt from expedited reporting (see section 10.3), this should be immediate, and no later than 24 hours after first becoming aware of the event.

To report an SAE, fax the SAE Form to:

0121 415 9135

Or scan and email the SAE Form to:

STOPACEi@trials.bham.ac.uk – Not secure for transfer of identifiable patient information.

stop.ace@nhs.net – Secure for transfer from another @nhs.net account.

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number within 1 working day, the site should contact the BCTU trials team. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Where an SAE Form has initially been completed by someone other than the Investigator, the original SAE form will need to be countersigned by the Investigator to confirm agreement with the causality assessment.

The CI will undertake review of all SAEs and may request further information from the clinical team at site, which should be made available immediately upon request. The CI will not overrule the severity or causality assessment given by the site Investigator but may add additional comment on these.

10.4.2 Provision of follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the BCTU trials team. Once the SAE has resolved, all critical follow-up information has been received and the paperwork is complete, the final version of the original SAE form completed at site must be returned to the BCTU trials office and a copy kept in the Site File.

10.5 Assessment of relatedness

When completing the SAE form, the PI will be asked to define the causality (relatedness) and the severity of the AE. In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which do not contribute to the event.

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 of any cardiovascular events that occur in patients who have discontinued ACEi/ARB treatment.

The following categories as outlined in *Table 4* will be used to define the causality of the adverse event. Events reported as definitely, probably or possibly being related to the trial treatment will be considered SARs.

Table 4: Categorisation of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
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. However, the influence of other factors may have contributed to the event (e.g. the	

	participant's clinical condition, other concomitant events or medication).	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship	

On receipt of an SAE Form, the Trials Office will forward it, with the unique reference number, to the CI (or delegate(s)) who will independently review the causality of the SAE. An SAE judged by the PI or CI (or delegate(s)) to have a reasonable causal relationship with the intervention will be regarded as a related SAE (SAR). The causality assessment given by the PI will not be downgraded by the CI (or delegate(s)). If the CI (or delegate(s)) disagrees with the PI's causality assessment, the opinion of both parties will be documented. Where the event requires further reporting, the opinion will be provided with the report.

10.6 Assessment of expectedness by the CI

The CI (or delegate(s)) will also assess all related SAEs for expectedness with reference to the following criteria (Table 5).

Table 5: Expectedness

Category	Definition
Expected	An adverse event that is consistent with the information about the trial related procedures or that is clearly defined in the relevant safety information.
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

10.6.1 The Reference Safety Information (RSI)

For participants in the 'Continue' arm, the reference document to be used to assess expectedness against the IMP is the 'Undesirable effects' section 4.8 of the example SmPC for that class of IMP, i.e. there is one for all ACEi and another for ARBs.

Reference Safety Information for ACEi: Lisinopril, 20mg tablets, Actavis UK, dated 13-Jun-2012.

Reference Safety Information for ARBs: Candesartan 16mg tablets, Actavis UK Ltd, dated 30-Apr-2012.

For assessment of expectedness in the trial, the following events will be considered expected from discontinuation of ACEi or ARB or combination of both. Therefore, this section of the Protocol will serve as the RSI for the experimental arm of the trial.

1. Hypertension
2. Hypokalaemia
3. Increased peripheral oedema
4. Gout
5. Change in urinary proteinuria
6. Weight gain
7. Increase in breathlessness
8. Cardiovascular events:
    a. myocardial infarction (MI)
    b. stroke or TIA
    c. heart failure

Cardiovascular events could potentially be expected from ACEi/ARB withdrawal but may equally be expected from progression of the patient's CKD.

10.6.2 Protocol defined expected SAEs

Although the trial treatments are well-established and form part of standard clinical practice for the trial population, a large number of SAEs are anticipated in the trial due to the heavy disease burden of the studied population, relating to their CKD, other co-morbidities and their treatment. The following events are expected as a consequence of the participant's clinical condition:

1. Events relating to an existing condition, unless these are thought to be possibly, probably or definitely related to the trial intervention. For example:
    a. Symptoms or complications of diabetes in a patient with known diabetes, including hyperglycaemia, hypoglycaemia, infection or complications of diabetic foot ulcers, or diabetic ketoacidosis.
    b. Worsening renal function, decline into ESRD or acute kidney injury.

c. Symptoms or complications of CKD including anaemia, uraemia, gout, hyperkalaemia, hyper- and hypo-volaemia, urinary tract infection or urosepsis.

d. Symptoms or complications of polycystic kidney disease (PKD) in a patient with known PKD including kidney or urinary tract infection, abdominal pain, kidney stones, haematuria or cyst changes.

e. Breathlessness relating to existing heart failure or chronic obstructive pulmonary disease.

f. Other events related to existing medical conditions.

2. Events related to CKD treatment. For example:

   a. Peritonitis in a patient on peritoneal dialysis.

   b. Catheter or exit site infection.

   c. Fistula failure, pain or infection.

   d. Graft rejection, infection or renal arterial stenosis in a patient that has undergone renal transplant.

   e. Complications and side effects of immunosuppression in a patient on immunosuppression.

   f. Other events related to non-trial CKD treatment.

3. Events which are common in the patient population (typically older people with multimorbidity), unless these are thought to be possibly, probably or definitely related to the trial intervention. For example:

   a. Falls or fractures

   b. Infections including chest infection and pneumonia

   c. Constipation, gastroenteritis, abdominal pain, nausea and vomiting.

10.7 Reporting SAEs to third parties

The Sponsor will be put on copy of all SAEs, SARs, SUSARs sent to the CI for review.

The independent DMEC may review any SAEs at their meetings.

BCTU will report details of all SARs (including SUSARs) to the MHRA, REC and Sponsor annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR). Additionally, BCTU will report SUSARs categorised as fatal or life

threatening to the MHRA, REC and Sponsor within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other SUSARs categorised as non-fatal or life threatening will be reported within 15 days to the MHRA, REC and Sponsor.

The REC and Sponsor will be notified immediately if a significant safety issue is identified during the course of the trial. Details of all SUSARs and any other safety issues which arise during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the site file and TMF.

10.8 Reporting urgent safety measures

If any urgent safety measures are taken, the BCTU 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 REC 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 Monitoring Pregnancies for potential Serious Adverse Events

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.

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

A "serious breach" is a breach which is likely to affect 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 General Data Protection Regulations (2018).

The CRFs will not bear the participant's name. The participant's 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 the following Forms (*Table 6*):

Table 6: Data Collection Forms

Form Name	Schedule for submission
Randomisation Notepad	Collected at randomisation
Baseline, and telephone and 3-monthly follow-up	As soon as possible after each follow-up assessment time point

CRFs	
Serious Adverse Event Form	Faxed within 24hrs of research staff at site becoming aware of event

11.3 Data handling and analysis

See section 10.4 for details of how to submit SAE forms.

Other than SAE forms, CRFs should 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. Online CRFs must be completed and submitted 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.

Missing and ambiguous data will be queried via Data Clarification Forms (DCFs), in accordance with the trial's Data Management Plan. The online CRF should be amended to resolve the query. A copy of the DCF should be kept in the site file.

Changes to the CRF will be recorded in the audit trail of the online system. A reason must be provided for changes made after data submission.

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. Since data entry on the electronic CRFs are attributable by virtue of the secure individual user log-in, submission of data on the electronic form will be taken as 'sign-off' to attest the data entered is accurate. Access to the electronic CRF is permitted only for those with

appropriate delegation by the site investigator. Any changes made on the electronic CRF are automatically tracked.

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 6 months after 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 7* below) [25]. This data was used for the basis of the sample size calculation.

Table 7:

Mean ± Std.Err (Std.Dev)	12 months before ACEi/ARB stopped	When ACEi/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 a linear regression model with the baseline eGFR score and all the minimisation variables included in the model as covariates. Longitudinal plots of the data over time will also be constructed for visual presentation of the data. As a secondary analysis, a mixed effects 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. During the trial, it is likely that patients will commence dialysis or may have a kidney transplant. This complicates the assessment of renal function, as any eGFR values past this point will not truly reflect the patient's renal function. To account for this, the primary outcome will also be analysed using more complex statistical methods such as pattern mixture models and joint modelling..

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 experiencing each outcome will be reported and the two arms will be compared using a log-binomial model. An adjusted relative risk and 95% confidence interval will be estimated. If the log-binomial model fails to converge, then a Poisson regression model with robust standard errors will be used.

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. Cox proportional hazard models will be fitted to obtain treatment effects which will be expressed as adjusted 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. However, since there is a chance of data missing not at random for patients going on to have dialysis or a kidney transplant, 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 the primary outcome. 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

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. A DMEC report and charter outlining the terms of reference (including information on stopping rules) will be agreed with the DMEC.

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 and corresponding outcome data has been entered onto the study database and validated as being ready for analysis.

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

This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (project ref: 11/30/07). Excess costs for patient recruitment, treatment and clinical monitoring remain 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. The views expressed in this Protocol are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

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 UK Policy Framework for Health and Social Care Research and the applicable regulatory requirements.

20. References

1. Levey, AS, Andreoli SP, Dubose T, Provenzano R and Collins AJ. Chronic kidney disease: common, harmful and treatable-World Kidney Day 2007. *Am J Nephrol,* 27, 108-12.

2. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375(9731):2073-2081

3. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney int.* 2011;80(1):93-104

4. Landray MJ, Emberson JR, Blackwell L, et al. Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. *Am J Kidney Dis* 2010; 56 (6):1082-94.

5. Quinn MP, Cardwell CR, Kee F, et al. The finding of reduced estimated glomerular filtration rate is associated with increased mortality in a large UK population. *Nephrol Dial Transplant* 2011; 26(3):875-80.

6. Caskey FJ, Wordsworth S, Ben T, et al. Early referral and planned initiation of dialysis: what impact on quality of life? *Nephrol Dial Transplant* 2003;18 (7):1330-8.

7. Black C, Sharma P, Scotland G, et al. Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *Health Technol Assess* 2010;14(21):1-184

8. Lewis EJ et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993; 329 (20):1456-62.

9. Lewis EJ et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345 (12):851-60.

10. Brenner BM et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345 (12):861-9.

11. Remuzzi G et al. Proteinuria predicting outcome in renal disease: nondiabetic nephropathies (REIN). *Kidney Int Suppl* 2004(92):90-6.

12. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329 (14):977-86.

13. Hou FF et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;354(2):131-40.

14. Hsu CY et al. Blood pressure and angiotensin converting enzyme inhibitor use in hypertensive patients with chronic renal insufficiency. *Am J Hypertens* 2001; 14 (12):1219-25.

15. Indermitte J et al. Risk factors associated with a high velocity of the development of hyperkalaemia in hospitalised patients. *Drug Saf* 2007;30(1):71-80.

16. Dagenais GR, S Yusuf MG Bourassa, et al. Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study. *Circu,* 2001. 104 (5): 522-6.

17. Dahlof B, RB Devereux, SE Kjeldsen et al Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol *Lancet,* 2002. 359(9311): 995-1003.

18. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*, 2002. 288(23): 2981-97.

19. Ruggenenti P et al. ACE inhibitors to prevent end-stage renal disease: when to start and why possibly never to stop: a post hoc analysis of the REIN trial results. *J Am Soc Nephrol* 2001;12 (12):2832-7.

20. Strippoli GF, Bonifati C, Craig M, Navaneethan SD, & Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev 2006* 18; (4).

21. Thomas MC, Jerums G et al. Increased tubular organic ion clearance following chronic ACE inhibition in patients with type 1 diabetes. *Kidney Int* 2005 67 (6) 2494-9.

22. Maschio G et al. Effect of the angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 1996; 334 (15):939-45.

23. Morimoto T et al. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. *J Eval Clin Pract* 2004; 10 (4):499-509.

24. Mann JF, RE Schmieder, M Mcqueen et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*, 2008. 372(9638): 547-53.

25. Ahmed AK et al. The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease. *Nephol Dial Transplant* 2010; 25 (12):3977-82.

26. Kovesdy CP, Anderson JE. Reverse epidemiology in patients with chronic kidney disease who are not yet on dialysis. *Seminars in dialysis.* Nov-Dec 2007;20(6):566-569.

27. Kalantar-Zadeh K, Kovesdy CP, Derose SF, Horwich TB, Fonarow GC. Racial and survival paradoxes in chronic kidney disease. *Nature clinical practice. Nephrology.* 2007;3(9):493-506

28. Juurlink DN et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351(6):543–51

29. Zannad F, Kessler M, Lehert P. Grunfeld JP et al Prevention of cardiovascular events in ESRD. Results of a RCT of fosinopril and implications for future studies. *Kidney Int* 70; 1318-1324, 2006.

30. Chan KE, Ikizler TA, Gamboa JL et al. Combined ACEi and ARB associate with increased of cardiovascular death in haemodialysis patients *Kidney Int* 80; 978-985, 2011.

31. Jain P, Cockwell P, Little J, et al. Survival and transplantation in end-stage renal disease: a prospective study of a multiethnic population. *Nephrol, Dial, Transplant* 2009;24(12):3840-3846.

32. National Institute for Health and Clinical Excellence. *Early identification and management of chronic kidney disease in adults in primary and secondary care. Clinical guidelines CG73*. 2008.

33. Beddhu S, Samore MH, Roberts MS, Stoddard GJ, Ramkumar N, Pappas LM, Cheung AK, Impact of timing of initiation of dialysis on mortality. J Am Soc Nephrol 2003: 14; 2305-2312.

34. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials *BMJ* 2013;347:f5680