AFiRM	
Application of Functional Renal MRI to improve assessment of chronic kidney disease (AFiRM)	
Version and Date of Protocol:	V2.0 04/SEP/2020
Sponsor:	University Hospitals of Derby and Burton NHS Foundation Trust
Chief Investigator:	Prof. Nicholas Selby nicholas.selby@nottingham.ac.uk
Local Study Reference:	DHRD/2018/100
IRAS Number:	271043
Trial registration:	Clinical Trials.gov ID: NCT04238299
Funder(s):	National Institute for Health Research (Efficacy and Mechanism Evaluation programme)
This protocol has regard for the HRA guidance	

Confidentiality Statement

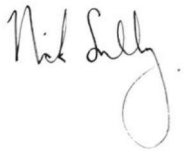
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities, and members of the Research Ethics Committee.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Derby CTSU's SOPs, and other regulatory requirement.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Protocol v2.0 4th September 2020 authorisation signatures:

Chief Investigator:
Signature: Date: 3/11/2020



Name: Prof. Nicholas Selby

For and on behalf of the Study Sponsor (if required):
Signature: Dr Teresa M. Grieve Digitally signed by Dr Teresa M. Grieve Date: 2020.11.13 15:34:58 Z Date: 13 / 11 / 2020

Name (please print): Dr Teresa M. Grieve
Position: Ass. Director R&D

KEY STUDY CONTACTS

Chief Investigator:	Professor Nicholas Selby Professor of Nephrology Centre for Kidney Research and Innovation Division of Medical Sciences and Graduate Entry Medicine University of Nottingham Medical School Royal Derby Hospital Campus Uttoxeter Road Derby, DE22 3DT 01332 724665 nicholas.selby@nottingham.ac.uk
Co-Investigator(s):	Professor Maarten Taal Professor of Medicine University of Nottingham M.Taal@nottingham.ac.uk Professor Phil Kalra Professor of Nephrology Salford Royal NHS Foundation Trust philip.kalra@srft.nhs.uk Professor Susan Francis Professor of MRI Physics University of Nottingham Susan.Francis@nottingham.ac.uk Professor Steven Sourbron Professor of MRI Physics University of Sheffield s.sourbron@sheffield.ac.uk Dr Iosif Mendichovszky Consultant Radiologist Cambridge University Hospitals NHS Foundation Trust im391@cam.ac.uk Professor Mark Gilthorpe Professor of Statistical Epidemiology University of Leeds M.S.Gilthorpe@leeds.ac.uk Dr Richard Feltbower Senior Lecturer in Epidemiology

	Department of Clinical and Population Science Unviersity of Leeds R.G.Feltbower@leeds.ac.uk Kirsten Cromie Research Statistician / Epidemiologist University of Leeds k.j.cromie@leeds.ac.uk
Study Manager/ Co-ordinator:	Rachelle Sherman Clinical Trials Manager Derby Clinical Trials Support Unit Royal Derby Hospital 01332 724736 uhdb.afirmstudy@nhs.net
Sponsor:	University Hospitals of Derby and Burton NHS Foundation Trust Royal Derby Hospital Uttoxeter Road Derby, DE22 3NE
Funder:	National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House, Enterprise Road Southampton SO16 7NS Tel: +44 (0)23 8059 5586 www.nihr.ac.uk
Clinical Trials Unit:	Derby Clinical Trials Support Unit Royal Derby Hospital Uttoxeter Road Derby, DE22 3NE 01332 724639 uhdb.DerbyCTSU@nhs.net
Central Image Analysis:	AFiRM Image Analysis Centre Contact: Professor Steven Sourbron Professor of MRI Physics University of Sheffield s.sourbron@sheffield.ac.uk
Biobank:	Joanne Brown, Senior Technical Manager Leeds Biobanking and Sample Processing Lab Level 7 Clinical Sciences Building

	St James's University Hospital Leeds LS9 7TF j.c.brown@leeds.ac.uk

STUDY SUMMARY

Study Title:	AFiRM study
Local Study Reference:	DHRD/2018/100
Study Design:	Prospective cohort study
Study Participants:	People with Chronic Kidney Disease (CKD): CKD category G3-4 or CKD category G1-2 with overt albuminuria (urine ACR>30mg/mmol)
Planned Number of Sites:	9
Planned Sample Size:	450
Follow Up Duration:	4 years active follow up Tracking of end stage kidney disease events for 10 years via UK Renal Registry
Planned Start Date:	01/Sep/2020
Planned Recruitment End Date:	28/Feb/2023
Planned Study End Date:	28/Feb/2027
Research Question/ Aims:	**Over-arching aim** To determine if multiparametric renal MRI can provide structural and functional assessment of the kidneys in a large cohort of people with CKD that will (1) provide prognostic information and (2) guide treatment options. **Primary research questions** To determine whether multiparametric renal MRI can differentiate patients with CKD progression from those with stable disease. We will also assess the ability of MRI to determine the type and severity of the dominant mechanisms of CKD progression and how these change over time.

FUNDING AND SUPPORT IN KIND

Funder(s)	Financial and Non-Financial Support Given
National Institute for Health Research (Efficacy and Mechanism Evaluation programme)	£1,954,960.31 (research costs)

ROLES & RESPONSIBILITIES

Sponsor

The Sponsor, University Hospitals of Derby and Burton NHS Foundation Trust, will take overall responsibility for appropriate arrangements being in place to set up, run and report on the research project. The sponsor is not providing funds for this study but has taken on responsibility for ensuring finances are in place to support the research.

Funder

The study is funded by National Institute for Health Research (NIHR) and this study will be run in accordance with NIHR guidance and principles.

Study Management Committees

Project Management Group (PMG)

The project management group will meet regularly to oversee the day-to-day management of the study, including all aspects of the conduct of the study such as review of study progress, data collection, data completeness and non-compliances. The PMG will be led by the Chief Investigator (CI) and supported by Derby Clinical Trials Support Unit. The PMG group will also include the Study Manager, co-investigators plus other relevant DCTSU staff and statistician as required. The core PMG will convene regularly (e.g. monthly) during the first 2.5 years of the project (either face-to-face or via teleconference), then as required thereafter. Extended PMG meetings to include Principal Investigators from each of the nine participating centres will be convened as required. Any problems with study conduct and participating centres will be raised and addressed during PMG meetings.

Independent Steering Committee

The Independent Steering Committee (ISC) will oversee and supervise the progress of the trial and ensure that it is being conducted according to the protocol and the applicable regulations. The ISC is an independent body that includes a majority of members who are not involved with the running of the trial. The proposed meeting schedule is six-monthly during the initial two years, then annually afterwards.

Data Monitoring and Ethics Committee

The data monitoring and ethics committee will review the accruing study data and will assess whether there are any safety issues that should be brought to the participants' attention or if there are any reasons to terminate the study. They will also review the scientific validity and the conduct of the study.

Protocol Contributors

A number of protocol contributors have been involved in the development of this protocol, these include; the Chief Investigator, Co-applicants, Statistician, Data Manager and Study Manager. Protocol contributors are responsible for inputting into the design of the study, ensuring that it is designed transparently and efficiently.

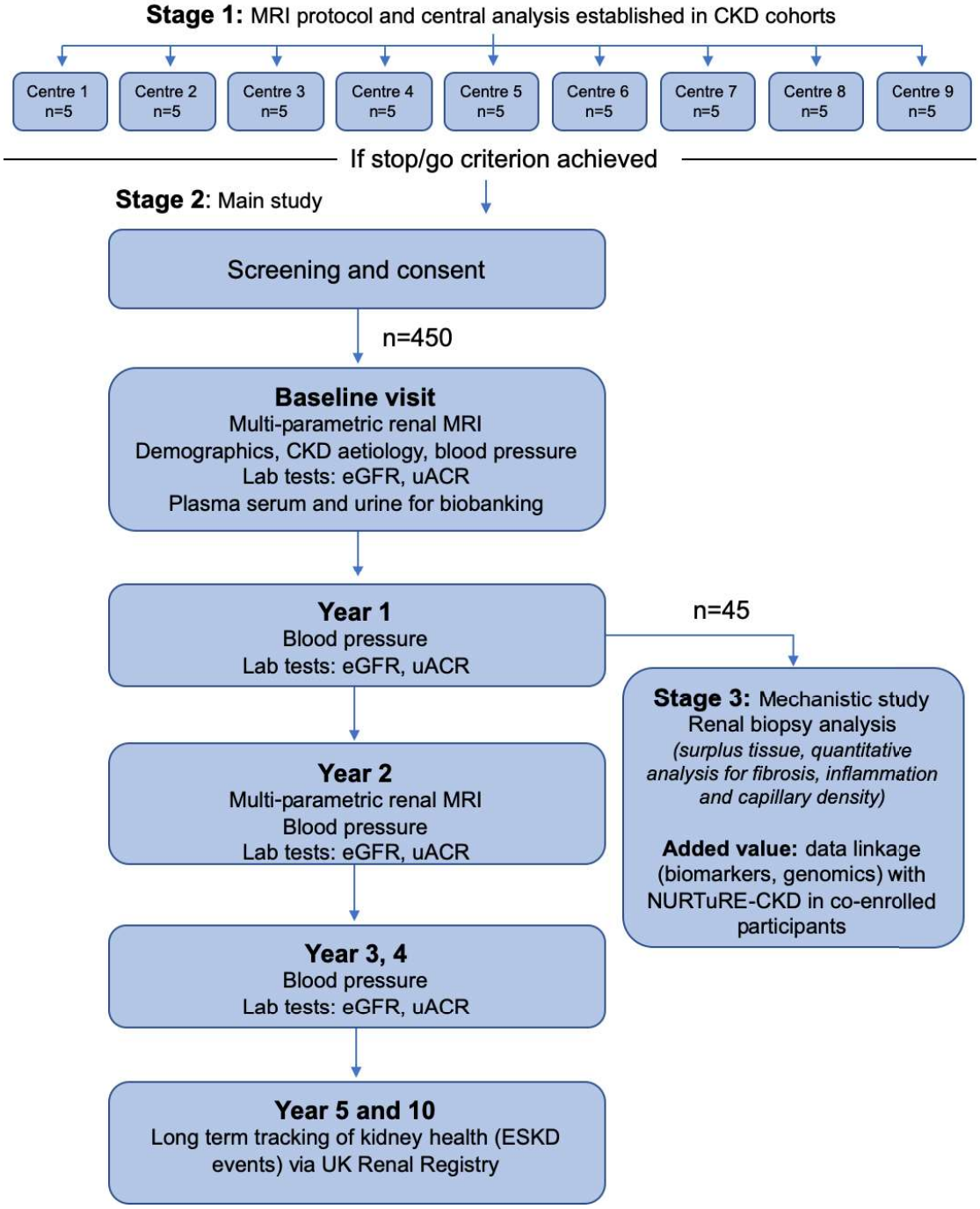
Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AKI	Acute Kidney Injury
CI	Chief Investigator
CKD	Chronic Kidney Disease
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
eGFR	Estimated glomerular filtration rate
ESKD	End Stage Kidney Disease
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GN	Glomerulonephritis
ICF	Informed Consent Form
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File
ISC	Independent Steering Committee
ISRCTN	International Standard Randomised Controlled Trials Number
MM	Multiple myeloma
MRI	Magnetic Resonance Imaging
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PMG	Project Management Group
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
uACR	Urinary albumin to creatinine ratio
UKRR	UK Renal Registry

STUDY FLOW CHART

Study flow diagram



NB – patients in Stage 1 will also be eligible to take part in Stage 2

STUDY PROTOCOL

1. BACKGROUND

Current imaging techniques for the kidney are limited. In most cases of acute and chronic kidney disease, standard ultrasound is the only examination performed. This provides limited structural information that cannot determine type or extent of renal injury and adds little to diagnostic and prognostic assessments. Renal biopsy remains the 'gold standard' for diagnosis of specific kidney diseases but is invasive and a proportion of patients have contraindications meaning biopsy is not possible. Biopsy is therefore performed in only a small proportion of patients and rarely on a serial basis to monitor response to therapy.

MRI has emerged as an imaging modality with promise to improve the understanding and characterisation of renal pathophysiology [1, 2]. It is a versatile technique in which structural and functional MRI measurements can be performed in a single multiparametric scan session to assess altered renal tissue microstructure, oxygenation, perfusion and blood flow. Compared to renal biopsy, MRI is non-invasive, safe and avoids sampling bias by characterising the entire kidney with high spatial resolution. MRI does not involve ionising radiation, is repeatable (allowing serial assessments over time) and the MRI measures do not require gadolinium contrast agents. A series of recent systematic reviews covering the main functional renal MRI measures conclude that evidence is now needed to accelerate the translation of multiparametric renal MRI for clinical use [3-8]. The reviews focussed on: arterial spin labelling (ASL, a measure of renal perfusion) [4]; Blood Oxygen Level Dependent (BOLD, sensitive to changes in renal oxygenation) [5]; longitudinal (T1) relaxation time (increases with scarring, correlates with fibrosis in the heart and liver [6, 9]); diffusion weighted imaging (DWI, sensitive to changes in renal tissue microstructure) [3]); and Phase Contrast (PC-MRI, a measure of renal artery blood flow) [8].

This study protocol has been developed by investigators within the UK Renal Imaging Network (UKRIN), a collaboration of MRI physicists, radiologists and nephrologists from UK renal MRI research centres. In September 2018 the MRC Partnership grant (MR/R02264X/1) UKRIN-MAPS (*UK Renal Imaging Network: MRI Acquisition and Processing Standardisation*) commenced (C.I. Francis [10]). UKRIN-MAPS will develop a platform for standardised multiparametric MRI image acquisition across Philips, Siemens and GE MR vendor platforms with associated central data analysis, crucial for coordinated multi-centre clinical trials. UKRIN-MAPS will develop harmonised protocols in healthy volunteers including subject test-retest reliability at sites, establishment of cross-site agreement, quality assurance (QA) using MR phantoms (objects used as stand-ins for human tissues to ensure that MRI systems and methods are operating correctly). A centralised process for image upload, quality control and analysis will be established.

This study will use the UKRIN-MAPS infrastructure, and address the need for a multicentre clinical study to establish how functional renal MRI relates to CKD progression and its underlying mechanisms.

2. RATIONALE

The limitations of existing imaging techniques for kidney disease present a pressing clinical need. Ten percent of the world's population, including 2.6million people in England [11], are living with chronic kidney disease (CKD). CKD can progress to end-stage kidney disease (ESKD) and increases cardiovascular risk [12]. This consumes considerable resources; CKD-associated costs in England are estimated at £1.45billion per annum [13]. Better imaging to determine pathophysiology and prognosis of kidney diseases would improve stratification of patients and allow better targeting of treatments.

Over-arching aim

To determine if multiparametric renal MRI can provide structural and functional assessment of the kidneys in people with CKD that will (1) provide prognostic information and (2) guide treatment options.

Primary research questions

To determine whether multiparametric renal MRI can differentiate patients with CKD progression from those with stable disease. We will also assess the ability of MRI to determine the type and severity of the dominant mechanisms of CKD progression and how these change over time.

3. OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

3.1. Objectives

i) Demonstrate feasibility of the standardised UKRIN-MAPS multiparametric MRI protocol for use in a patient cohort across study sites;
ii) Collect serial multiparametric MRI to characterise patients with and without CKD progression in a UK-wide multicentre clinical study;
iii) In a mechanistic sub-study, compare multiparametric renal MRI with 'gold-standard' renal biopsy to calibrate the MRI-detectable pathological processes that help differentiate CKD progression from non-progression.

3.2. Outcomes

The following outcome measures will be recorded:

Primary outcome

- CKD progression, defined as a 40% decline in eGFR between study entry (baseline visit) and year 4 study visit
  OR
  development of ESKD (eGFR<15ml/min or initiation of RRT).

Secondary outcomes

- Individual components of the primary outcome analysed separately
- eGFR trajectory (ml/min/yr) at each study time-point; rapid progression will be defined as a decline of ≥5ml/min/year.
- Albuminuria at each study time-point
- MRI measures at 0 and 24 months
- Acute Kidney Injury (AKI) events (as per KDIGO criteria) [14]
- Cardiovascular events
- All-cause mortality

4. STUDY DESIGN

This is a prospective observational cohort study with serial renal MRI scanning (baseline and 2 years), annual active participant follow-up for four years, and remote tracking of end stage kidney failure events via the UK Renal Registry from four to ten years.

The study design also incorporates an internal pilot study (Stage 1) after the baseline visit of the first five patients at each site (total 45 patients) to demonstrate feasibility of performing the renal MRI protocol (see section 10).

The study also includes a mechanistic sub-study in participants who have undergone a renal biopsy for clinical reasons, in whom additional analyses of the renal biopsy will be performed and compared to MRI measures to assess the latter for their prognostic utility.

5. STUDY SETTING

This is a multi-centre centre study, running in nine UK centres. Each site will have access to specialist nephrology clinics and to a 3 Tesla MRI scanner with capacity to perform the UKRIN-MAPS renal MRI protocol. Participants will be recruited from secondary care nephrology outpatient clinics.

6. ELIGIBILITY CRITERIA

6.1. Inclusion Criteria

- Age 18-75 years
- CKD category G3-4 (eGFR 15-60ml/min/1.73m^2) **OR** CKD category G1-2 (eGFR ≥60ml/min/1.73m^2) with overt albuminuria (urine ACR>30mg/mmol)
- Capable of giving informed consent

6.2. Exclusion Criteria

- Autosomal dominant polycystic kidney disease (ADPKD)
- Glomerulonephritis (GN) actively receiving immunosuppression, or having done so within the preceding 90 days.
    - Note: GN **not** requiring immunosuppression (e.g. most cases of IgA nephropathy) **will** be eligible for inclusion.
    - Immunosuppression defined as any of: >10mg per day of prednisolone or equivalent corticosteroid; calcineurin inhibitor; cytotoxic agent (e.g. cyclophosphamide); azathioprine; mycophenolate mofetil; specific monoclonal antibodies for GN (e.g. Rituximab, Belimumab).
- Multiple myeloma (MM)
- Acute Kidney Injury (AKI) within the 90 days prior to consent (AKI defined as per KDIGO criteria [14])
- Solid organ transplant
- Known single kidney
- More than five simple cysts in one kidney on previous renal imaging
- Contraindications to MRI
- Current participation in other research studies that would conflict with this research study, in the opinion of the principal investigator.

7. STUDY PROCEDURES

7.1. Recruitment

7.1.1. Patient Identification

Recruitment will primarily be from nephrology clinics; the clinical care teams will identify potential participants prior to the research team approaching to discuss the study further.

7.1.2. Screening

Screening will be performed using information in nephrology clinic records/hospital notes/electronic medical records. No additional assessments or procedures will be required.

7.2. Consent

Written informed consent will be obtained prior to the participant undergoing any study specific procedures (including the collection of identifiable participant data). Participants will be given at least 24 hours from the time of receiving the Participant Information Sheet to providing written consent to ensure that they have sufficient time to consider their participation. Information and consent forms may be sent out to potential participants via post or email to facilitate remote consent discussion, where this is deemed appropriate in the opinion of the Principal Investigator (PI).

The Principal Investigator (PI) will retain overall responsibility for the informed consent of participants at each site and will ensure that any person delegated responsibility to participate in the informed consent process (e.g. research nurses) is duly authorised, trained and competent according to the REC approved protocol and applicable guidelines and regulations. All study personnel undertaking consent must be named in the delegation log.

The right of a participant to refuse participation without giving reasons will be respected and participants will be free to withdraw from the study at any time without giving reasons and without prejudicing his/her further treatment.

7.3. Study Assessments

Procedures	**Visits**					
	Screening	**Baseline**	**Follow up (active)**			
			12 months	24 months	36 months	48 months
Eligibility assessment	x					
MRI safety questionnaire	x			x		
Informed consent		x[1]				
Demographics[2]		x				
CKD aetiology (clinical diagnosis or renal biopsy)		x				
Medical history (including cardiovascular events)		x				
Review of clinical status[3], medication prescriptions, socioeconomic status			x	x	x	x
Vital signs including blood pressure		x	x	x	x	x
EQ-5D-5L questionnaire		x	x	x	x	x
POS-Renal symptom questionnaire		x	x	x	x	x
Blood and urine tests[4]		x	x	x	x	x
Concomitant medications		x	x	x	x	x
Multiparametric renal MRI[5]		x		x		
Samples for biobanking[6]		x				
Adverse event assessments			x	x	x	x
Mechanistic sub-study only – renal biopsy sample shipping and analysis		x				

[1] consent may be taken remotely, e.g. over the phone to support social distancing measures, and may occur any time between screening and baseline
[2] age, sex, ethnicity, first language, education status, marital status, employment, socio-economic status, smoking history, alcohol intake, dietary status
[3] health utilisation questionnaires to obtain details regarding hospital admissions and GP visits
[4] Routine biochemistry, haematology, serum creatinine, eGFR, CRP, uACR
[5] to be arranged within five weeks of visit
[6] see Section 7.3.4

7.3.1. Baseline participant visit

After providing informed consent, participants will be invited to attend a baseline study visit. Where possible this should be timed to coincide with a routine outpatient nephrology clinic visit, but if this is not possible the visit can be arranged at an alternative convenient time.

At this visit, the following information will be collected:

- Demographics: age, gender, ethnicity, first language, education status, marital status, employment, socio-economic status (e.g. individualised measure or index of multiple deprivation (IMD) score), smoking history, alcohol intake, dietary status (vegetarian/vegan).
- CKD aetiology (kidney biopsy or clinical diagnosis).
- Renal ultrasound report (if available)
- Medical history: all previous illnesses including cardiovascular disease, diabetes and previous AKI.
- All current medications including over the counter preparations and supplements/herbal preparations.
- Height, weight and blood pressure
- One prior outpatient serum creatinine and eGFR result. If there are multiple results available, the measurement closest to 12 months prior to the baseline visit should be chosen; if no results are available, this should be indicated in the CRF.
- One prior outpatient urine Albumin:Creatine Ratio (uACR) (mg/mmol) value. If there are multiple results available, the measurement closest to 12 months prior to recruitment should be chosen; if no results are available, this should be indicated in the CRF.
- Participants will be asked to complete quality of life (EQ-5D-5L) and symptom (POS-Renal) questionnaires at each visit (included in Appendix 15.3). The EQ-5D-5L questionnaire will support subsequent health economic analyses, and the POS-Renal questionnaire provide additional clinical comparative data between groups.
- Blood sample: Routine biochemistry and haematology panel (as per Section 7.3.4).
- Urine sample: uACR (mg/mmol).
- Additional blood samples to be collected for biobanking (see Section 7.3.4).
- A renal multiparametric MRI scan will be arranged to occur within five weeks of the study visit.

7.3.2. Follow up participant visits

Participants will be invited to attend Study visits at 12, 24, 36 and 48 months. Where possible this will be timed to coincide with a routine outpatient nephrology clinic visit, but if this is not possible the visit can be arranged at an alternative convenient time. If appropriate, in line with clinical practice, the visit may be performed remotely, via a suitable platform for video or telephone consultations. The research team will still need to be able to access blood and urine results where these are done in the community.

At each of these visits, the following should be undertaken:

- Review to determine any changes in clinical status (health utilisation questionnaire to obtain details regarding hospital admissions and GP visits), medication prescription and socio-economic status since the previous visit.
- Weight and blood pressure
- Questionnaires (EQ-5D-5L and POS-Renal)
- Blood sample: Routine biochemistry and haematology panel (as per Section 7.3.4)
- Urine sample: uACR (mg/mmol)
- **At the 24month study visit only**: a second renal multiparametric MRI scan will be arranged to occur within five weeks of the study visit.

Dates will be recorded for all data collection items.

7.3.3. UKRIN-MAPs multiparametric renal MRI protocol

The core sequences of the multiparametric renal MRI protocol have been defined within UKRIN-MAPS, these are summarised in Figure 1. The final protocol and acquisition scheme for each MRI measure will be developed through the UKRIN-MAPS grant and a detailed SOP developed for MRI acquisition protocols.

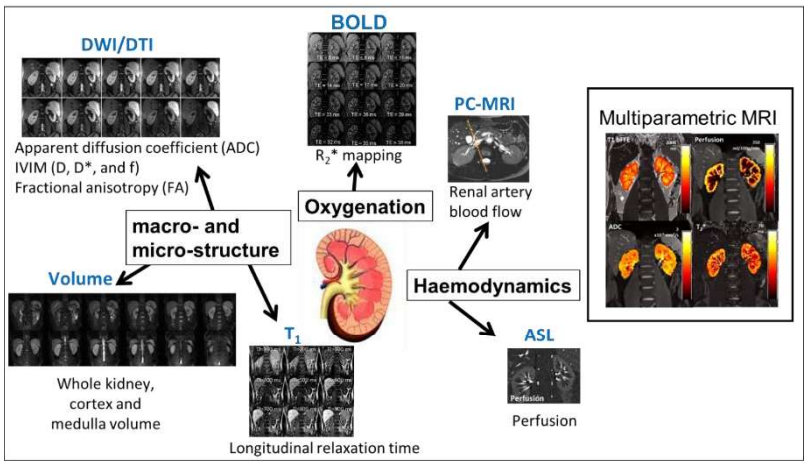


Figure 1: Multiparametric Renal MRI protocol and example multiparametric images. ASL = arterial spin labelling, BOLD = Blood Oxygenation Level Dependent contrast, DWI and DTI = diffusion weighted imaging and diffusion tensor imaging, PC-MRI = Phase Contrast MRI, T_1 = longitudinal relaxation time mapping.

For the two-hours preceding an MRI scan, participants will be requested to refrain from eating or drinking.

A 1-hour UKRIN-MAPS multiparametric renal MRI protocol will include:

- *Localizer and structural scans*: Localizer scans will be acquired to plan the matched slice placement of the functional multiparametric renal MRI measures. Structural T_1- and T_2-weighted scans will be collected for segmentation and volume assessment of whole kidney, cortex and medulla [15]. In addition, B_0 and B_1 maps will be collected in each participant to assess data quality.
- *Longitudinal (T_1) relaxation time mapping*: T_1 increases with inflammation and fibrosis, and has been shown to correlate with fibrosis in the kidney, heart and liver [6, 9, 16]. A respiratory-triggered inversion recovery (IR) SE-EPI scheme [17] or shortened MOdified Look-Locker Inversion recovery (ShMOLLI) scheme [18] will be used.

- *Diffusion weighted imaging (DWI)*: DWI have been shown to be sensitive to changes in renal tissue microstructure [3, 16, 19]. Respiratory-triggered fat suppressed spin-echo echo-planar imaging (SE-EPI) DWI data will be acquired across an optimised number of b-values for a given number of directions to determine apparent diffusion coefficient (ADC), as well as fitting an IVIM model (D, D*, f).
- *Phase Contrast MRI (PC-MRI):* Renal artery blood flow in the right and left renal arteries will be measured in a breath hold using a single slice perpendicular to the renal artery. A non-contrast enhanced MR angiogram will determine renal artery bifurcations and aid PC-MRI slice placement.
- *Arterial spin labelling (ASL)*: There are a number of approaches to renal ASL to assess renal perfusion, comprising different labelling schemes (FAIR or pCASL labelling scheme [4]) and readout protocols (for example, EPI versus balanced fast field echo (bFFE) schemes [20]). These options are being evaluated for each MR vendor within the UKRIN-MAPS grant, the final ASL protocol will be chosen on completion of this evaluation.
- *Blood Oxygen Level Dependent (BOLD) mapping*: This provides a measure of changes in renal oxygenation [5]: BOLD R_2* data will be acquired using a multi-echo fast field echo (mFFE) scheme.

7.3.3.1 Incidental findings

All sites have a policy in place to manage incidental findings on MRI scans that are acquired for research purposes, and any incidental findings that arise during this study will dealt with according to local policy, which will include informing participants and their medical teams of results that may have clinical significance.

If any participants who had not previously been recognised to be suffering from depression or anxiety report on the EQ-5D-5L questionnaire that they are experiencing severe or extreme depression or anxiety this will be reviewed by the principal investigator who will determine the appropriate clinical response.

7.3.4. Blood and urine samples for analysis and biobanking

At each study visit, the following blood and urine tests should be performed at local NHS laboratories (5-10ml of blood), or via community phlebotomy services where required:

- Urea and electrolytes
- Serum creatinine and estimated GFR (eGFR) calculated using the CKD-EPI equation
- Calcium and phosphate
- Serum albumin
- Lipid profile
- Random blood glucose
- HbA1c in mmol/mol
- Bicarbonate
- Full blood count
- High sensitivity C-reactive protein (CRP)

- Serum Parathyroid hormone
- Urine albumin to creatinine ratio (uACR) in mg/mmol

Patients will be asked to provide additional consent to the long-term storage of blood and urine samples for biobanking. **Where consent has been obtained, additional samples should be collected at the baseline visit only:**

- 2x EDTA tubes, centrifuged and separated into 10 aliquots
- 2x SST tubes, centrifuged and separated into 10 aliquots
  Buffy coat (taken from the blood samples used for plasma) for DNA extraction (single sample)
- Approx. 40ml urine

An SOP for collection, centrifuging, aliquoting, local storage and central shipping of samples will be provided.

7.3.5. Renal Biopsy analysis

Participants who have undergone a routine renal biopsy as part of clinical care in the six months prior to study entry will be asked to participate in a substudy that will comprise at least 10% of the whole cohort. Participant consent for the substudy will include consent for long-term storage of tissue and use in future research.

Biopsy tissue that has been stained in clinical laboratories for routine diagnosis will be transported to the Biorepository facility at University of Birmingham for digital scanning and further analysis. Residual kidney biopsy tissue embedded in paraffin blocks will also be transported to the Biorepository facility.

For core analysis, kidney biopsies will be stained e.g. with H&E, PAS and Masson's Trichrome. If all of these are not available from the clinical laboratory, additional sections may be cut at the Biorepository and stained. Additional sections will be cut for all specimens and immunohistochemical staining will be conducted for specific cell types (e.g. CD32 positive cells (fibroblasts), Collagen III, leukocyte common antigen (LCA), inflammatory cells (CD3(Tlymphocyte)/CD20(B-lymphocyte)/CD68(macrophage)/CD56(natural killer cell)) and elastase). Sections will be digitally photographed for standardised analysis that will include:

- Confirmation of clinical diagnosis
- Quantitative assessment of glomerulosclerosis score, extent of interstitial fibrosis, inflammation, peritubular capillary density, collagen accumulation, inflammatory cell subtypes

Clinical laboratories will also be asked to supply digital images of immunofluorescence stains and electron microscopy performed for clinical diagnosis if these are available. Surplus tissue from paraffin blocks will be stored in the University of Birmingham Biorepository facility and sections will be supplied to investigators as required. Tissue blocks will be returned to sites if requested for clinical reasons.

7.3.6. Long term tracking via UK Renal Registry

Patient outcomes will be followed up at 5 and 10 years after the baseline visit remotely, via the UK Renal Registry (UKRR). To facilitate this, participants are required to sign up to a patient portal (e.g. PatientView) that facilitates linkage between their medical records and the UKRR. This is a mandatory part of the study and patients will be asked to agree to this via the study consent process.

Site staff will need to set up the participant on the patient portal to enable the flow of data to the UKRR by ticking the appropriate box on the renal system. Instructions will be provided in the study manual. This is a routine process for UK nephrology patients, many patents already consent to do this as part of their clinical care.

The participant's NHS number and date of birth will be provided to the UKRR to ensure the correct follow up data is retrieved.

7.4. Withdrawal Criteria

Participants will be withdrawn from the study only if they withdraw their consent. The study will be discontinued only if for unforeseen circumstances it becomes clear that it is no longer feasible. If patients experience an outcome event during follow up (other than death), they will continue to be followed up to observe for other specified outcomes unless they withdraw their consent.

7.5. Storage and Analysis of Samples

Samples will be stored in a linked anonymised format and labelled using a barcode linked to the study number to permit accurate linkage to study data and the consent form.

Samples for NHS pathology analysis will be labelled and disposed of in accordance with local NHS procedures.

Serum, plasma and urine samples for biobanking will be stored at each participating site initially at -20^{0}C and transferred to -80^{0}C within 72 hours of collection. Samples will be frozen within four hours of aliquoting. Frozen samples will be transferred on dry ice by courier from each participating site to the Leeds Biobanking and Sample processing lab periodically. All shipments will contain a complete inventory of all samples, along with the name of the person responsible for sending the samples. After completion of recruitment and follow-up, samples will be shipped from the Leeds Biobank to different laboratories for analysis. Any sample left after analysis will either be returned to the Leeds Biobank or destroyed. A master database of all frozen samples will be held at the Leeds Biobank in a password protected file.

It is the responsibility of the study site to ensure that samples are appropriately labelled in accordance with the study procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this study will be transported,

stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.6. End of Study

The end of study will be defined as when all data have been received and queries resolved after the final year 4 study visit. The Study Manager will notify the Sponsor, participating sites and REC within 90 days of the end of study. The clinical study report will be written within 12 months of the end of study.

8. SAFETY REPORTING

8.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to study procedures.
Related AE	An untoward and unintended response in a participant to a study procedure. This means that a causal relationship between the study procedure and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Related SAE	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study procedures.
Related & Unexpected SAE	A serious adverse event that; • is believed with reasonable probability to be due to one of the study procedures. • the nature and severity of which is not consistent with the information provided in the protocol i.e. it is not listed as an

	expected occurrence.

8.2. Operational Definitions for (S)AEs

There are a number of adverse events that may be experienced by participants during their time on the study that are related to their chronic kidney disease and ongoing treatment. These are not expected to be reported for this study and include but are not limited to:

- Hospital admission unrelated to study procedures; cardiovascular events; medical procedures associated with preparation for renal replacement therapy; commencement of renal replacement therapy; mortality unrelated to study procedures

For this study, only SAEs not listed above should be recorded and reported.

8.3. Recording and Reporting SAEs

All reportable SAEs occurring during the duration of the study (from the time of written informed consent until the participant's last visit) must be recorded within the CRF. The PI is responsible for checking for SAEs when participants attend for study visits. There is no requirement for AEs not meeting the serious criteria defined in section 8.1 to be recorded or reported.

Any related SAEs must be reported by the investigator using the electronic SAE Report Form (available via the eCRF). The completed form should be completed online within 24 hours of the site becoming aware of the event. An automated email alert will inform Derby CTSU & the CI when the form has been entered and saved The CI will need to review electronically within 1 working day.

In the event the eCRF cannot be accessed, the site may use the paper SAE report form which should be sent to Derby CTSU per below:

Derby CTSU contact information:
Email: uhdb.randdsae@nhs.net **Phone:** 01332 724736 / 01332 724639 *(to be followed up with a written report)*

Derby CTSU will send the SAE report to the CI for review within 1 working day.

All related and unexpected SAEs must be reported to the REC using the 'non-CTIMP safety report to REC form' from the HRA website within 15 days of the CI becoming aware of the event. Safety information will be reviewed during PMG and DMEC meetings.

8.3.1. Assessment of SAEs

8.3.1.1 Severity

The investigator should determine the severity of the SAE;

- Mild: no interference with daily activities.

- Moderate: moderate interference with daily activities.
- Severe: considerable interference with daily activities (e.g. inability to work).

NOTE: to avoid confusion or misunderstanding the term "severe" is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as "serious" which is described in the safety definitions.

8.3.1.2 Causality

Clinical judgement should be used to determine the relationship between the study procedures and the occurrence of each AE;

- Not-related: There is no evidence of a causal relationship between the event and study procedures.
- Related: There is evidence of a causal relationship between the event and study procedures i.e. a relationship to the study procedures cannot be completely ruled out.

8.3.1.3 Expectedness

The assessment of expectedness is only required if the event is deemed to be related to study procedures.

- Expected: Event previously identified and described in the protocol.
- Unexpected: Event not previously described in the protocol.

8.4. Reporting Urgent Safety Measures

If any urgent safety measure is taken the research team should inform the Derby CTSU within 24 hours using the Derby CTSU's safety incident reporting form. The Derby CTSU will inform the REC and participating sites of the measures taken and the circumstances giving rise to those measures within 3 days on implementation of the urgent safety measure.

9. DATA HANDLING

9.1. Data Collection Tools and Source Document Identification

A CRF (or eCRF) will be designed to capture all data from the study assessments and questionnaires. Data will be entered into an electronic database that will store all study data securely.

Each participant will be assigned a study specific identifier, allocated at recruitment, for use on CRFs, other study documents and the electronic database, as well as the XNAT platform used for MRI data management. Samples for storage will be labelled with a barcode that is linked to their unique identifier. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study.

MRI data management will be via the UKRIN XNAT (www.xnat.org) imaging informatics platform, hosted by MRC-funded Dementia Platform UK's Imaging Infrastructure.

XNAT provides a web-based interface for uploading and sharing imaging data and has been used extensively for many ongoing imaging studies in the UK. Imaging data, along with associated data and metadata will be stored in this way.

9.1.1. Central Image Processing

After upload on XNAT, the MRI data will be centrally reviewed for image quality in the AFiRM Image Analysis Centre (IAC) and processed to extract the imaging biomarkers. For this purpose, the anonymised MRI data will be temporarily downloaded from XNAT onto secure workstations in the IAC (University of Sheffield), then reviewed and analysed by qualified image analysts. After analysis the results will be uploaded back onto XNAT (calculated images) and onto the electronic data capture system of AFiRM (imaging biomarkers and quality reports) and the local copy of the images in the IAC will be permanently deleted.

9.2. Source Data

Source documents will be filed at the investigator's site and may include but are not limited to consent forms, current medical records, laboratory results and records which may be paper or electronic. Sections of the CRF may also completely serve as source data, where there is no prior written or electronic record of data, for example the EQ-5D-5L. Only research staff listed on the Delegation Log shall have access to study documentation other than the regulatory requirements listed below. Direct access to source data / documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Derby CTSU, Sponsor's designee and for inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

9.3. Data Handling and Record Keeping

The investigator and trial team will ensure that the participant's identity is protected at every stage of their participation within the trial, according to the Data Protection Act 2018. If any patient information needs to be sent to a third party the trial team will adhere to maintaining pseudo-anonymous participant parameters in correspondence.

Access to the trial database will be restricted by role-based permission to authorised trial personnel. Users will be suitably trained on the system prior to being granted access. Individual user accounts will be password protected and will not be shared between members of the trial team.

The database will be a cloud-based electronic data capture (EDC) system hosted by a fully validated 3rd party vendor. The database will be compliant with ICH-GCP and MHRA guidelines for computerised systems. Derby CTSU will be responsible for database design, build and data validation while the provider of the software will be responsible for hosting and storage of the study data.

Data will be entered into the eCRF by site staff. After data entry is performed, validation checks will be carried out on the data to ensure accuracy and consistency according to the data validation plan. All data queries generated as a result of these checks will be available online for resolution by the site. After data entry is complete and all data queries have been resolved, the database will be locked and released for statistical analysis.

9.4. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

9.4.1. Long term storage of data (research database)

Anonymised data collected in the study, including biosamples, imaging and clinical data will be stored long term for use in future research; consent for this will be provided by individual participants on the main study consent form. A data access and management plan will be developed to provide a framework by which researchers can access these data for legitimate research work, and to detail the oversight arrangements for this process.

9.5. Archiving

At the end of the study, following completion of the end of study report, the Sponsor will securely archive all centrally held study related documentation for 5 years, excluding data intended for future research use as described in section 9.4.1. At the end of the defined archive period arrangements for confidential destruction will be made.

It is the responsibility of each PI to ensure that data and all essential documents relating to the study are retained securely for a minimum of 5 years after the end of study. Once the Sponsor has confirmed that the study can be archived, Derby CTSU will notify sites that the ISF may be archived, and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request.

10. STATISTICS AND DATA ANALYSIS

10.1. Statistical Analysis

A comprehensive statistical analysis plan will be developed to describe the proposed analyses in detail. Cause and effect as well as predictive capability of the renal MRI measures (alone and in combination) will be explored in relation to progression of CKD (as defined in the primary and second outcomes). Different pre-defined definitions of CKD progression will be evaluated to reflect progression over the initial four year study period (40% decline in eGFR), current clinical practice (e.g. eGFR trajectory at each annual assessment) and model-derived definitions of CKD progression obtained using the rich longitudinal eGFR data to minimise potential uncertainty associated with a single-event clinical assessment of patient progression [21]. Multilevel and latent growth curve mixture

models will be used to accommodate random structure within the data hierarchy and the heterogeneity/uncertainty amongst the clinical and MRI measures. Baseline factors associated with the risk of CKD will examined in a causal framework using a directed acyclic graph (DAG) [22] to specify *a priori* all potential causal influences of baseline clinical features and patient characteristics on subsequent outcomes. Mixture modelling will be informed by the DAG to investigate causal relationships between patients differentiated by clinical or multiparametric MRI measures within an integrated approach that assesses patient trajectories over the study time period. Models will determine the utility of MRI measures in isolation and in conjunction with regular clinical data to differentiate CKD progression from non-progression. Potential causal mechanisms and their extent of influence on CKD is assessed for the entire study population and contrasted to biopsy analyses for patients within the sub-study.

10.2. Sample Size Calculation

The focus on understanding the complex interplay between MRI measurements and disease progression does not allow identification of a specific effect size. Our sample size is defined pragmatically, based on feasibility and cost. Event rates in published studies of similar large CKD cohorts are: 13% ESKD at 26 months [23]; 25% ESRD or halving of eGFR at 5.7 years [24]; 34.7% ESKD at 4.7 years [25]. A conservative estimate of 10% event rate in 450 patients will generate confidence intervals of ±2.8% around simple cross-sectional estimates, which compares favourably to published studies. The proposed longitudinal analyses will improve upon this level of precision by capitalising on repeated measures within the multilevel and latent growth mixture modelling analyses.

10.3. Planned Recruitment Rate

Nine centres will participate.

Months 0-12: recruitment of first 45 participants (5 per site)

- Study recruitment rate: 4 per month
- Site recruitment rate: 0.5 per month

Months 13-30: recruitment of 405 participants (45 per site).

- Study recruitment rate: 22.5 per month
- Site recruitment rate: 2.5 per month

10.4. Internal feasibility study and Interim Analysis

After the first five participants at each site (total 45 patients) have undergone the baseline study visit, an interim analysis will be undertaken to test whether all elements for renal MRI acquisition, upload and analysis are successfully in place. The feasibility outcome assessed will be: the percentage of complete data collection and analysis for the following MRI measures: kidney volume; renal artery blood flow; cortical perfusion; cortical and medullary T_1; cortical and medullary R_2*; cortical and medullary ADC.

Success criteria will be defined as: Ideal ≥95% of a maximum of 405 individual MRI measures complete (9 measures x 45 participants); Acceptable ≥90% of measures complete (≥total 365).

The Derby CTSU and/or Sponsor may suspend or prematurely terminate either the entire study, or the study at an individual site, for significant reasons that must be documented (e.g. an unacceptable risk to participants, serious repeated deviations from the protocol/ regulations or technical problems that prevent adequate MRI acquisition). If this occurs the Derby CTSU/Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e. participants, investigators, participating sites, REC, regulatory bodies).

10.5. Missing or Spurious Data

Missing data will be addressed by multiple imputation or inverse probability weighting, ensuring that careful assessment and compatibility with analytical models is undertaken [26].

11. MONITORING, AUDIT & INSPECTION

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Derby CTSU/ Sponsor may visit the participating sites to conduct audits/ inspections.

Monitoring will be conducted by the Derby CTSU according to the study monitoring plan; the extent and nature of on-site monitoring will be determined by ongoing central monitoring of site recruitment and rate of data collection, data completeness, rate of non-compliances and other appropriate factors.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Assessment and Management of Risk

The study does not involve invasive procedures and MRI scanning does not involve ionising radiation, or administration of radioactive substances. The sponsor has performed an initial risk assessment per their SOP and determined that the study carries no greater risk than standard care.

12.2. Peer review

This study has been peer reviewed as part of the NIHR EME application process.

12.3. Public and Patient Involvement (PPI)

PPI input has been via face to face meeting (Derby PPI group) plus regular email working with key PPI representatives. PPI involvement in study design included: confirmation that the research area is important; specific changes to study design (e.g. helped decide number and

logistics of follow up visits, inclusion criteria); co-production of plain English summaries; and input into the grant submission to NIHR.
During the study an independent Patient and Public Involvement (PPI) group will be formed in accordance with NIHR INVOLVE Guidelines. The group will meet six monthly during the first two years, with subsequent face-to-face meetings timed at points when significant results will be generated. Between scheduled meetings, ad hoc working via email or teleconferences will occur as needed. The functions of the PPI group will include reviewing study progress including recruitment, retention and feedback from sites. Working with the CI and Study Manager, the PPI group will co-produce patient facing materials and review any written materials for patients to ensure they are easy to read and understand. The PPI group will advise on design and format of dissemination activities for participants of the study and to the wider patient and public. We will ask PPI members to reflect on their role and what they have learned and share learning from this as part of our overall dissemination plan.

12.4. Research Ethics Committee (REC) & Regulatory Considerations

The study will be conducted in compliance with the approved protocol and the Declaration of Helsinki. The protocol and all related documentation (e.g. informed consent form, participant information sheet, questionnaires) have been reviewed and received approval by a Research Ethics Committee (REC). The investigator will not begin any participant activities until approval from the HRA and REC has been obtained and documented. All documentation and correspondence must be retained in the trial master file/investigator site file. Substantial amendments that require HRA and REC (where applicable) review will not be implemented until the HRA and REC grants a favourable opinion (with the exception of those necessary to reduce immediate risk to participants).

It is the responsibility of the Derby CTSU to ensure that an annual progress report (APR) is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, annually until the study is declared ended. The Derby CTSU is also responsible for notifying the REC of the end of study (see Section 6.9) within 90 days. Within one year of the end of study, the Sponsor will submit a final report with the results, including any publications/abstracts to the REC.

Before any site can enroll a patient into the study confirmation of capacity must be sought from the site's research and development (R&D) department. In addition, for any amendment that will potentially affect the site's permission, the research team must confirm with the site's R&D department that permission is ongoing (Section 11.10).

12.5. Protocol Compliance

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable. Accidental protocol deviations (known as non-compliances) may happen and as such these must be reported within the eCRF and non-compliances will be reviewed during PMG meetings. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action, and could potentially be classified as a serious breach.

12.6. Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

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

If a serious breach is identified the investigator should notify the Derby CTSU immediately (i.e. within 1 working day) using the 'Non-CTIMP Notification of a Serious Breach' form. The report will be reviewed by the Derby CTSU and CI, and where appropriate, the Derby CTSU will notify the REC within 7 calendar days of being made aware of the breach.

12.7. Data Protection and Patient Confidentiality

The study will be conducted in accordance with the Data Protection Act 2018. The investigator must ensure that participant's anonymity is maintained throughout the study and following completion of the study. Participants will be identified on all study specific documents (except for the informed consent form and enrolment log) only by the participants study specific identifier (participant ID). This identifier will be recorded on documents, biological samples and the database. The Investigator Site File will hold an enrolment log detailing the participant ID alongside the names of all participants enrolled in the study.
All documents will be stored securely with access restricted to study staff and authorised personnel. UHDB, as the Sponsor, will act as the data controller for the study.

12.8. Financial and Other Competing Interests for the Chief Investigator, Principal Investigators at Each Site and Committee Members for the Overall Study Management

There are no financial or other competing interests to be declared by the study team. Committee members will be asked to declare any competing interests by completing a declaration prior to joining.

12.9. Indemnity

As the Sponsor is an NHS Trust, NHS indemnity applies for negligent harm therefore compensation cannot be paid when there is no negligence attributable. Exceptionally, an "ex-gratia" payment without admission of liability may be considered if a person is harmed during the study.

Where MRI scans take place on non-NHS sites, this will be determined by the participating organisation and they will be expected to put appropriate contractual arrangements in place (e.g. a service level agreement).

12.10. Amendments

Changes to the research project after approval must be made by formally amending the protocol, IRAS form or other study documentation. The Derby CTSU is responsible for

deciding if an amendment should be deemed substantial or non-substantial, in consultation with the Sponsor. Amendments will be submitted to the relevant regulatory bodies (REC, HRA) for review and approval. The amendment must be shared with the participating organisations to allow the site to review and put in place arrangements for the amendment. Amendments will not be implemented until all relevant approvals are in place. Choices surrounding differences in the implementation of the multiple statistical models proposed will in part be informed by the nature of the data as encountered and in accordance with best statistical practice; hence, the evaluation of multiple causal inference and prediction models will not constitute sufficient variance of protocol to warrant formal amendments. The report will include a full disclosure of all models undertaken, even where shown to be fruitless or uninformative.

12.11. Access to Final Study Dataset

Access to the final study dataset will be restricted to the Sponsor, Chief Investigator and central study team (Co-Investigators). Representatives of the Derby CTSU will also have access to the final study dataset.

Data generated during this study will be made available to other researchers (including co-investigators and collaborating centres) in line with the NIHR's and MRC's policy on data sharing, see section 9.4.1.

Requests for access to the research database, XNAT images and stored samples will be managed by University Hospitals of Derby & Burton NHS Foundation Trust and only non-commercial researchers with appropriate ethical approval in place will be granted access, in line with NIHR requirements.

13. DISSEMINATION POLICY

13.1. Dissemination Policy

The dissemination plan for this proposal will target a range of stakeholders. This will ensure dissemination across all of the clinical (nephrology, radiology) and scientific (MR physics) academic groups, industry (scanner manufacturers, SMEs, global pharmaceutical companies) as well as patients and the public. The PMG will develop a communications plan with substantial input from the PPI group. We will also capitalise on existing networks, UK Renal Research Infrastructure (UKKRC, CSGs and links with Kidney Research UK), European/International initiatives (e.g. Renal COST Action PARENCHIMA, of which Dr. Sourbron (Co-applicant) is Chair and to which many UKRIN members are contributors) and build on preceding work within UKRIN-MAPS.

During the life of the project, the PMG will perform a scoping exercise to identify the different stakeholders to whom dissemination activities will be targeted. We will attempt to keep key stakeholders involved through updates during the study to maximise engagement at time of presentation of results (e.g. via professional groups' newsletters, external facing website). A

description of the study design will be published and at significant timepoints throughout the project results will be presented at scientific conferences and published in peer-reviewed journals. MRI conferences (International Society for Magnetic Resonance in Medicine) and nephrology conferences (UK Kidney Week, European Renal Association and the American Society of Nephrology) will be targeted. When significant results are published, our University media offices will produce press releases and maximise impact via online and social media platforms, using tailored outputs (including visual abstracts/infographics) that will be designed specifically for target audiences. We will disseminate to the general public through a website and via social media. We will disseminate results and share expertise via research networks (UKRIN, PARENCHIMA), patient groups (Kidney Care UK, Kidney Patient Involvement Network) and charities (Kidney Research UK, KRUK). In particular, KRUK has an active public affairs programme that can engage with parliamentarians and other key healthcare policy influencers.

13.2. Authorship Eligibility Guidelines and any Intended Use of Professional Writers

Authorship will be decided according to International Committee of Medical Journal Editors (ICMJE) guidelines (link here). It is anticipated that a writing committee will be formed, led by the Chief Investigator, including co-investigators and relevant principle investigators from participating sites.

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15. APPENDICES

15.1. Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
0	1.1	15/Apr/2020	N. Selby	Updated per REC provisional opinion requirements. Addition of exclusion criterion for participation in other research studies. Further information on the use of the questionnaires in the study.
1	2.0	04/Sep/2020	R Sherman / N Selby	Added additional information on the long-term tracking of CKD events via the UK Renal Registry. Adapted protocol to account for the need for remote visits (including remote consent) due to distancing measures required following the COVID19 pandemic. Updated contact details where appropriate. Removed examples of contraindications to MRI in the exclusion criteria section Updated the safety reporting section to allow for electronic SAE reporting via the eCRF. Minor updates to biobanking and biopsy sections.

15.2. Appendix 2 – Questionnaires

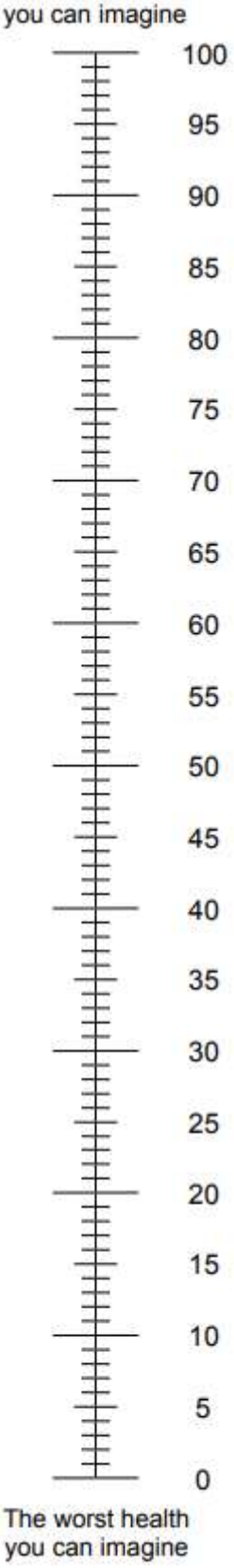
15.2.1. EQ-5D-5L (2 pages)

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility ○ I have no problems in walking about ○ I have slight problems in walking about ○ I have moderate problems in walking about ○ I have severe problems in walking about ○ I am unable to walk about **Self-Care** ○ I have no problems washing or dressing myself ○ I have slight problems washing or dressing myself ○ I have moderate problems washing or dressing myself ○ I have severe problems washing or dressing myself ○ I am unable to wash or dress myself **Usual Activities** ○ I have no problems doing my usual activities ○ I have slight problems doing my usual activities ○ I have moderate problems doing my usual activities ○ I have severe problems doing my usual activities ○ I am unable to do my usual activities (e.g. work, study, housework, leisure, activities)	**Pain / Discomfort** ○ I have no pain or discomfort ○ I have slight pain or discomfort ○ I have moderate pain or discomfort ○ I have severe pain or discomfort ○ I have extreme pain or discomfort **Anxiety / Depression** ○ I am not anxious or depressed ○ I am slightly anxious or depressed ○ I am moderately anxious or depressed ○ I am severely anxious or depressed ○ I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box
  below.

Your health today = ☐



15.2.2. POS-RENAL (1 page)

Below is a list of symptoms, which you may or may not have experienced. Please put a tick in the box to show how you feel each of these symptoms has affected you and how you have been feeling over the past week.

	Not at all No effect	**Slightly** But not bothered to be rid of it	**Moderately** Limits some activity or concentration	**Severely** Activities or concentration markedly affected	**Overwhelmingly** Unable to think of anything else
Pain	0	1	2	3	4
Shortness of breath	0	1	2	3	4
Weakness or lack of energy	0	1	2	3	4
Nausea (feeling like you are going to be sick)	0	1	2	3	4
Vomiting (being sick)	0	1	2	3	4
Poor appetite	0	1	2	3	4
Constipation	0	1	2	3	4
Mouth problems	0	1	2	3	4
Drowsiness	0	1	2	3	4
Poor mobility	0	1	2	3	4
Itching	0	1	2	3	4
Difficulty sleeping	0	1	2	3	4
Restless legs or difficulty keeping legs still	0	1	2	3	4
Feeling anxious	0	1	2	3	4
Feeling depressed	0	1	2	3	4
Changes in skin	0	1	2	3	4
Diarrhoea	0	1	2	3	4
Any other symptoms (please state what they are)					
1)	0	1	2	3	4
2)	0	1	2	3	4
3)	0	1	2	3	4