Accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease: prospective longitudinal study in a multi-ethnic population

eGFR-C Study

STUDY PROTOCOL: VERSION 1.3 30th March 2015

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Chief Investigator:	**Dr Edmund Lamb** **East Kent Hospitals University NHS Foundation Trust**
Coordinating Centre:	**Birmingham Clinical Trials Unit (BCTU)**
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Safety Reporting

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

Chief Investigator and Co-Sponsor Signatures

The Chief Investigator and the Co-Sponsors have discussed this protocol. The Investigator agrees to perform the investigations and to abide by this protocol.

The Investigator agrees to conduct the study in compliance with the approved protocol, EU Good Clinical Practice (GCP), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent) and the Research Governance Framework (2005 2nd Edition; as amended).

eGFR-C Study Protocol Version 1.1, 1st September 2014

Previous version: Version 1.0, 1st August 2013

The protocol has been approved by:

Chief investigator
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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 Study Steering Committee prior to seeking approval from the Main Research Ethics Committee (MREC).

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

Principal investigator

<insert name>

_____

Signature Date

Name of Institution

<insert name> _____

Each Principal Investigator should sign this page and return a copy to the eGFR-C Study Office

Table of Contents

List of Abbreviations

ACR	Albumin to creatinine ratio
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease-epidemiology consortium
CRF	Case Report Form
CVi	Within-individual biological variation
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Control Trial Number
MDRD	Modification of Diet in Renal Disease
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Service Research
PI	Principal Investigator
PIS	Participant Information Sheet
MREC	Main Research Ethics Committee
RCV	Reference change value
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SMG	Study Management Group
SSC	Study Steering Committee

Summary & Study Schema

EXECUTIVE SUMMARY	
Title	Accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease (CKD)
Acronym	eGFR-C
Study design and methods	**Multi-centre UK prospective longitudinal cohort study** - 1300 participants will undergo baseline (month 0) and final (month 36) reference GFR, estimated GFR (eGFR) and urinary albumin-to-creatinine ratio (ACR) tests. Additionally they will provide ACR and eGFR tests at 6-monthly intervals. A subset of the cohort (n=375) will receive annual reference GFR tests. **Biological variability study –** In a further sub-study 20 participants will undergo the reference test four times over four weeks. **Modelling of monitoring and cost effectiveness -** Optimal monitoring regimens and cost-effectiveness will be assessed using data from the longitudinal study and the biological variability study.
Total number of participants planned	1320
Study duration per participant	36 months
Accrual period	18 months
Estimated total study duration	66 months
Primary study objectives	1. To estimate and compare the accuracy and precision of GFR-estimating equations based on the MDRD equation and three CKD-EPI equations using either creatinine or cystatin C or a combination of both in people with stage 3 CKD. 2. To estimate the accuracy and precision of the GFR-estimating equations according to ethnic group (particularly Caucasians, African-Caribbean and South Asian), and baseline diabetes and proteinuria. 3. To evaluate and compare how accurately these GFR-estimating equations reflect change in GFR over three years. 4. To establish which GFR-estimating equation, together with ACR, or ACR alone, most accurately predicts those people that have progressive loss of kidney function (CKD progression). 5. To estimate and model disease progression (decline in GFR or increase in ACR) according to ethnic group (particularly Caucasians, African-Caribbean and South Asian), and baseline diabetes and proteinuria.

	6. To compare the effectiveness and costs of monitoring strategies for identifying people that have progressive loss of kidney function (CKD progression) utilising different GFR-estimating equations and test schedules, accounting for differences in risk of progression.
Main inclusion criteria	• Aged 18 years or older • Patients with stage 3 CKD (GFR 30-59 mL/min/1.73 m^2), diagnosed using MDRD/CKD-EPI eGFR (at least two consecutive test results in this range at least 90 days apart, with the most recent test in the last 12 months) • Written informed consent
Main exclusion criteria	• History of untoward reactions to iodinated contrast media or allergy to topical iodine • Episode of acute kidney injury in previous 6 months (as defined by the Acute Kidney Injury Network criteria) • Amputation of whole or part-limb • Pregnant or breastfeeding • Known current alcohol or drug abuse • Kidney transplant recipient • Any condition with an expected survival of less than study duration • Inability to comply with study schedule and follow-up • Inability to provide informed consent e.g. due to cognitive impairment

LAY SUMMARY

The best measure of kidney function is accepted to be the glomerular filtration rate (GFR), which measures the ability of the kidney to filter blood and is widely used in clinical practice. A low GFR suggests poor kidney function. An estimate of GFR can be obtained from a simple blood test. In 2006, the Department of Health recommended that all NHS laboratories in England should routinely estimate and report GFR using equations based on the measurement of a substance in blood called creatinine. Similar recommendations were made throughout the rest of the UK and internationally. Creatinine is normally filtered and excreted by the kidneys, but if the kidneys function is reduced its concentration in blood increases. Hence a high creatinine concentration in blood equates to poor kidney function (i.e. low GFR). Age, gender and race can also affect creatinine in the blood, so adjustments can be made to the way in which GFR is estimated. The introduction of GFR reporting as part of routine clinical practice in the UK, plus more widespread detection of kidney disease through testing for excess protein in urine (proteinuria /albuminuria), has increased the number of people diagnosed with chronic kidney disease (CKD): approximately one in seven of the UK population have been diagnosed with CKD using these methods. However, there are concerns regarding the accuracy of this testing and its ability to detect deterioration in kidney function. More accurate testing would enable better identification and monitoring,

ultimately improving outcomes for people with CKD, whilst reducing risks of misdiagnosis. Cystatin C, a small protein that can be measured in blood, has been proposed as an improved marker of GFR. However, cystatin C is approximately ten times more expensive to measure than creatinine.

This study will assess the accuracy of current and alternative tests of kidney function against a reference test (see below) in a large group of people (1300 from six centres) with moderate (stage 3) CKD, who will be followed over a three year period. It will include people with diabetes and proteinuria, and people of Caucasian, African-Caribbean and South Asian descent.

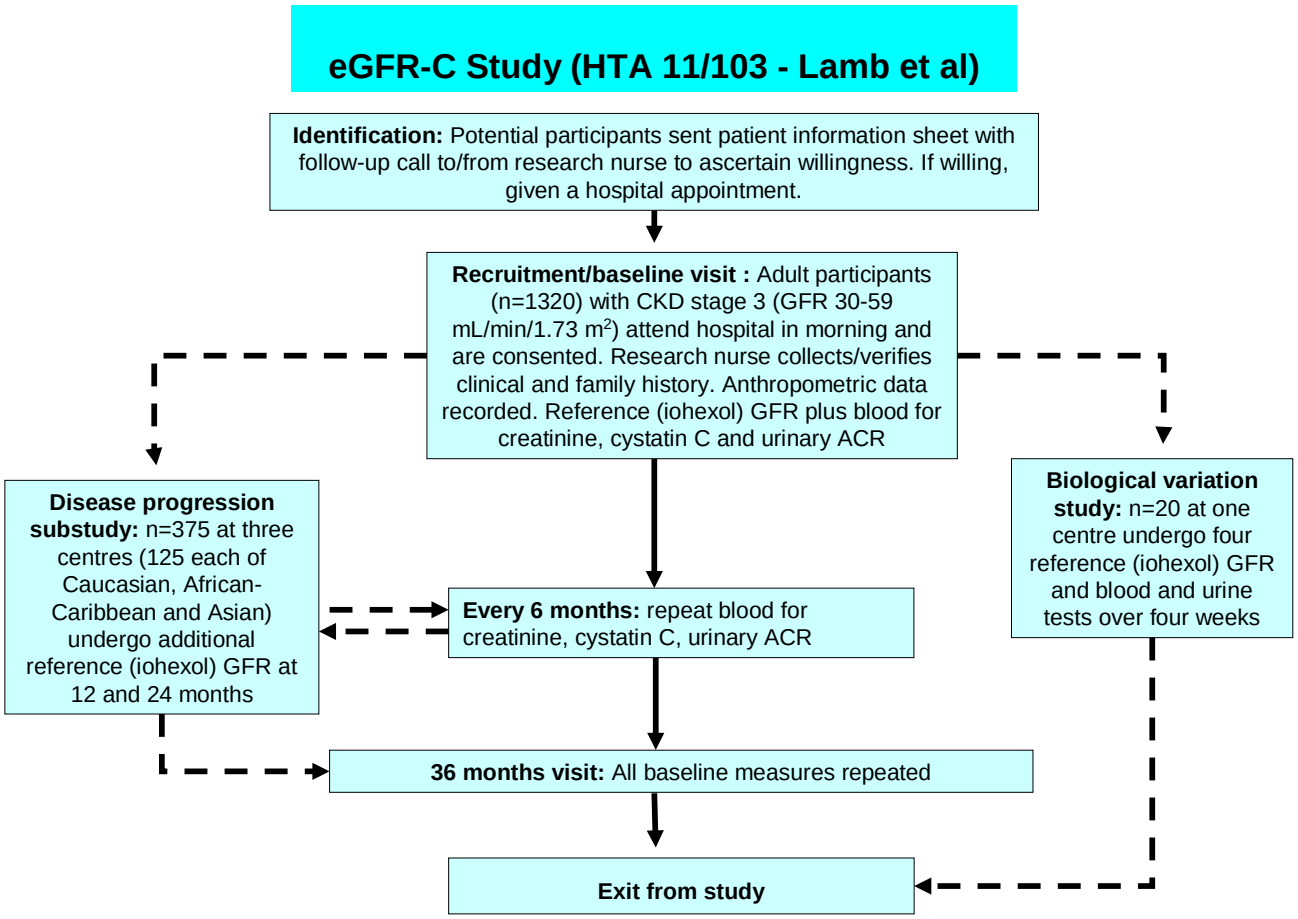
The study will recruit people with stage 3 CKD from hospital clinics and from GP surgeries at six major UK centres (Birmingham, Canterbury, Derby, London, Leicester, Salford). Participants will be given an initial (reference) GFR test when they enter the study with a second follow-up reference test three years later. The reference test involves injecting a small amount of iohexol, a non-radioactive iodine-containing substance widely used for this purpose, into a vein. Blood samples will be taken over the next 4 hours to see how quickly the iohexol disappears from the blood stream. The rate at which iohexol disappears is due to renal excretion (i.e. via urine) and is equivalent to the level of kidney function. Blood tests for monitoring kidney function, including testing for creatinine, cystatin C and urinary albumin, will be done every six months during the study period.

In the study, iohexol measured GFR will be accepted as the reference ('gold standard') measure of kidney function. Each GFR-estimating equation will be compared against it. The alternative estimated measures of GFR, derived from measuring substances (creatinine and cystatin C) in the blood, will be compared against the reference test. An important outcome is how much the reference test changes over the three years of the study, and how well the alternative measures reflect this change. We will also collect accurate test cost data for further analysis of cost-effectiveness (e.g. do the relative costs of the tests justify any change in practice due to improved performance of one test compared to another?).

Participants will need to provide informed consent; those who are unable to do so will not be enrolled in the study. The main risk is of allergy to iodine contained within the reference test. This is very rare and individuals with a known allergy to iodine will be excluded.

Study Schema

Figure 1



1 Introduction

1.1 Background

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function for ≥3 months with implications for health. CKD is prevalent in the population in general:[1-3] the 2009 Health Survey for England identified approximately 13% of the UK population as having CKD.[4] Most commonly it is identified using estimation of glomerular filtration rate (GFR) or detection of protein in the urine (albuminuria/proteinuria).

GFR is accepted as the best overall measure of kidney function and is central to diagnosis, staging and management of CKD. Ideally GFR would be measured using reference procedures which follow the clearance of an infused exogenous substance (e.g. inulin, ^{125}I-iothalamate, ^{51}Cr-EDTA or iohexol[5]). However, these methods are cumbersome and impractical for general kidney disease detection and management. Estimation of GFR (estimated GFR [eGFR]) using equations based on serum creatinine with adjustments for age, gender and race are widely used as surrogate measures of GFR. Estimation of GFR on every blood creatinine request received by laboratories has been recommended by the Department of Health.[6] In England, the National Institute for Health and Care Excellence (NICE) have made recommendations regarding which people should be tested for the presence of CKD (e.g. those with diabetes or hypertension) and have recommended that GFR should be estimated 6-monthly in people with stage 3 CKD (GFR 30-59 mL/min/1.73 m^2),[7] comprising approximately 6-7% of the overall UK population.[3, 8] It is estimated that more than 50 million GFR estimates are produced by UK NHS laboratories every year.

The aim of disease detection is to identify and manage those most likely to progress to kidney failure and/or who are at high risk of morbidity and mortality. In addition to the accurate identification of CKD, the ability of tests to identify which individuals with CKD will have high risk (i.e. progressive or mortal) disease is a crucial issue. Whilst introduction of routine GFR estimations is generally deemed to have brought significant health advantages,[9] many people with stage 3 CKD are not at increased risk of progressive disease and there are concerns that CKD detection using creatinine-based approaches may be identifying individuals who are at low risk and unlikely to benefit from active management (e.g. blood pressure lowering, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, cardiovascular risk reduction).[10] Recently, newer equations utilising cystatin C instead of, or in addition to, creatinine have been proposed. Endorsement of cystatin C testing in international guidance,[11] together with the increasing availability of

cystatin C assays on large, automated laboratory test platforms will increase the pressure on NHS laboratories to introduce this test, which is significantly more expensive than creatinine testing. Given the high costs of cystatin C testing compared to creatinine, it is critical that its diagnostic accuracy and prognostic ability are carefully validated ahead of widespread introduction into the NHS.

The ability of tests to identify which individuals with CKD will have high risk (i.e. progressive or mortal) disease is seen as a crucial issue. A significant problem has been the ability of GFR-estimating equations to identify progression of kidney disease given the biological variability of its main determinant (serum creatinine). There have been no prospective studies of the ability of GFR estimating equations to monitor progression and no studies at all of GFR estimating equations incorporating cystatin C; there have also been no validations of GFR estimating equations in British ethnic minority populations. The proposed study will address these important issues.

Measuring GFR

Standard clearance of inulin, including urine collection, remains the 'gold-standard' method for GFR measurement, but few studies use this as the method is cumbersome and inulin is not easily measured. Most evaluations of GFR equations have used radiolabelled plasma clearance methods which are assumed to be closely related to inulin clearance. Radiolabelled iothalamate plasma clearance was the method used for developing the Modification of Diet in Renal Disease (MDRD) Study [12] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[13] GFR-estimating equations (see below), whilst the CKD-EPI equation validation dataset used a variety of reference GFR methods including iohexol.[13] Although regarded as the reference approach for the assessment of kidney function, it is increasingly appreciated that non-inulin plasma clearance methods are not all equivalent.[14] Furthermore, as with any physiological measurement, GFR has an intrinsic biological variability, understanding of which is critical to the appreciation of disease-related change. Using a variety of reference markers, values (coefficient of variation, CV%) ranging between 5.5% and 11.6% have been reported for the biological variation of GFR.[15-21] However, most of these estimates were not derived using classical biological variation studies as described by Fraser and Harris.[22]

Estimating GFR

The MDRD Study equation ($MDRD_{creatinine}$), which estimates GFR adjusted for body surface area (BSA), was originally developed in 1999.[12] A simplified ('4-variable') version of the equation which requires knowledge only of serum creatinine concentration, age, gender and race (black or white) was later published[23] and

subsequently re-expressed for use with a standardised serum creatinine assay.[24] Generally, the MDRD equation has been seen to perform better, and offer practical advantages, over other GFR equations that had been used previously. Its use has been endorsed by national professional healthcare organisations[25] including those in the UK.[7] However, accuracy of the equation is sub-optimal. In the CKD field, accuracy of GFR estimating equations is commonly expressed as the P_{30}, the percentage of eGFR values within 30% of 'true' GFR. This metric captures aspects of both imprecision (measurement error) and bias (systematic over- and/or under-estimation). Reported P_{30} values for the MDRD equation typically range between 73% to 93%.[26]

The MDRD equation has also been criticised on the basis that it significantly underestimates GFR (particularly in individuals with GFR greater than 60 mL/min/1.73 m^2) and has poor precision.[13] A revised equation, the Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{creatinine}$) equation has been published and is thought to partially address this issue, producing less biased estimates of GFR at higher levels of kidney function,[13] although reportedly less accurate estimates as GFR falls below 60 mL/min/1.73 m^2.[26] P_{30} values for the $CKD\text{-}EPI_{creatinine}$ equation are slightly superior to those of the MDRD equation in studies that have undertaken a head-to-head comparison.[26]

Cystatin C has been proposed as an improved marker of GFR compared to creatinine.[27, 28] Recently, the CKD-EPI Collaboration have published two further CKD-EPI equations; one based on cystatin C ($CKD\text{-}EPI_{cystatin\ C}$) and one using both cystatin C and creatinine ($CKD\text{-}EPI_{creatinine\ and\ cystatin\ C}$).[29] Members of the current study group have recently published the only independent validation to date of these latter equations.[30]

Estimating GFR in British ethnic minority populations

People from South Asian and African-Caribbean backgrounds are at 3 to 5-fold increased risk of developing established renal failure compared to Caucasians.[31, 32] They are also at greater risk of complications from diabetes and high blood pressure than the rest of the population. Whilst GFR-estimating equations have been validated in African-Caribbean communities from North America[33] and endemic Asian populations,[34-39] there is no independent validation in British African-Caribbean populations and no data at all amongst Asians from the Indian sub-continent. Although it is often assumed that progression is higher in black and Asian[40] ethnic groups compared to whites, this remains unproven.[41, 42]

Progression of kidney disease

There is no consistent definition of what constitutes renal progression in the literature. Many studies have used a doubling of serum creatinine, corresponding to an approximate halving of GFR, as an end-point defining progression, but this is insufficiently sensitive to be useful in clinical practice. Kidney Disease Improving Global Outcomes (KDIGO) have defined progression as a move to a higher disease category (e.g. stage 3A [GFR 45-59 mL/min/1.73 m^2] to stage 3B [GFR30-44 mL/min/1.73 m^2]) confirmed by a fall in GFR of greater than or equal to 25% (e.g. a decline from 60 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2), an increase in albuminuria, or a greater than 10%/year decline in GFR (e.g. a decline from 60 mL/min/1.73 m^2 to less than 54 mL/min/1.73 m^2 in one year).[11] NICE defined progression as a decline in GFR of more than 5 mL/min/1.73 m^2/year, or more than 10 mL/min/1.73 m^2/5 years.[7]

Progression is not necessarily common even amongst people with known CKD e.g. amongst people with stage 3 CKD only 1.3% progressed to stage 5 CKD (established renal failure, typically requiring dialysis or transplantation) over 5 years.[43] Amongst community dwelling older (greater than 65 years) adults with stage 3 CKD, Hemmelgarm et al. reported mean decline of GFR of 3.6 mL/min/1.73 m^2/year and 2.8 mL/min/1.73 m^2/year respectively in male and female subjects with diabetes and somewhat lower values amongst subjects without diabetes (1.9 mL/min/1.73 m^2/year and 1.1 mL/min/1.73 m^2/year amongst males and females respectively).[44] In the REIN study, proteinuric (greater than 1 g/24 h) non-diabetic subjects with GFRs in the approximate range 30-50 mL/min/1.73 m^2 showed a decline of GFR of 7.0 mL/min/1.73 m^2/year with slightly lower values being observed in those receiving renin-angiotensin-aldosterone system (RAAS) blockade.[45]

In East Kent, of 4506 people in primary care with baseline eGFR 30-59 mL/min/1.73 m^2, 18% had a fall in eGFR of over 10% in a 1 year period (SEiK study, Paul Stevens unpublished data). However, apparent increases in GFR were equally common. What is not known is whether such increases are real, or whether they reflect imprecision and inaccuracies of the creatinine-based estimate of GFR that was used.

There are some data, mainly restricted to small studies in people with diabetes, describing disease progression in terms of decline in reference GFR measurements.[46, 47] Generally, disease progression in people with diabetes has been described as following a broadly linear decline, being influenced by blood pressure and albuminuria and ameliorated by antihypertensive medication/RAAS

blockade.[46, 48, 49] A similar pattern has been observed using estimated rather than measured GFR.[50]

1.2 Clinical data

Identifying progressive kidney disease

A significant problem is the ability of GFR-estimating equations to identify progression of kidney disease against background change in GFR (i.e. that due to 'normal' ageing; commonly cited as approximately 1 mL/min/1.73 m^2/year) given the biological and measurement variability of both reference and estimated GFR. The intra-individual variation (CV_I) of the main determinant (serum creatinine) of eGFR has been reported as 4.3%[51] to which should be added intralaboratory imprecision (CV_A) of approximately 3.0%.[25] On this basis, the critical difference or reference change value (RCV) for serum creatinine is 13% (i.e. this is the difference that can be considered 'real' with 95% probability). The power function in the MDRD equation (-1.154, Table 1) increases the impact of CV_I to an average of 5.4%. Consequently the RCV for eGFR derived using the MDRD equation becomes 14.4%. As an example of this, in an individual a GFR of 60 mL/min/1.73 m^2 will need to fall below 51 mL/min/1.73 m^2 before it can be considered a significant decrease.* Some,[52, 53] although not the majority[54-57] of data suggests that the biological variation of serum cystatin C is greater than that of creatinine. If this were the case then it would clearly impact on the ability of cystatin C based GFR-estimating equations to detect changes in true GFR vis-à-vis serum creatinine.

GFR changes of the order discussed above exceed the limit that most nephrologists would consider a clinically insignificant change. However, there are no prospective longitudinal data assessing the relative abilities of GFR-estimating equations to detect change in underlying 'true' GFR. One recent study has addressed the accuracy of GFR estimating equations compared to ^{125}I-iothalamate measured GFR over time in people with kidney disease.[58] The authors concluded that GFR estimating equations accurately reflected changes in measured GFR over time. The study was robust (3,532 participants with CKD followed for a mean of 2.6 years), but was retrospective, and did not include data derived using cystatin C.[58] Observational data suggests that for identification of progressive CKD, the combination of eGFR using cystatin C and albumin-to-creatinine ratio (ACR) ranks highest, followed by eGFR using cystatin C alone, then the combination of ACR and eGFR using creatinine, and finally eGFR using creatinine alone.[59-61] The combined use of

* The RCV % is constant, but clearly gives rise to differences in terms of mL/min/1.73 m^2 depending on the starting point. e.g. a 14.4% fall at 30 mL/min/1.73 m^2 only requires a decrease of 4.3 mL/min/1.73 m^2, whereas a 14.4% fall at 60 mL/min/1.73 m^2 requires a decrease of 8.6 mL/min/1.73 m^2.

cystatin C and creatinine in a GFR estimating equation, which is claimed to be less influenced by ethnicity, as a predictor of progression has not been tested.

1.3 Rationale for the study and assessment of risk

Whilst there is significant literature describing the accuracy of creatinine-based eGFR against reference methods (see Section 2.1 above), there are no studies addressing the ability of GFR estimating equations, including those incorporating cystatin C, to detect change in GFR. Furthermore, there are no data addressing the accuracy of these equations in British ethnic minority populations. This study will assess whether eGFR using either creatinine or cystatin C, or a combination of both, is superior at detecting changes in GFR as measured by a reference GFR method. The utility of baseline eGFR and urinary ACR to predict which people are likely to show progressive kidney disease will also be tested. We have chosen plasma iohexol clearance as the reference measure of GFR for this study because it is equivalent to inulin clearance, is widely used in clinical and research practice, is non-radioisotopic, can be measured accurately and precisely, and is cheap.[16, 62, 63] We have found that the test can be accurately and safely delivered by research nurses and encountered no adverse events amongst 400 recently studied older people.[30] We have chosen to study the CKD-EPI and MDRD equations because these are the only GFR estimating equations anchored to both creatinine and cystatin C reference methodology, and therefore likely to generate data that will be valid in perpetuity.

The study population will be a large cohort of people with stage 3 CKD including subjects of African-Caribbean and South Asian ethnicity and including subjects with diabetes and proteinuria. This will build on the findings of previous research, but using a prospective design with regular reference GFR measurements: the impact of medication on disease progression will be estimated and included in the model. The model will be used to define optimal sampling times for high and low risk participants, and other significant subgroups defined by the model. We will also use a classical study design to establish the intra-individual biological variability of both reference and estimated GFR: this information will be used as one of the handles in defining progression and assessing the ability of GFR-estimating equations to detect it. A simple economic evaluation of the relative costs of the different tests will be included to enable cost-effectiveness modelling.

1.4 Assessment and management of risk

The assessment and management of risk is detailed in the separate eGFR-C Risk Assessment document. An on-going evaluation of risk will continue throughout the study.

The main risk to participants in this study is from the use of iohexol (Omnipaque 240). Iohexol is a non-ionic contrast agent widely used in radio-imaging procedures. Very rarely anaphylactoid reactions to iohexol are reported. Reported incidences of death from the use of water-soluble intravascularly administered contrast agents, including iohexol, range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 (0.01 percent). Deaths are predominantly due to cardiac arrest. Isolated reports of hypotensive collapse and shock are also found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005 percent) patients. Reports of common side effects (e.g. sensation of warmth and pain upon injection) appear to be less common with iohexol than with other contrast agents (Manufacturer's product information, GE Healthcare Inc). Other less severe adverse reactions include nausea, urticaria and brochospasm. The risk of an adverse reaction to iohexol may be mitigated by the use of lower dose. For example, the dosage recommended for use in adults for contrast enhanced computed tomography studies is between 120 mL and 250 mL. In the present study, participants will receive 5 mL of Omnipaque 240. The procedure will be undertaken in a hospital setting with full resuscitation facilities available.

2 Study Design

The study will evaluate the performance of GFR-estimating equations, including novel equations incorporating cystatin C, in assessing and monitoring measured GFR in people with stage 3 CKD. The data will be analysed to assess the impact of ethnicity, proteinuria and diabetes on equation performance. There are three studies that will run concurrently:

1. **Main study:** This will comprise a 3-year longitudinal prospective cohort study using 6-monthly estimates of GFR, and baseline and final reference GFR values to assess and compare the accuracy and precision of each estimate of GFR and change in GFR. The study will be undertaken at 6 centres (Birmingham, Canterbury, Derby, Leicester, London and Salford) and will recruit 1300 subjects. Investigators will be blinded to the results of the reference tests. We will include assessments in high risk subgroups and ethnic groups.

2. **Sub-study of patterns of disease progression**: 125 Caucasian, 125 African-Caribbean and 125 South Asian subjects (i.e. n=375 in total), stratified within ethnicity by risk of disease progression (approximately 60 with diabetes and/or proteinuria and 60 with neither diabetes nor proteinuria) will undergo additional

testing to that described in (1), with a reference GFR measurement each year over the 3 year study period. The study will enable a model of disease progression to be developed based on reference GFR measurement enabling optimal monitoring frequencies in the high-risk cohort to be defined. This number of subjects should provide a range of values over the main factors considered to influence disease progression and allow assessment of covariates in the statistical model. Further assessment of covariates will be performed by combining the data from this sub-study with the main study.

3. **Study of intra-individual biological variability:** At the Canterbury centre, a study will be undertaken to define the normal biological variability of the reference GFR test, in addition to the eGFR and urinary ACR tests. An additional twenty people with stage 3 CKD will undergo four iohexol reference measures of GFR in four successive weeks, with standardisation for time of day (morning after a light breakfast) and day of week. It is not anticipated that these subjects will also participate in the main study, although there would be no objection to them so doing.

3 Study Objectives

The aims of the study are:

1. To estimate and compare the accuracy and precision of GFR-estimating equations based on the MDRD equation and three CKD-EPI equations using either creatinine or cystatin C or a combination of both in people with stage 3 CKD.
2. To estimate the accuracy and precision of the GFR-estimating equations according to ethnic group (particularly Caucasians, African-Caribbean and South Asian), and baseline diabetes and proteinuria.
3. To evaluate and compare how accurately these GFR-estimating equations reflect change in GFR over three years.
4. To establish which GFR-estimating equation, together with ACR, or ACR alone, most accurately predicts those people that have progressive loss of kidney function (CKD progression).
5. To estimate and model disease progression (decline in GFR or increase in ACR) according to ethnic group (particularly Caucasians, African-Caribbean and South Asian), and baseline diabetes and proteinuria.
6. To compare the effectiveness and costs of monitoring strategies for identifying people that have progressive loss of kidney function (CKD progression) utilising different GFR-estimating equations and test schedules, accounting for differences in risk of progression.

4 Selection of Participants

Participants who potentially fulfil the inclusion criteria for this study must have their eligibility confirmed by medically qualified personnel with access to and a full understanding of the potential participant's medical history. If eligibility has been assessed and documented by medically qualified personnel, then the process of receiving informed consent may be delegated as appropriate and as documented on the eGFR-C Delegation and Signature Log.

4.1 Inclusion criteria

- Aged 18 years or over
- Patients with stage 3 CKD (GFR 30-59 mL/min/1.73 m^2) as defined internationally,[11] diagnosed using MDRD/CKD-EPI eGFR (at least two consecutive test results in this range at least 90 days apart, with the most recent test in the last 12 months)
- Written informed consent

4.2 Exclusion criteria

- History of untoward reactions to iodinated contrast media or allergy to topical iodine
- Episode of acute kidney injury in previous 6 months (as defined by the Acute kidney Injury Network criteria)
- Amputation of whole or part-limb
- Pregnant or breastfeeding
- Known current alcohol or drug abuse
- Kidney transplant recipient
- Any clinical condition with an expected survival of less than study duration
- Inability to comply with study schedule and follow-up
- Inability to provide informed consent e.g. due to cognitive impairment

5 Recruitment

A flowchart of the recruitment process is shown in the Study Schema (**Figure 1**) together with the investigation schedule.

Participants will be recruited to the main study from six centres and their dependent Participant Identification Centres (approximately n=220 each) as follows:

1. Birmingham: secondary care
2. Canterbury: secondary care
3. Derby: primary and secondary care
4. Leicester: primary and secondary care
5. Salford: secondary care
6. London: Kings College Hospital: primary and secondary care

Recruitment in secondary/tertiary care will be from CKD clinics. Potential participants will be identified by the research team at each of the recruiting centres (e.g from individual renal unit databases or other local registries). The recruitment procedure is described in more detail in section 7.2.

In the primary care centres, letters will be sent to GPs inviting them to participate in the study. GPs who agree to participate in the study will then invite potential participants by mail. People who wish to participate in the study will contact the research nurse who will then recruit them into the study as described in section 7.2.

There will be no selection of participants to the main study based on ethnicity.

It is expected that most participants in the sub-study of patterns of disease progression will be recruited from three centres (n = approximately 125 each site). All centres will be free to recruit participants from any of the targeted ethnic groups into the sub-study, but based on the local populations sub-study recruitment is expected to follow the below pattern:

1. Birmingham: approximately 75% South Asian and African-Caribbean and 25% Caucasian participants
2. Leicester: approximately 50% South Asian and 50% Caucasian participants
3. London: Kings College Hospital: approximately 75% African-Caribbean and 25% Caucasian participants

Individuals will be stratified within ethnicity by risk of disease progression (at each of the three sites approximately 60 with diabetes and/or proteinuria and 60 with neither diabetes nor proteinuria). Participants will be identified from primary or secondary

care as above. All consecutive patients will be invited to participate in the sub-study until the above ethnic stratification is achieved.

Participants (n=20) will be recruited to the study of intra-individual biological variability at Canterbury. Suitable consecutive participants will be invited.

6 Study Procedures and Schedule of Assessments

6.1 Screening procedures

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

In the primary care centres, GPs who agree to participate in the study will invite potential participants by mail. A research assistant will visit consenting practices to help staff identify eligible people from the CKD register, for example using READ code searches. MIQUEST (Morbidity Information QUery and Export Syntax) software will be used to extract an up-to-date dataset. The research assistant will produce stamped addressed invitation letters to eligible people for signature by the GP. The invitation will be sent out along with the patient information sheet. Potential recruits will be given a dedicated study phone line to use to indicate willingness to participate. People who wish to participate in the study will contact the research nurse who will then discuss the study with them as described above: assuming they remain willing to participate they will be given an appointment to attend the hospital when signed informed consent will be obtained (see below).

Adequate time will be given for consideration by the participant before taking part. In primary care it will be left to the potential participants to contact the research nurse at their convenience (see above). Assuming they are willing to participate, they will be given an appointment to attend the hospital (and instructions relating to test preparation) for consent, registration and the baseline assessments to be undertaken (see section 7.4). Potential participants in secondary/tertiary care, identified by the research team at each of the recruiting centres (e.g. from individual renal unit databases or other local registries) will be invited by mail. In some cases the research nurse or participant's clinician may introduce the study to the participant before providing them with the invitation letter and patient information sheet. The invitation will be sent out or provided along with the patient information sheet. Potential participants will have at least 24 hours to read study information before being contacted by the research nurse to discuss the study with them and to see if they are willing to participate in the study. Assuming they remain willing to participate they will be given an appointment to attend the hospital when signed informed consent will be obtained (see below).

6.2 Informed consent procedure

Eligibility should be assessed and documented by a clinician and then the process of obtaining written informed consent may be delegated as appropriate (to a suitably trained member of the local research team). This must be clearly documented on the eGFR-C Delegation and Signature Log.

Potential participants will initially be provided with a written Participant Information Sheet (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 study to them and inviting them to participate in the study. They will have time to consider the study and decide whether or not they wish to take part, and to discuss the study with their family and friends if they would like to. If the potential participant has any questions or queries about the study during this time they will have the opportunity to discuss the study with the research nurse. The potential participant will then either be contacted by, or will contact, a member of research team at their local centre. If they remain willing to participate in the study they will be offered an appointment to attend clinic. At this clinic appointment potential participants will have plenty of time to discuss the study further and to have any questions that they may have about the study answered. The complex nature of the study and the requirement to spend approximately five hours at the hospital for the reference test, on between two and four occasions, will be carefully explained. The investigator or designee will explain that there is no obligation for a patient to enter the study, that study entry is entirely voluntary, and that it is up to the patient to decide whether or not they would like to join. It will also be explained that the patient can withdraw at any time during the study, without having to give a reason and that their decision will not affect the standard of care they receive. Translated material and translators will be used for non-English speakers. Where possible there will be an independent translator made available to ensure that participants are fully informed and supported to make decisions about enrolment in the study.

At the secondary care centres reasons for non-participation will be recorded if the information is volunteered.

At the first appointment (time zero) the research nurse will go through the registration form including the eligibility checklist. Assuming the patient is eligible they will be asked to sign a separate consent form and will be registered into the study (see section 7.3). Informed consent will be obtained before any study-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 eGFR-C Study Office.

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.

When potentially interested participants of the ethnicity described in Section 5 attend clinic for baseline assessment, they will be asked if they would be willing to be involved in the 375 patient sub-study of patterns of disease progression which will involve additional reference (iohexol) GFR at 12 and 24 months as detailed in the Participant Information Sheet. Consent to join the 375 patient sub-study will be documented on the Consent Form.

When potentially interested participants attend clinic for baseline assessment at Canterbury they will be asked if they would be willing to be involved in the 20 patient study of intra-individual biological variability involving four reference (iohexol) GFR and blood tests over four weeks. Interested participants will be given a separate information sheet to consider detailing involvement in the study and, if willing to participate, will sign a separate Consent Form to document their consent to involvement in the 20 patient biological variation study.

6.3 Withdrawal

Participants may withdraw at any time during the study if they choose not to continue or if their clinical team feel that continued participation in the study is inappropriate.

Full details of the reason(s) for withdrawal should be recorded on the Case Report Forms (CRFs) if healthcare professional-initiated, otherwise a simple statement reflecting participant preference will suffice. Participants who withdraw from study testing, but continue with on-going follow-up and data collection should be followed-up in accordance with the protocol, unless the participant elects not to be included.

6.4 Registration procedures

After all eligibility criteria have been confirmed and informed consent has been received, the participants can be registered into the study.

Telephone and online registration

Participants can be entered into the study via a secure 24 hour internet based registration service (**https://www.trials.bham.ac.uk/egfrc**). Each researcher will be provided with a unique log-in username and password in order to access the online system. Online registration is available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance and occasional network problems.

Registration Forms will be provided to investigators and should be completed and used to collate the necessary information prior to registration. All questions and data

items on the Registration Form must be answered before a Study Number can be given. If data items are missing registration 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 Study Number be allocated. A confirmatory email will be sent to the local Principal Investigator and the named research nurse.

With the participant's prior consent their General Practitioner (GP) should be informed of their study participation.

Back-up registration

If the internet based registration service is unavailable for an extended period of time, a back-up paper registration will also be available at the BCTU. In this instance, investigators should ring the BCTU registration service, available 9-5 Monday - Friday (telephone number **0800 953 0274**).

6.5 Baseline assessments

Participants will attend hospital in the morning having been advised to avoid eating a meal with high meat or fish content after 10 pm the evening before.[a] After obtaining informed consent and registering the patient in the study the clinical and investigational baseline assessments will be undertaken.

- A clinical (including cardiovascular) and drug history will be recorded using a standardised questionnaire: information on ethnicity will be gathered using a modified version of the 2011 UK Census Questionnaire
- Height will be measured to the nearest 0.1 cm with a rigid stadiometer
- Body weight will be measured in light indoor clothing to the nearest 0.1 kg
- Waist circumference will be recorded to the nearest 0.1 cm at the mid-point between the lower costal margin and the level of the anterior superior iliac crest
- Hip circumference will be recorded to the nearest 0.1cm, from the widest point of the hips and the maximum protrusion of the gluteal muscles
- Brachial blood pressure will be measured as recommended by the British Hypertension Society (http://www.bhsoc.org/how_to_measure_blood_pressure.stm) three times in the sitting position using standardised Omron M7 digital

[a] N.B. participants will be asked about meat/fish consumption, but if affirmative this should not be a barrier to proceeding with the baseline assessments. The request to avoid meat/fish consumption after 10 pm the evening before the study visit applies to all study visits.

sphygmomanometers (Omron Healthcare, Milton Keynes, UK). The second and third blood pressure readings will be recorded and the average calculated by the study database

- Blood (12 mL) will be taken for serum creatinine and cystatin C measurement and sample storage (see below)
- A urine sample will be collected for ACR
- Further aliquots of serum/plasma and urine will be stored at -80^{o}c for potential analysis of future markers. These may include, but not be limited to, albumin, asymmetric dimethylarginine, beta trace protein, bone alkaline phosphatase, B-type natriuretic peptide, calcium, cholesterol, clusterin, C-reactive protein, growth differentiation factor 15, hepatocyte growth factor, 1,25-dihydroxyvitamin D, fibroblast growth factor 23, fibulin-1, 25-hydroxyvitamin D, interleukin-18, insulin-like growth factor-binding protein 7, kidney injury molecule-1, matrix gla protein, neutrophil gelatinase associated lipocalin, parathyroid hormone, phosphate, tissue inhibitor of metalloproteinases-2, symmetric dimethylarginine, total alkaline phosphatase, trefoil factor-3, troponin I and T. Refer to the laboratory manual for details of aliquot preparation and storage.
- An iohexol reference GFR measurement will be undertaken in addition to estimation of GFR using four GFR estimating equations

6.6 Blinding of Test Results

Results of tests undertaken specifically for the purposes of the study (including the iohexol reference GFR measurement, and the central laboratory serum creatinine and cystatin-C eGFR measurements) will not be made available to treating clinicians and participants whilst the study is ongoing and therefore will not influence patient management. There is no possibility of releasing results to clinicians because they are being tested in batches throughout the study. The exception to this will be a reference or estimated GFR result of less than 15 mL/min/1.73 m^2, which will be notified to the Chief Investigator. Study samples will be labelled with study ID, and tested blinded to clinical information and results of all previous test results. Clinicians will have access to standard laboratory tests as per usual practice.

6.7 Assessment schedule

Table 1: Schedule of visits (V) and assessments by month (M)

	Screening	V1 M1 (consent, registration and baseline assessment)	V2 M6	V3 M12	V3 M18	V5 M24	V6 M30	V7 M36
Identify suitable participants, review inc. / exc. criteria. Explain study procedures. Participant information sheet and cover letter to be sent potential participants.	x							
Contact secondary care participants after 1 or more days to determine willingness to participate. Primary care participants will contact study centre if willing to participate. Offer follow-up appointment.	x							
Confirm eligibility, consent, register in study		x						
Demographic and medical history, anthropometric and clinical assessment		x		(x)		(x)		x
Baseline and final blood tests (serum creatinine, cystatin C) plus aliquot storage)		x						x
Monitoring blood tests (serum creatinine, cystatin C) plus aliquot storage)			x	x	x	x	x	
Urine test (ACR)		x	x	x	x	x	x	x
Iohexol (GFR) clearance test		x		(x)		(x)		x

Note 1: schedule for sub-studies of disease progression and biological variation will differ slightly from above. In the sub-study of disease progression participants will have additional iohexol (GFR) clearance tests at 12 and 24 months (x). In the study of intra-individual biological variation participants will have additional iohexol (GFR) clearance, blood (serum creatinine, cystatin C) and urine (ACR) tests at 2, 3 and 4 weeks and will then exit the study.

Note 2: visits should take place and samples be collected within ± one month of the planned date according to the study schedule (e.g. the V2 visit and samples should occur between 5 and 7 months after study commencement). If the visit will occur outside of these limits, the study office should be contacted.

Note 3: all iohexol assessment visits should start before midday with meat/fish having been avoided since 10pm the evening before. 6 monthly follow-up visits can take place at any point in the day although the participant should again avoid meat/fish since 10pm the evening before.

Note 4: to avoid meat/fish and similar high protein intake, suggested permitted foods will be listed in the study manual.

6.8 Study Duration

The recruitment period will end once 1320 participants have been entered into the study, and the last participant has completed the baseline iohexol GFR clearance test. The recruitment period is expected to last 18 months. The follow-up phase of the study will cease when the last participant has completed the 36 month final iohexol GFR clearance test.

6.9 Follow-up of participants beyond study closure

The 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 study and collect long-term outcome and health resource usage data without needing further contact with the study participants. This will facilitate future studies linking markers of kidney function testing measured during the study period to longer-term outcomes in participants.

7 Study Procedures

7.1 Management of Participants

Throughout the study, the participants will be managed according to their usual care as determined by their local clinical staff. None of the study test results will be available to participants or treating clinicians whilst the study is ongoing, and thus they will not alter any management decisions.

Reference standard test

GFR will be measured in participants using an iohexol clearance method. A 5 mL bolus of Omnipaque 240 (518 g/L iohexol corresponding to 240 g/L of iodine, GE Healthcare www.gelifesciences.com) followed by 10 mL of normal saline will be injected into the antecubital vein. Blood samples will be collected at 5, 120, 180 and 240 minutes after injection. Exact time of the samples in relation to the bolus injection will be accurately recorded. Participants will be allowed free access to fluids during the collection procedure, but will be asked to refrain from excessive exercise and protein intake (i.e. meat and fish). Selected food as detailed in the study manual will be permitted.

Study tests

Blood samples will be collected using standard venepuncture and phlebotomy procedures including the use of a tourniquet. Blood will be collected in appropriate gel separating tubes following the manufacturer's recommended order of draw. The random urine sample will be taken into a plain sterilin pot.

Sample storage and transport

Samples will be transported to the local laboratory, where plasma/serum will be separated by centrifugation. Aliquots of serum/plasma and urine will then be stored at -80°C within 6 hours of venepuncture pending transportation to the central laboratories (St. Thomas's [iohexol, ID-MS creatinine] or Canterbury [enzymatic creatinine, cystatin C, ACR] depending on analyte) for analysis. See study manual for further details.

7.2 Laboratory procedures

A study manual documenting all laboratory procedures will be created. All analyses will be undertaken in accredited laboratories by staff registered with the Health Care Professions Council. GFR will be estimated using the simplified ID-MS traceable version of the MDRD equation and the three CKD-EPI equations (Table 2).

Table 2. Equations to be used to estimate glomerular filtration rate (GFR)

Abbreviation	GFR equation expressed as a single equation
$MDRD_{creatinine}$ [24]	$175 \times Scr^{-1.154} \times age^{-0.203} \times 0.742$ [if female] $\times 1.212$ [if black]
CKD-$EPI_{creatinine}$ [13]	$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black] , where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1
CKD-$EPI_{cystatin\ C}$ [29]	$133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932$ [if female] where Scys is serum cystatin C, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.
CKD-$EPI_{cystatin\text{-}creatinine}$ [29]	$135 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-0.601} \times \min(Scys/0.8, 1)^{-0.375} \times \max(Scys/0.8, 1)^{-0.711} \times 0.995^{Age} \times 0.969$ [if female] $\times 1.08$ [if black] where Scr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for females and 0.9 for males, α is -0.248 for females and -0.207 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

8 Recording and Reporting of Adverse Events

FAX SAE forms to the eGFR-C Study Office on:

0121 415 9135

Assessment of Safety

There are no novel medical devices or Investigational Medicinal Products (IMPs) used as part of this study. Any study-related Serious Adverse Events (SAEs) which require immediate reporting will be reported on a study-specific SAE form and will follow the procedure/timeframes outlined in this section of the protocol.

Other outcomes, which may also be considered safety outcomes, but which are anticipated outcomes for this group of patients (and therefore not considered study-related), will not be reported as adverse events for this study.

Administration of Iohexol (i.e. reference method)

The only study-related safety risk to participants involves the administration of iohexol (contrast medium) required for the reference GFR, which does not form part

of routine clinical practice and takes approximately five hours to complete. The associated risks *may* include:

- risk from venepuncture and vein cannulation
- idiosyncratic reaction to iohexol
- theoretical risk of deteriorating kidney function with injection of iohexol

These risks are in all cases extremely low. Emergency procedures, if required, will follow standard hospital protocols and as the participants will be in designated clinical areas full resuscitation equipment will be available. The repeated blood tests required will be taken by staff who are experts in phlebotomy. Where possible, a cannula will be left in situ following injection of iohexol, relieving pain or distress from repeated venepuncture.

Adverse Events (AEs)

Generic definitions of different types of AEs are listed in **Table 3.**

Table 3: AE definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study subject participating in a study and which does not necessarily have a causal relationship to the study procedure(s)
Adverse Reaction (AR)	Any untoward and unintended response in a subject to a study procedure where a causal relationship can't be ruled out
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: 1. results in death; 2. is life-threatening; 3. requires hospitalisation or prolongation of existing hospitalisation; 4. results in persistent or significant disability or incapacity; or 5. consists of a congenital anomaly or birth defect

It will be left to the Investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's withdrawal from on-going study participation. Most AEs that will occur in this study, whether they are categorised as serious or not, will be 'expected' for this patient population and will **NOT** be subject to immediate reporting as SAEs to the **eGFR-C** Study Office.

Serious Adverse Events (SAEs)

The following SAEs that could be reasonably '**expected'** for this group of patients during the course of the study are:

- nausea
- mild urticaria, with or without pruritus
- transient sensation of mild warmth
- hematomas and ecchymoses around injection site
- bronchospasm

These represent minimal risk to participants, so for the purposes of this study these SAEs do **NOT** require reporting to the **eGFR-C** Study Office on an SAE form. These events should continue to be recorded in the source data according to local practice.

Disease related morbidity and routine treatment or monitoring of a pre-existing condition that has not worsened will **NOT** be considered as SAEs and should **NOT** be reported to the **eGFR-C** Study Office.

Participant deaths will also be recorded on an SAE form in order to collect and review full details.

Serious Adverse Events (SAEs) for immediate reporting

The main theoretically possible recognised reportable SAEs associated with this study relates to the administration of iohexol required for the reference GFR. SAEs occurring within 24 hours of iohexol administration (and not listed as 'expected' as defined above) will always be reportable to the **eGFR-C** Study Office on an SAE form. The assessment of relatedness and expectedness to the administration of iohexol is a clinical decision based on all available information at the time.

SAEs outside of this timeframe can also be reported if it is the opinion of the Investigator that there is a possible causal relationship to another aspect of the study. An assessment of relatedness and expectedness will also be undertaken by the Chief Investigator (or designee).

Assessment of Relatedness

The following categories, as outlined in **Table 4** will be used to define the relatedness (causality) of the SAE.

Table 4: categorisation of relatedness

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

Assessment of Expectedness

This study protocol will be used as the reference document to assess study related and/or procedural SAEs. **Table 5** gives definitions of expectedness with respect to SAEs.

Table 5: categorisation of expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with known information about the study related procedures or that is clearly defined in this protocol
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with known information about the study related procedures

Reporting Timeframes

All SAEs as defined above as requiring reporting on an SAE form must be reported to the **eGFR-C** Study Office within 48 hours of discovery of the event; these will immediately be referred to the Chief Investigator or delegated deputy.

Site Investigators should also report any SAEs as required by their own institutional policies.

SAE Reporting Procedures

Completed SAE forms should be faxed to the **eGFR-C** Study Office on **0121 415 9135** within the specified timeframes. The Investigator at each site will be required to respond to any related queries raised by the **eGFR-C** Study Office as soon as possible.

Expedited Reporting to the Main Research Ethics Committee

Related and Unexpected SAEs

SAEs categorised by an Investigator as both suspected to be related to the study and unexpected will be subject to expedited reporting to the MREC.

The Chief Investigator (or designee) will undertake urgent review of all such SAEs and may request further information immediately from the clinical team at site. The Chief Investigator will not overrule the causality, expectedness or seriousness assessment given by the site Investigator but may add additional comment on these. Related and Unexpected SAEs will be notified to the MREC by the **eGFR-C** Study Office within 15 days after the Study Office has been notified.

The **eGFR-C** Study Office (on behalf of the Chief Investigator) will report all related and unexpected SAEs to the MREC concerned using the standard National Research Ethics Service (NRES) SAE report form for non-CTIMPs.

The **eGFR-C** Study Office (on behalf of the Chief Investigator) will also inform all Investigators concerned of relevant information about SAEs that could adversely affect the safety of participants.

In addition, at regular time points, the Study Steering Committee will be provided with details of all SAEs.

Annual Progress Reports

An annual progress report (with safety information included) will be submitted to the MREC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. Progress Reports will also be submitted to the Funder in accordance with their requirements.

Reporting urgent safety measures to the Main Research Ethics Committee

If any urgent safety measures are taken BCTU shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MREC of the measures taken and the circumstances giving rise to those measures.

Notification of Serious Breaches of GCP and/or the protocol

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

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

(b) the scientific value of the study.

The BCTU on behalf of the Co-Sponsors shall notify the MREC in writing of any serious breach of:

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

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

The Co-Sponsors will be notified immediately of any case where the above definition applies during the study conduct phase.

9 Data Management and Quality Assurance

Birmingham Clinical Trials Unit (BCTU), School of Health and Population Sciences, College of Medical & Dental Sciences, Public Health Building, Edgbaston, Birmingham, B15 2TT
Telephone: 0121 415 9130
Fax: 0121 415 9135
Email: eGFR-C@trials.bham.ac.uk

The named clinicians at the participating sites will enter data onto the CRFs. Where this duty is delegated to other staff, this will be recorded in a delegation log. Investigators will keep their own study file logs which link participants with anonymised CRFs.

Data from this study will be handled by the BCTU, a full-time research facility dedicated to, and with substantial experience in, the design and conduct of clinical research. The BCTU recognises the responsibilities of a data management centre with respect to the ethical practice of research and the adequate protection of human subjects.

9.1 Confidentiality of Personal Data

The study will collect personal data about participants, medical records will be reviewed for all patients and routine physical examinations will be performed.

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. With the patient's consent, their name, NHS number and date of birth will be collected at study entry to assist with long-term follow-up. Patients will be identified using only their unique study number and date of birth in mmm/yyyy format on the CRFs, samples and correspondence between the Study Office and the participating site.

Investigators will keep their own study file logs which link patients with anonymised CRFs. The Investigator must maintain documents not for submission to the Study Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

The Study Office will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Representatives of the eGFR-C study team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

The patient consent form, which will be sent to the BCTU will, out of necessity, contain identifiable personal data. These will be stored separately from the study record. The consent form will be sent to BCTU, with the patient's consent, to monitor that the consent process has been completed correctly.

Participants will be informed that their study data and information will be securely stored at the study office at the BCTU, and will be asked to consent to this. The data will be stored on a secure computer database, and all personal information obtained for the study will be held securely and treated as strictly confidential. Any data processed outside of the BCTU will be anonymised.

9.2 Long-Term Storage of Data

In line with the Medicines for Human Use (Clinical Trials) Regulations, once data collection is complete on all participants, all data will be stored for at least 5 years (but ideally not less than 15 years). Any queries or concerns about the data, conduct or conclusions of the study can also be resolved in this time. Limited data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board.

Study data will be stored within the BCTU under controlled conditions for at least 3 years after closure. Long-term offsite data archiving facilities will be considered for

storage after this time. The BCTU has standard processes for both hard copy and computer database legacy archiving.

9.3 Data collection

When available, case report forms (CRFs) can be entered online at https://www.trials.bham.ac.uk/egfrc. Authorised staff at sites will require an individual secure login username and password to access this online data entry system. Paper CRFs must be completed, signed/dated and returned to the Study Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above. The exception to this will be the SAE Form which must be co-signed by the Investigator.

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

The CRFs will comprise the following forms:

Form	Summary of data recorded	Schedule for submission
Registration Notepad	Patient details (name, NHS number, date of birth, sex and ethnicity), confirmation of eligibility and clinical details. Collected from patient and hospital notes.	Details collected via online registration at baseline.
Baseline and 36 month data collection form	Clinical history and current medication details, anthropometric measurements (height, weight, hip and waist circumference, blood pressure, samples collection, death and withdrawal information. Collected from patient and hospital notes. Form identified by study number and date of birth in mmm/yyyy format.	Faxed/sent/submitted online after each follow-up assessment time point (baseline and 36 months main study, additionally at 12 and 24 months for the disease progression sub-study and at baseline, 2, 3 and 4 weeks for the intra-individual biological variability study)
Serious Adverse	Details of any SAE occurring within 24 hours of the iohexol testing.	Faxed within 24 hours of research staff becoming aware of event.

Event Form	Collected from hospital notes. Form identified by study number and date of birth in mmm/yyyy format. Also submitted to study office to record full participant death details.	
Laboratory Data Collection Form	Results of blood and urine tests, eGFR and GFR results. Collected from patient samples. Form identified by study number and date of birth in mmm/yyyy format.	Details submitted online and laboratory will retain source data from tests on CRFs and own databases. Samples collected at centres at baseline, 6, 12, 18, 24, 30, 36 months, and baseline, 2, 3 and 4 weeks for the intra-individual biological variability study. The samples will be sent to the laboratories and analysed in batches (assayed in duplicate for the intra-individual biological variability study).
Follow-up data collection form	Samples collection information, death and withdrawal information. Form identified by study number and date of birth in mmm/yyyy format.	Faxed/sent/submitted online after each follow-up assessment time point (6, 12, 18, 24 and 30 months).

Data reported on each form 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 form. All missing and ambiguous data will be queried. All sections are to be completed before returning. 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 completed originals should be sent to the Study Office and a copy filed in the Investigator Site File.

Study forms may be amended by the Study Office, as appropriate, throughout the duration of the study. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

All laboratory test results will be entered onto the online system at the central testing laboratories. Authorised staff at the laboratories will require an individual secure

login username and password to access this online data entry system. Relevant source data in the laboratories will be stored for a minimum of 10 years.

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

9.4 Data handling and analysis

Data analysis will be undertaken by statisticians within BCTU and the University of Birmingham, and by the statistical co-applicant based at the University of Kent. All data transferred between units will be fully anonymised and transferred in encrypted form.

Personal data and sensitive information required for the eGFR-C study will be collected directly from study participants, their samples and hospital notes on data collection forms, coded with the participant's unique study number and date of birth in the mmm/yyyy format. The consent form will also be faxed to the eGFR-C study office. As this document has identifiable details this will be with consent from the participant. Participants will be informed about the transfer of this information to the eGFR-C study office at the BCTU and asked for their consent. The data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by BCTU staff.

All personal information received in paper format for the study will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the eGFR-C study (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations.

10 Archiving

Archiving will be authorised by the BCTU on behalf of the Co-Sponsors following submission of the end of study report.

Principal Investigators are responsible for the secure archiving of essential study documents (for their site) as per their NHS Trust policy. All essential documents will be archived for a minimum of 5 years after completion of study.

11 Statistical Considerations

11.1 Outcome Measures

11.1.1 Main study

11.1.1.1 Primary outcome measures

i) Percentage error in eGFR compared to reference GFR. Values will be computed (for objectives 1 and 2) using baseline data for each of the four eGFR equations, and the proportions within 30% (P_{30}) of the reference standard quoted and compared as a measure of accuracy and precision.

ii) Difference in rate of change in eGFR compared to rate of change in reference GFR. Rates of change will be estimated (for objective 3) using linear regression and the change per annum and percentage change per annum compared to baseline values computed. Large error will be defined as differing by more than 3 mL/min/1.73 m^2/year or by 5 percent points per annum.

11.1.1.2 Secondary outcome measures

iii) Progressive loss of kidney function defined as decline in GFR of more than 10 mL/min/1.73 m^2/3 years or increase in albuminuria category as defined by KDIGO (used for objective 4).

iv) Cost per quality adjusted life year (QALY) (used for objective 6).

11.1.2 Sub-study of patterns of disease progression

v) Difference in rate of change in eGFR compared to rate of change in reference GFR based on measurements made every 12 months (objective 5).

11.1.3 Additional study of intra-individual biological variation

vi) Within-individual (CV_I) variation and the critical difference (reference change value, RCV) for reference GFR and the estimated GFR equations.

11.2 Sample size

We will recruit 1300 people to the main study, 375 of whom will be part of the sub-study of disease progression (125 South Asian, 125 African-Caribbean and 125 Caucasian participants). Based on a drop-out rate of 20% this will provide 1000 evaluable participants in the main cohort, and 100 in each of the ethnically defined subgroups. An additional 20 people will be recruited for the study of intra-individual biological variation. Participants in this additional study will not be ineligible for the main study, but it is not expected that they would take part.

1000 evaluable participants will provide over 90% power to detect a difference of 5% in the P_{30} for the main study comparison of the $MDRD_{creatinine}$ equation and the $CKD\text{-}EPI_{creatinine\ and\ cystatin\ C}$ equation. The sample size is informed by a simulation study estimating expected differences in P_{30} and rates of change. Power estimates are based on the proportion of statistically significant ($P<0.05$) results observed in 1000 simulations using values of P_{30} informed by recent studies.[12, 13, 26, 29, 30] The key difference considered is between a P_{30} of 81% and 86% - a difference considered clinically important and likely to occur with the expected scale of known differences in imprecision between the equations. The calculation is conservative in that it only takes imprecision into account. If there is a systematic bias then the power will be greater than 90%. The sample size of 100 evaluable participants in the ethnic subgroups will allow P_{30} estimates to be reported with 95% confidence interval width of 10%.

Annual rates of change over 3 years will be estimated by linear regression. Two cut-points for errors in rates of change have been proposed: greater than 3 mL/min/1.73 m^2/year error and greater than 5 percent point difference per year.[58] Based on the measurement error corresponding to P_{30} measures of 81% and 86%, the study has over 90% power to detect differences in the proportions with greater than 3 mL/min/1.73 m^2/year error and over 80% power to detect differences in proportions with greater than 5% error.

11.3 Statistical analysis

A separate Statistical Analysis Plan for the eGFR-C study provides a detailed description of the planned statistical analyses. A brief outline of these analyses is given below.

11.3.1 Primary outcome analysis

Main study

Data will be analysed to address two main questions: (1) which of the GFR-estimating equations is the most accurate assessment of reference GFR; and (2) which most accurately reflects change in GFR? In each case, data will be further analysed to assess whether observed relationships amongst African-Caribbean and South Asian subjects differ from those observed amongst Caucasians, and whether diabetes and proteinuria are predictors.

11.3.1.1 Which of the GFR-estimating equations is the most accurate assessment of reference GFR?

The primary comparison (for which the study is powered) will be between the $MDRD_{creatinine}$ equation (current practice) and the $CKD\text{-}EPI_{creatinine\ and\ cystatin\ C}$ equation. The primary analysis will use the baseline data to estimate P_{30} values for all GFR estimating equations and compare P_{30} values between GFR estimating equations using McNemar's test for paired data. An estimate of the difference in P_{30} values together with a 95% confidence interval will be presented. Additional pairwise comparisons will be made between these two equations and the $CKD\text{-}EPI_{cystatin\ C}$ and $CKD\text{-}EPI_{creatinine}$ equations.

The mean and median differences between iohexol GFR and each of the estimates of GFR will provide measures of bias.[64] Differences in precision will be assessed by comparing the interquartile range (IQR) of the estimated GFR. Accuracy will be assessed by establishing the proportion of GFR estimates within 30% (P_{30}) of iohexol GFR, and also as root mean square error (RMSE) of the differences. For bias, IQR, P_{30} and RMSE 95% confidence intervals (CIs) will be estimated using boot-strapping procedures where necessary.

11.3.1.2 Which GFR-estimating equation most accurately reflects change in GFR?

We will compute the average rate of change in measured and estimated GFR across 3 years follow-up, and the difference between them (the error). eGFR

data will be modelled as a linear function of time as described by Padala et al[58] utilising all available (maximum 7) eGFR time points compared to the difference between final and baseline reference GFR values. Rates of change will be expressed both as the absolute regression slopes (standardised per year), and as a percentage change per year comparing the slope to the baseline value.

The percentage of participants demonstrating large error with the respective GFR estimating equations will be compared using McNemar's test.

Large error between measured and estimated GFR will be defined as

- greater than 3 mL/min/1.73 m^2/year (primary definition)
- greater than 5% difference in slope (secondary definition)

We will also summarise the ability of the equations to detect changes in GFR over three years defined as

- change in iohexol GFR>10 mL/min/1.73 m^2 (primary)
- change in iohexol GFR>25% (secondary)
- change in iohexol GFR > the reference change value (RCV) derived in variability study (secondary)

The sensitivity, specificity, positive and negative predictive values and likelihood ratios for the four eGFRs for detecting these changes will be calculated using standard approaches and presented with 95% CIs.

11.3.2 Secondary outcome analysis

11.3.2.1 Which GFR-estimating equation, together with ACR, or ACR alone, most accurately predicts those people that have progressive loss of kidney function (CKD progression)?

Models will be constructed to predict time to progression based on baseline eGFRs and ACR. Progression will be defined in terms of decline in reference GFR (change in iohexol GFR>10 mL/min/1.73 m^2) or an increase in albuminuria category, as defined by KDIGO. Progression will only be detected at one of 6 time points, hence piecewise survival models will be fitted to determine whether the prognostic value of ACR and the estimated GFRs is independent of other risk factors. We will develop a prognostic model utilising age, gender, ethnicity, BMI, waist circumference, MABP, diabetes mellitus, smoking status, and presence of vascular disease in addition to baseline ACR and the various eGFRs. Both proportional and non-proportional hazards will be considered. Bootstrap validation will be used with these prediction models.

11.3.2.2 Cost-effectiveness modelling of the optimal strategy

Whilst our longitudinal cohort will not have adequate power to detect differences in progression, our estimates of the accuracy of eGFR (main study), patterns and determinants of progression (sub-study), and intra-individual biological variation (additional study) can be combined in a model to evaluate the impact of alternative monitoring strategies on detection of progression to stage 4 CKD. True GFR values will be modelled over time for representative cohorts of people, and performance of alternative monitoring strategies in detecting progression to stage 4 CKD (varying in timing and choice of eGFR equation) will be simulated utilising estimates of measurement error and accuracy. Outcome variables which will be assessed will include sensitivity, false positive progression rates, and delays in detecting progression. These modelling approaches can then contribute to the economic evaluation to establish the most cost-effective monitoring strategy.

A decision analytic model will be implemented which will incorporate the information describing the performance of the alternative monitoring strategies, and will consider the impact of the error in eGFR measures on patient outcomes. Data on the type and frequency of tests for the alternative monitoring strategies is being collected over time, along with the description and frequency of any adverse events, and these will help to inform the costs and outcomes of each of the monitoring strategies. Data describing long term patient outcomes that may occur beyond the end of the study will be obtained from secondary sources. This will enable the impact of the error in the eGFR measures on patient outcomes such as myocardial infarction, the need for kidney transplant, and renal failure to be incorporated into the analysis.

This cost-effectiveness analysis will take the form of a cost-utility analysis in which the outcome measure will be the cost per quality adjusted life year (QALY). In the short term the alternative testing strategies are unlikely to impact on the quality of life (QoL) of the patients over the period of the study (hence why no QoL data is being collected in this study); however failure to detect the progression of CKD may impact on later patient outcomes if the appropriate treatment is not administered in a timely manner. The cost and QoL of these later patient outcomes will be informed by secondary sources, and will be incorporated into the economic evaluation.

In the first instance prior to the economic evaluation being undertaken a systematic review of the cost-effectiveness literature on CKD will be implemented. This will inform as to the types of approaches to the modelling of CKD that have been undertaken in the past, and will also help to identify

the parameters that will be necessary to extrapolate the model beyond the time horizon of the study.

11.3.2.3 Sub-study of patterns of disease progression - How does GFR progress over time and what are the optimal monitoring times?

The rate of decline (mL/min/1.73 m^2/year) in reference GFR, and the difference between reference GFR and estimated GFRs (referred to as error), measured every 12 months will be modelled over time using a longitudinal linear or nonlinear (exponential decline) random coefficients regression model to estimate average and variability in disease progression and error. Parameters of the model for each outcome will be estimated using maximum likelihood. The fixed effect component of the models will adjust the expected value of the population average to take account of significant covariates. Outcomes will be modelled on the natural and log-transformed scales. Covariates to be explored in the model will include gender, age, diabetes, duration of diabetes, ethnicity, albuminuria, baseline GFR, blood pressure, BMI, waist circumference, smoking status and presence of vascular disease. The effect of covariates on the population average intercept and longitudinal time effect parameters will be assessed. The method of backward elimination will be used to remove covariates which are not significant from the model. Between and within patient variability in the rate of decline of reference GFR will also be estimated. Linear relationships between disease progression and drug name or drug class will be explored.

Analysis will be undertaken using NONMEM version 7.1.2, R open source software and PFIM version 3.2.2 optimal design algorithms (R open source software). The PFIM algorithms will be used to calculate the D-optimal[65] sampling times from the disease progression model based on reference GFR for people with diabetes and/or proteinuria, and for those people with neither of these conditions. The point estimates and the covariance matrix of model estimates will be used in the optimal design algorithms to ensure the solution is robust to model uncertainty. Optimal monitoring strategies will be selected from a set of designs with sampling every six months, and monitoring strategies with a number of sampling points (between two and six) will be compared. Optimal monitoring strategies will be calculated for other important subgroups of the population found to be significant in the disease progression model. The monitoring strategies identified will be used as the basis for further simulations.

Additional disease progression modelling will be performed on eGFRs and ACR. Parameter estimates and estimates of within- and between-patient variability will be compared to those for reference GFR.

11.3.2.4 Additional study of intra-individual biological variation

Pre-analytical variables will be standardised. Participants completing less than 2 of the 4 planned reference test procedures will be excluded from analysis. All samples for all analytes will be assayed in duplicate and the analytical variance (SD_A^2) will be calculated from the differences between the duplicate measurements. The data will be initially examined and the requirement to normalise the data using a logarithmic transformation will be considered. Outliers will be excluded using Cochran's test and Reed's test, as described by Fraser and Harris.[22] The total (CV_T), analytical (CV_A), group (CV_G) and within-individual (CV_I) components of variation will be calculated using nested ANOVA.[22] The critical difference (reference change value, RCV) for significant changes in serial results ($P<0.05$) and the number of specimens required to estimate the homeostatic set-point of an individual (within $\pm$10% with a confidence of 95%) will also be estimated. The derived RCV for the reference GFR will be used to test the ability of estimated GFR equations to detect a true change in GFR (see 12.3.1.2 above).

11.4 Interim analyses

Interim analyses will focus on ensuring that the recruited sample (both overall and in the sub-study of disease progression) reflects the targeted groups.

Targets for recruitment of participants with proteinuria (ACR >30 mg/mmol) and diabetes will ensure that at least 20% and no more than 80% are within these groups.

Targets for the African-Caribbean and South Asian groups are for proportions of 10-15% in the overall study, and 125 of each recruited to the disease progression sub-study.

At regular intervals during the recruitment phase the recruitment pattern will be examined against these metrics and adjustments made to the recruitment process if required.

11.5 Final analyses

There are five stages of analysis in the study:

1) The additional study of biological variation (12.3.2.4) will be analysed as soon as all 20 participants have completed and test results are available (expected to be in Year 1).
2) The analysis of accuracy of the equations for measuring eGFR (12.3.1.1) will be based on analysis of baseline values, and will be completed once baseline test results are available on all participants (expected to be in Year 3)
3) The modelling of GFR progression over time (12.3.2.3) will be undertaken after the last participant in the disease progression sub-study has undergone the final reference GFR assessment.
4) The final analysis of the accuracy of change in eGFR (12.3.1.2 and 12.3.2.1) will be undertaken after the last participant has undergone their final reference GFR assessment (expected to be in Year 6).
5) The health economic analysis will be undertaken when the final analysis of accuracy of change is complete (12.3.2.2).

11.6 End of study

The end of study will be 6 months after the last data capture. The last data capture will be 36 months following recruitment of the last participant.

12 Direct Access to Source Data

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

13 Ethics Requirements

The Co-Sponsors will ensure that the study protocol, PIS, consent form, GP letter and submitted supporting documents have been approved by the MREC prior to any participant recruitment. The protocol and all agreed substantial protocol amendments will be documented and submitted for ethical approval prior to implementation.

Before a site can enrol participants into the study, 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 study, the Chief Investigator/ Co-Sponsors will ensure that the MREC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The Chief Investigator will supply the Co-Sponsors with a summary report of the clinical study, which will then be submitted to the MREC within one year after the end of the study.

14 Monitoring Requirement for the Study

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

There will be an independent study steering committee (SSC). This will comprise an independent chairperson (Dr Charlie Tomson, Consultant Nephrologist, Bristol), one other independent nephrologist, a patient representative, the study statistician, an independent statistician, the chief investigator, the study lead research nurse and one co-applicant. This group will meet at the beginning of the study and thereafter up to six monthly depending on progress.

The study will not have an independent data monitoring committee.

15 Finance

The National Institute for Health Research is funding this study through its Health Technology Assessment programme.

16 Indemnity

This is a clinician-initiated study, ABPI guidelines for patient compensation by the pharmaceutical industry will not apply.

The Co-Sponsors hold Public Liability (negligent harm) and Clinical Trial (negligent harm) insurance policies, which apply to this study. Participants may be able to claim compensation, if they can prove that either Co-Sponsor has been negligent. However, as this study is being carried out in a hospital setting, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical study. Compensation is only available via NHS indemnity in the event of clinical negligence being proven. The Co-Sponsors do not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees.

Participants *may* also be able to claim compensation for injury caused by participation in this study without the need to prove negligence on the part of the Co-Sponsors or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the relevant Insurers.

There are no specific arrangements for compensation made in respect of any serious adverse events occurring though participation in the study, whether from the side effects listed, or others yet unforeseen.

Hospitals selected to participate in this study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary should be provided to Co-Sponsors, upon request.

17 Dissemination and Publication

The Chief Investigator will coordinate dissemination of data from this study. All publications and presentations, including abstracts, relating to the study will be authorised by the eGFR-C Study Management Group. The results of the analysis will be published in a peer reviewed journal either in the name of all of the members of the Study Management Group listed individually or in the name of the eGFR-C Collaborative Study Group collectively in a peer reviewed journal (provided that this does not conflict with the individual journal's policy). In the latter case all contributors to the study will be listed, with their contribution identified. Study participants will be sent a summary of the final results of the study, which will contain a reference to the full paper.

All publications using data from this study to undertake original analyses will be submitted to the Study Management Group for review before release. To safeguard the scientific integrity of the study, data will not be presented in public before the main results are published without the prior consent of the Study Management Group.

18 Statement of Compliance

The study will be conducted in compliance with the approved protocol, EU GCP and the Research Governance Framework.

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