Renal function **A**ssessment with **P**oint of care creatinine **I**n **D**iverse populations (**RAPID**)

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LIST OF ABBREVIATIONS

AE	Adverse Event
CAG	Confidential Advisory Group
CI	Chief Investigator
Cr	Creatinine
CRF	Case Report Form
DMC	Data Monitoring Committee
DTPA	Diethylenetriamine Pentaacetic Acid
GAfREC	Governance Arrangement for NHS Research Ethics
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form
KCH	King's College Hospital
PI	Principal Investigator
PIS	Participant Information Sheet
POC	Point of Care
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File

STUDY SUMMARY

STUDY OVERVIEW	
Full title	Renal function Assessment with Point of Care creatinine In Diverse populations (RAPID)
Objectives	Study A • To compare capillary POC-Cr with venous serum enzymatic creatinine concentrations (serum Cr) in people of different ethnicities performed by health care professionals and patients • To compare estimated glomerular filtration rate (eGFR) using POC-Cr and serum Cr with formal GFR assessment in people of different ethnicities • To define a threshold of POC-Cr concentration in different ethnicities which are confirmatory of eGFR <60mls/min/1.73m2 (Kidney Disease Improving Global Outcomes; KDIGO Definition Stage 3) and a range of POC-Cr which may require further confirmation Study B • To conduct an observational cohort study of serial capillary self-testing POC-Cr for at least one week. • To compare single and serial capillary POC-Cr compared with single venous creatinine concentration IDMS traceable enzymatic assay • To assess test success rate, safety, training time, patient experience and acceptability of serial capillary POC-Cr testing
Type of trial	Two centre cross-sectional study and prospective longitudinal cohort study
Trial design and methods	375 participants (including > 40 of African/African-Caribbean ancestry) having venous serum creatinine and 99mTc-DTPA nuclear medicine or venous GFR filtration panel testing will be recruited to a cross sectional study (Study A) At least 40 patients with CKD will be recruited to a longitudinal study (Study B) Demographics, medical and transportation details will be recorded Finger-prick capillary creatinine will be assessed by POC-Cr device; Venous serum creatinine concentration (Isotope Dilution Mass Spectrometry (IDMS) Traceable Enzymatic assay). Participants will be trained to use POC-Cr device, asked to self-monitor up to four times per day and report details including test failure and adverse events. Patient experience and acceptability will be assessed using Service User Technology Acceptability Questionnaire.
Health condition(s) or problem(s) studied	Chronic Kidney Disease
Target sample size	At least patients 415 (Study A: 375; Study B: At least 40)
Trial duration per participant:	Study A: 1 Day Study B: 1 week

Main inclusion/exclusion criteria:	**Inclusion criteria**: • Is 18 years of age or older • Is willing to complete all study procedures • Study A: Patients undergoing formal nuclear medicine (99mTc-DTPA) glomerular filtration rate testing or willing to have a venous GFR filtration panel (Study A only) • Study B: Has Chronic Kidney disease (CKD) KDIGO criteria or is at risk of CKD due to heart disease or diabetes as determined by physician **Exclusion criteria**: • Unable or unwilling to give informed consent • Any condition which would make finger prick contraindicated e.g. severe skin conditions, bleeding disorder • Study A: If formal GFR testing has been requested only because estimated GFR is not considered to reflect true GFR (e.g. liver disease)
Statistical methodology and analysis:	• Accuracy compared to venous serum creatinine and 99mTc-DTPA testing or GFR filtration panel will be calculated for POC-Cr capillary blood testing performed by patients and health care professionals. • Total, between-day, and within-day precision will be evaluated by comparing up to four POC-Cr capillary concentrations for at least seven days and compared to day 1 and 8 venous serum creatinine concentrations.
STUDY TIMELINES	
Study Duration/length	End date 30/06/2025
Expected Start Date	1/7/20
End of Study definition and anticipated date	Last patient completed final study visit
Key Study milestones	• Month 1-28: Recruitment • Month 29: Data analysis • Month 30 Outcome presentation/publication
STORAGE of SAMPLES (if applicable)	
Human tissue samples	N/A
Data collected / Storage	Pseudoanonymised data will be stored for 5 years after study completion in secure filing cabinets in the renal research team locked room.

1 BACKGROUND AND RATIONALE

People of black or Asian and minority ethnicities (BAME) have a 3-5 fold increase in requirement for dialysis to treat kidney failure and present with kidney disease at younger ages. Prevention of progression to kidney failure is often possible at earlier stages of kidney disease[1] but kidney disease is often silent until later stages[2]. Frequently people from BAME have more advanced disease at diagnosis with fewer options for treatment. Early detection is likely to reduce the incidence of kidney failure, which currently costs 3% of the total NHS budget. Screening people of high-risk ethnicities has been reported to be cost effective[3,4] in other countries but the feasibility of community screening of high-risk groups in the UK has not been explored.

Point of care (POC) testing with finger-prick blood monitoring are now available to assess kidney function (creatinine) with the finger-prick method, giving results in less than a minute without additional cost of venous blood-taking, transportation and processing. An Australian screening program with POC-Cr reported that 99% of participants found it convenient and 96% felt that the immediate results and feedback helped them understand their condition better[5]. Opportunities for POC-Cr screening led by allied health care professionals (AHP) before radiological investigations[6] are being explored and an NIHR 'Horizon scanning report' assessing the potential role of POC-Cr testing for detection and monitoring of CKD[7] recommended assessment of clinician and patient clinical need but POC-Cr screening for people at high risk of CKD, including ethnic minority groups has not been investigated.

Our recent engagement event hosted by The Africa Advocacy Foundation (AAF) highlighted lack of trust, anxiety and inconvenience attending current health care appointments. Rapid availability of POC-Cr results could provide instant information about kidney health for high-risk groups in the BAME community (e.g. in faith-based settings). This approach was highly welcomed by engagement event participants if sign posting to relevant services and tailored educational material was available. However, there have been conflicting reports of correlation between venous and capillary (finger-prick blood) creatinine concentrations[8] and no formal assessment of performance POC-Cr in people of different ethnicities' has been undertaken.

Recently, use of ethnicity in kidney function testing has been recommended to be removed. New biomarker GFR filtration panels which do not require adjustment for ethnicity have been

demonstrated to provide better estimation of measured GFR and can be performed without the need for costly nuclear medicine assays[9]. In addition, assessment of lean body weight may enhance estimation equations[10] but have not been assessed in combination with POC-Cr testing.

In other chronic diseases, self-monitoring is associated with feelings of security, reassurance, control, high motivation and levels of satisfaction[11] and has transformed care for millions of individuals (e.g. glucose testing). Self-monitoring with POC-Cr testing could empower kidney patients to participate in their own care, enable timely intervention at times of deterioration, and reduce unnecessary hospital visits and damage to veins. Home POC-Cr testing has been demonstrated in a small paediatric study to be an acceptable alternative to hospital testing[12].

Self-monitoring with POC-Cr was strongly supported by AAF engagement participants if appropriate self-care material and education is provided and proposed benefits included privacy of personal monitoring or in a faith-based community setting at the individual's convenience. This approach was considered ideal for those identified to have early CKD at screening event with minimal health care professional contact. However, in order to harness the benefits of POC-Cr self-monitoring it will be important to understand and interpret intra-patient variability in capillary blood results, potentially without need for complete alignment with laboratory tests. Conversely, self-monitoring may introduce increased anxiety and requirement for additional interaction with health care services and concurrent understanding of feasibility (training required, number of successful tests) and patient experience (including acceptability of monitoring frequency) of self-monitoring POC-Cr is critical.

Our overall aim is to develop and pilot a UK community-based screening and CKD monitoring program to address health inequalities in CKD, focusing on people from ethnic minority groups.

Essential preliminary data using hand-held POC-Cr device is required to secure future funding for this work. Hand held POC-Cr has been reported to perform less well than larger 'table-top' POC-Cr devices when capillary blood testing is compared with venous creatinine sampling[13] but has been chosen for this study because it requires only a finger-prick sample with a simple cheap hand-held device and therefore can easily be used in community settings[14] and by patients[15].

2 OBJECTIVES

2.1 Primary Objectives

Study A

- To compare estimated glomerular filtration rate (eGFR) using POC-Cr and serum Cr with formal GFR assessment in people of different ethnicities.

Study B

- To conduct an observational cohort study of serial capillary self-testing POC-Cr for at least one week.
- To compare capillary POC-Cr with venous serum enzymatic creatinine concentrations (serum Cr) in people of different ethnicities performed by health care professionals.
- To compare serial capillary POC-Cr compared with single venous creatinine concentration IDMS traceable enzymatic assay.

2.2 Secondary Objectives

Study A

- To define a threshold of POC-Cr concentration in people of different ethnicities which are confirmatory of eGFR <60mls/min/1.73m2 (Kidney Disease Improving Global Outcomes; KDIGO Definition Stage 3) and a range of POC-Cr which may require further confirmation.
- To compare capillary POC-Cr with venous serum enzymatic creatinine concentrations (serum Cr) in people of different ethnicities performed by health care professionals

Study B

- To assess test success rate, safety, training time, patient experience and acceptability of serial capillary POC-Cr testing

3 STUDY DESIGN

Study A: Cross-sectional cohort study

Study B: Observational longitudinal cohort study

Research Ethics Committee approval and R&I approval will be sought for the study. Participants who meet the entry criteria will be recruited and consented by the investigator, or any GCP qualified member of the local research team who has delegated responsibility for study recruitment. Participants will be recruited from King's College Hospital, Royal London Hospital outpatients and wards and nuclear medicine department. Participants will be offered a minimum of 24 hours to reflect on the patient information sheet (PIS), which will be provided during initial discussion. Participants will be selected purposively to include a range of age, gender, ethnicity (at least 50% African/Afro Caribbean), severity of renal disease and clinical settings. Participants in study A will be able to participate in study B if they wish to do so.

Demographics, Body mass index, waist circumference and lean body mass (Fresenius - Body Composition Monitor and clinician estimated), mobility at home, mode of transportation to come to hospital, length and cost of travel, carer details, drug history, number of hospital visits and GP visits per year and reason for laboratory creatinine testing (e.g. monitoring Ig A nephropathy) will be recorded. Data will be transferred following pseudo-anonymisation into a study specific database by the research team.

POC-Cr testing

Capillary POC-Creatinine concentration will be assessed by NovaMaxCreat (NovaBio) and Epoc (Siemens) POC hand-held devices. A quality control will be performed for each POC-Cr device each day by the study nurse and by participants, ensuring the reagent batch conforms the manufacturers' quality specifications. POC reagents will be stored and used following manufacturers' specifications.

Study A: POC-Cr will be assessed using the NovaMaxCreat and Epoc devices. Finger-prick capillary whole blood samples will be taken (0.05 uL for NovaMaxCreat and 0.9 uL for Epoc) using lancets by the research team. Venous serum creatinine for routine care (Isotope Dilution Mass Spectrometry (IDMS) Traceable Enzymatic assay) and 99mTc-DTPA glomerular filtration rate testing (where available) will be extracted from hospital laboratory databases. Participants not undergoing routine ^{99}mTc-DTPA glomerular filtration rate testing will also have a ' eGFR filtration panel assessment – Beta-2-microglobulin, cystatin-C (processed by Synlab/ViaPath) and beta-trace-protein concentration (processed by Affinity laboratories), assessment on their venous blood sample.

Participants will be trained to use the POC-Cr device by the research team and time taken recorded and asked to perform one POC-Cr test.

In addition, the Epoc Blood Analysis system, will also measure capillary potassium concentrations, which will be compared to serum potassium (taken from the venous blood sample for routine clinical care). This will be tested in the laboratory using the Roche Chemistry Analyser Cobas 8000.

Study B: Participants will be trained to use the POC-Cr device, NovaMaxCreat (NovaBio) by the research team and time taken recorded. Participants will be taught how to perform quality controls. All sample results will be digitally recorded by the device and downloaded after the device is returned. Participants will be asked to do one test at the hospital (with a simultaneous lab creatinine on site for validation), then to self-monitor four times per day (first thing in morning, midday, before evening meal/early evening, before bed) and each test recorded in a paper diary or electronically as desired. Details reported will include date and time of test, test success, device and non-device failures (test results, missed testing and reasons for missed test (e.g. forgot, did not want to test) and adverse events (e.g. pain or infection or prolonged injury after sampling, pre-syncopal or syncopal episode).

For participants who perform finger-prick testing for capillary blood glucose monitoring, both samples (creatinine using NovaMaxCreat and glucose using their usual device) can be taken from the same finger-prick test. However, participants will be advised to take the creatinine sample first.

Participants will also be given the option to test more frequently or for longer than one week if desired and to report the reason for additional tests (concerned about previous result, demonstration for friend or family member). Reassurance will be given to participants about possibility of abnormal results and research team contact provided for discussion and repeat testing if desired of changes in results. Participants can have the opportunity (after consent) to trial self-testing on site, and decide if they wish to participate in self-monitoring at home.

Service User Technology Acceptability Questionnaire (SUTAQ): The SUTAQ questionnaire has been developed to measure the acceptability of telehealth and remote monitoring of chronic disease and includes assessment of quality of life, well-being, psychological processes and other patient-reported outcome measures (PROMs) which are evaluated with six acceptability scales: enhanced

care, increased accessibility, privacy and discomfort, care personnel concerns, kit as substitution and satisfaction.[14] We have piloted the SUTAQ with minor adaptation developed with PPIE in our outpatient department. SUTAQ answers will be collected by the research team on tablet devices for Study B. Permission has been provided to use the SUTAQ by Dr Shahi Hirani.

Samples (for Study A) will be sent to:

i) Synlab UK - King's College Hospital NHS Foundation Trust (Cystatin C, Beta-2-microglobulin)

ii) Affinity Biomarker Labs, Suite 602 Cumberland House, 80 Scrubs Lane, London (beta-trace-protein)

The study sites and corresponding principal investigators are included in the table below.

Site	Study A and /or B	PI
King's College Hospital	A + B	Dr Rouvick Gama
Queen Alexandra Hospital, Portsmouth	B	Dr Nicholas Sangala

4 STUDY SCHEDULE

Enrolment process:

Study A: Participants will be identified through database screening (Renalware and PIMS/Electronic Patient Records) and approached in outpatient or wards by research specific staff and provided with a patient information sheet (PIS).

Study B: Participants will be identified and approached in outpatients by clinical staff and provided with a patient information sheet (PIS).

Participants who meet the inclusion and exclusion criteria for the study will not require any further screening prior to involvement in the study. Participant will provide written consent and samples taken for analysis.

Follow up: None, unless required following an Adverse Event. In such cases, the follow up will be as determined by the Principal Investigator.

Participant withdrawal criteria and procedures: If a participant wishes to withdraw their consent their information will be destroyed.

End of the study: The end of the study will occur after the final patient is recruited and final sample collection.

Table 1: Study A - Schedule of Assessments

	Pre Screening	Study Visit
Visit No		1
Informed Consent		X
Medical History		X
Vital Signs and lean body mass Bioimpedence		X
Eligibility confirmation	X	X
Concomitant Medication Review		X
Venous Serum Creatinine		X
POC-Cr		X
99mTc-DTPA		±2 days of POC-Cr
Or Biomarker panel		X
Adverse Events Review		X

Table 2: Study B - Schedule of Assessments

	Pre Screening	Baseline	Home Monitoring	Final Visit
Visit No		Day 1		Day 8
Window of flexibility for timing of visits:				Day 7-10
Informed Consent		X		
Medical History		X		
Vital Signs		X		
Eligibility confirmation	X	X		
Concomitant Medication Review		X		X
Venous Serum Creatinine		X		X
POC-Cr Health Care Professional		X		X
POC-Cr Patient		X	X	X
Test success reporting			X	
Adverse Events Review		X	X	X
SUTAQ Questionnaire				X

5 CONSENT

The participant must personally sign and date the latest approved version of the Informed Consent form before any of the study specific procedures are performed.

Written versions of the Participant Information and Informed Consent will be presented to the participants detailing the exact nature of the study, what it will involve for the participant, the implications and constraints of the protocol and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

If he/she wishes to consider the information, the participant will be allowed as much time as he/she needs. He/she will be offered sufficient opportunity to question the Investigator, GP or other independent parties to decide whether he/she will participate in the study. Participants will not be rushed into making a decision. However, the convenience of the participant will also be considered including the right to immediate consent.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. A member of the research team will go through the written information with the potential participant giving the opportunity for questions to be asked. Only researchers experienced in consent procedure and trained in Good Clinical Practice will take consent from participants.

In gaining consent from the participant we will ensure that the participant is able to:

1. Understand the purpose and nature of the research

2. Understand what the research involves including potential benefits and burden

3. Understand that the alternative to taking part is for them to receive standard medical care and that this is not affected by participation

4. Retain information long enough to make an effective decision

5. Make a free choice

The original signed form will be retained at the study site.

If there is any further safety information that may result in significant changes in the risk/benefit analysis, the PIS and Informed Consent Form (ICF) will be reviewed and updated accordingly. All

participants that are actively enrolled on the study will be informed of the updated information and given a revised copy of the PIS/ICF in order to confirm their wish to continue on the study.

Non-English speakers will be offered the opportunity to participate with a translator if available.

6 ELIGIBILITY CRITERIA

Each participant must meet all the inclusion criteria, and none of the exclusion criteria, at entry to the study. Those who are ineligible or decline to participate will be captured on the secure and encrypted recruitment and screening log.

6.1 Inclusion Criteria

- Is 18 years of age or older
- Is willing to complete all study procedures

- Study A: Patients undergoing formal nuclear medicine (99mTc-DTPA) glomerular filtration rate testing or willing to have a venous GFR filtration panel (Study A only)
- Study B: Has Chronic Kidney disease (CKD) KDIGO criteria or is at risk of CKD due to heart disease or diabetes as determined by physician

6.2 Exclusion Criteria

- Unable or unwilling to give informed consent
- Any condition which would make finger prick contraindicated e.g. severe skin conditions, bleeding disorder
- Study A: If formal GFR testing has been requested only because estimated GFR is not considered to reflect true GFR (e.g. liver disease)

7 RECRUITMENT

Patients who meet the entry criteria may be recruited and consented by the investigator, or any GCP qualified member of the local study team who has delegated responsibility for the study. Participants will be recruited from King's College Hospital, Royal London Renal Units and Nuclear Medicine Departments. Potential participants will be identified when presenting for their routine hospital clinic visits or during an inpatient admission. Members of the site staff will pre-screen and screen for potential eligible study participants using the inclusion/exclusion criteria.

Screening logs will be kept on the secure renal research study hard drive and will be encrypted for confidentiality. All eligible and ineligible patients, plus those declining to participate will be logged on the secure screening log. Patients who fulfil the inclusion criteria will have their eligibility confirmed by the research team. After confirming eligibility, eligible patients will be approached by an appropriately trained member of the clinic team to ascertain interest in entering the study. This individual will give a comprehensive verbal explanation of the study. Time for questions throughout the discussion will be given and questions adequately addressed. Potential participants will be given enough time to reflect on the patient information sheet (PIS), which will be provided during the initial discussion with the patient.

If the participant is willing to take part then they will be asked to sign the consent form with a member of the research team countersigning. A copy of the consent form will be given to the participant, and an electronic copy will be filed securely with the participant's records.

8 STATISTICAL METHODS

Study A: Readings taken with measured with NovamaxCreat and Epoc blood analysis system will be analysed separately. Bland-Altman plots and Passing-Bablok regressions will be generated for POC-Cr concentrations using Stata version 21 or later. The analytical error percentage compared to the reference standards (IDMS enzymatic traceable and 99mTc-DTPA and GFR filtration panel) (=100×([POC device] – [reference standard])/[reference standard]) will be calculated for each POC-Cr recording in each participant. In addition, average analytical error percentage and a 95% confidence interval (95%CI) will be calculated following Clinical Laboratory Standards Institute procedures.[16] Criteria used to check analytical error percentage will be derived from the 'Desirable Specifications for Allowable Total Error (ATE)' database for creatinine (ATE=8,87%)[15] and from the Laboratory Working Group of the National Kidney Disease Education Program (NKDEP) for eGFR (ATE=10%) .[17] Although the 10% ATE for eGFR is actually a performance specification for creatinine, it has been used in as an acceptable total error for eGFR.[18,19,20] Categorical agreement of POC-Cr concentrations with the reference standards will be calculated using the unweighted Kappa statistic. Error analysis using predefined minor and major classification errors will be performed for POC-Cr concentrations.

POC-Cr concentrations and reference standards will also be assessed by Deming regression and Pearson's correlation coefficient. Bias offset required will be recorded

Proportion of patients correctly identified to have CKD eGFR <60mls/min/1.73m^2 will be reported. Sensitivity and Specificity of different Cr thresholds calculated.

Study B: Number of tests attempted per participant, daily frequency of testing and proportion of successful attempts will be reported. Reasons for unsuccessful attempts and adverse events will be described and quantified if appropriate. Time taken to train per patient will be reported in minutes as median and IQR.

Accuracy of self-monitoring for the first and last reading taken by the participant will be assessed as outlined in Study A. Total, between-day, and within-day precision will be evaluated by comparing up to four POC-Cr capillary concentrations for seven days and compared to day 1 and 8 venous serum creatinine concentrations. Mean and standard deviation for each time point during the week, and within the day will be compared by an independent means *t*-test and *F*-test, respectively, using Stata Version 21 or greater. A *p*-value of less than 0.05 will be considered significant.

SUTAQ scale scores, relationships between scales and group differences on scales will be reported and compared with demographics, frequency, success and accuracy of testing.

9 PATIENT AND PUBLIC INVOLVEMENT (PPI)

We hosted an engagement event with Africa Advocacy Foundation (London Research Design Service funded) for sixteen African/Afro Caribbean participants who strongly welcomed future opportunities to have CKD screening in their local community and self-monitoring. Key recommendations that have contributed to this proposal and for future work include:

- BAME champions from PPI events will be used to explain study details if required
- Studies should NOT be African ancestry specific as perception of 'victimisation' – 'high risk' group recruitment preferred.
- Concern about home surveillance due to 'spying' – would need adequate reassurance about data safety/ownership
- A focussed dissemination event not desired but text/WhatsApp message and email to website link to findings with preferred presentation format in video/ infographics

In addition, King's Kidney Care PPIE Group including patients with CKD have contributed to this proposal. They were highly supportive of the proposal and considered the potential for POC kidney function testing to be 'transformative' due to it being 'accessible, cost-effective, reliable,

rapid and simple' and that 'real time feedback' through a future App development would increase patient confidence. They welcomed the opportunity to enable patients to participate more actively in their care, and recommended that up to four times daily testing would be acceptable to patients for one week (in keeping with diabetes testing). King's Kidney Care PPIE Group and Africa Advocacy Engagement participants will help with review of study patient material, data interpretation and dissemination.

10 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the KCH R&I Office and deemed sufficient to cover the requirements of the study. The research costs for the study have been supported by British Renal Society.

11 DATA HANDLING AND MANAGEMENT

All paper data recording sheets will be stored in lockable filing cabinets at the renal research team office for 5 years. Electronic data spreadsheets will be kept on the private renal research team T drive and will be password protected. Patients details, will be replaced by a study ID number before data is transferred in to a contracted general data protection regulation (GDPR) compliant storage provider, named Redcap (Research Electronic Data Capture). This will be removed after 5 years.

All staff involved in this research project will ensure data is handled with strict confidentiality in line with local trust policies. Data will be reviewed regularly by the research team.

12 MATERIAL/SAMPLE STORAGE

No samples will be stored from the study.

13 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by KCH R&I.

The study was deemed to require regulatory approval from the following bodies (list). Each approval will be obtained before the study commences.

- HRA
- REC

14 ADVERSE EVENTS AND INCIDENT REPORTING

14.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the intervention/treatment/procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

14.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

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 the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

Expectedness

Category	Definition
Expected	An adverse event which is consistent with the available information about the intervention/treatment/procedure in use in this study.
Unexpected	An adverse event which is not consistent with the available information about the intervention/treatment/procedure in use in this study*

* this includes listed events that are more frequently reported or more severe than previously reported

14.3 Procedures for recording adverse events

- All Adverse events will be recorded in the CRF following consent.

14.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF.

All SAEs (except those specified in section 14.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete an

SAE form and the form will be emailed to the R&I Office (kch-tr.research@nhs.net) within 1 working day of becoming aware of the event.

14.5 Serious Adverse Events that do not require reporting

- Hospital Admission – admissions are very common in patients with kidney disease and therefore do not require reporting.

14.6 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC, Health Research Authority and R&I office of the measures taken and the circumstances giving rise to those measures.

14.7 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

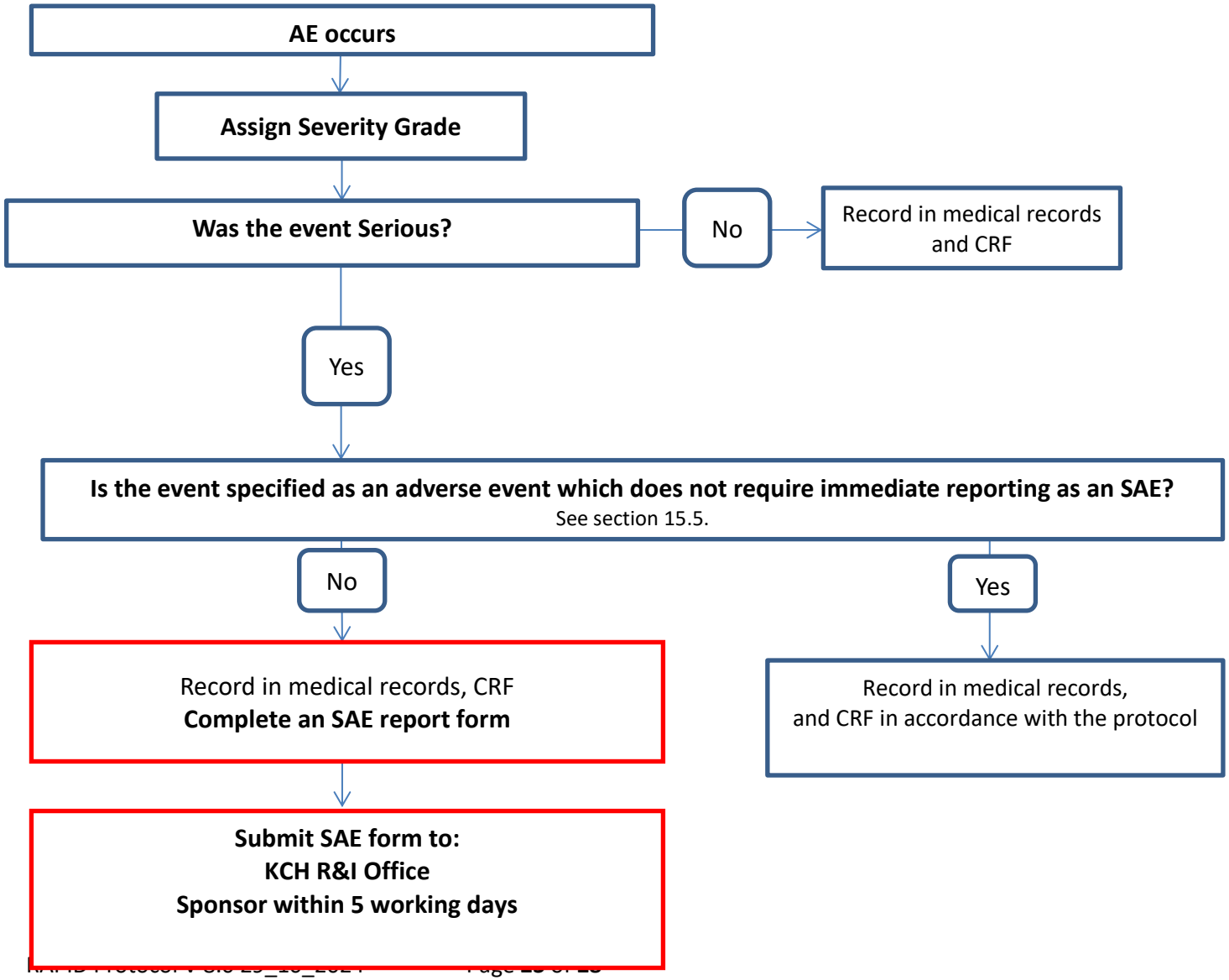
A protocol violation is a breach which is likely to effect to a significant degree –

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

(b) the scientific value of the study.

The CI and R&I Office should be notified immediately of any case where the above definition applies during the study conduct phase.

Flow Chart for SAE reporting



14.8 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.

b. It is contrary to specified or expected standard of patient care or service.

c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d. It puts the Trust in an adverse position with potential loss of reputation.

e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

15 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

16 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

17 INTELLECTUAL PROPERTY

All intellectual property rights and know-how in the protocol and in the results arising directly from the study shall belong to KCL.

18 INDEMNITY ARRANGEMENTS

King's College London provides insurance for research involving human participants that covers legal liabilities arising from its actions or those of its staff (subject to policy terms and conditions).
KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees; substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office

19 ARCHIVING

During the study, all data will be kept securely and confidentially at the Renal Research office. After the study has ended, paper data recording sheets, the Trial Master file and patient consent forms will be archived at a long-term storage facility (Iron Mountain) for 5 years. Data spreadsheets will be encrypted, name and contact details removed, and stored on a private Renal research team folder with limited access.

20 PUBLICATION AND DISSEMINATION POLICY

The research team plans to disseminate the study research findings in the following settings:

- Conference presentation of study process and results at UK Kidney Week, American Society of Nephrology Conference or the European Renal Association conference and related Renal Conference
- Publication of results in a renal specific recognised impact journal.

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22 APPENDICES

Appendix 1: PROTOCOL VERSIONS

Versions No	Version Date	Status
V 1.2	17 Mar 2020	Old
V 2.0	9 May 2020	Old
V 3.0	5 May 2022	Old
V 4.0	18 Oct 2022	Old
V.5.0	13 Mar 2023	Old
V 6.0	11 Aug 2023	Old
V 7.0	16 May 2024	Old
V 8.0	29 October 2024	Current