Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage chronic kidney disease

- Full title
  Use of *F*erumoxytol *e*nhanced *M*agnetic *R*esonance *A*ngiography for cardiovascular assessment *in* late-stage *C*hronic *K*idney *D*isease

- Short title
  FeMRA in CKD

- Version number
  4.0

- Sponsor
  NHS Greater Glasgow & Clyde

- Funder

- Protocol authors
  Dr Sokratis Stoumpos, Dr Giles Roditi, Dr Patrick Mark, Mr David Kingsmore, Dr Aleksandra Radjenovic

Revision/Amendment Number	Date	Protocol Version
Revision 1	13/09/2016	2.0
Amendment 1 (substantial)	17/11/2016	3.0
Amendment 2 (substantial)	10/10/2017	4.0

Chief investigator (CI):	Title and Position:
Dr Sokratis Stoumpos MSc MRCP British Heart Foundation Cardiovascular Research Centre University of Glasgow 126 University Place Glasgow G12 8TA Tel: +44 141 330 2079 Mobile: +44 781 874 2133 E-mail: sstoumpos@nhs.net	Clinical Research Fellow and Specialist Registrar in Renal Medicine *University of Glasgow*
Principal investigators (PIs):	**Titles and Positions:**
Dr Patrick B Mark PhD FRCP	Reader and Honorary Consultant Nephrologist *University of Glasgow*
Mr David B Kingsmore MD FRCS	Consultant Vascular Surgeon and Honorary Clinical Associate Professor *Queen Elizabeth University Hospital*
Dr Giles Roditi DMRD FRCP FRCR	Consultant Cardiovascular Radiologist and Honorary Clinical Associate Professor *Queen Elizabeth University Hospital*
Dr Aleksandra Radjenovic PhD	Senior Lecturer *University of Glasgow*
Co-investigators:	**Titles and Positions:**
Dr Martin Hennessy	Registrar in Interventional Radiology *Queen Elizabeth University Hospital*
Dr Angela Bradshaw	Lecturer *University of Glasgow*

Dr Ram Kasthuri Mr Alex Vesey Ms Tracey Hopkins	Consultant Interventional Radiologist *Queen Elizabeth University Hospital* Registrar in Vascular Surgery *Queen Elizabeth University Hospital* Superintendent Radiographer *Queen Elizabeth University Hospital*
Sponsor Contact: Dr Maureen Travers Clinical Research & Development NHS Greater Glasgow & Clyde West Glasgow Ambulatory Care Hospital Dalnair Street Glasgow, G3 8SJ Tel: +44 (0) 141 232 1813 Email: Maureen.Travers@ggc.scot.nhs.uk	**Sponsor Pharmacist:** Dr Elizabeth Douglas MRPharmS Senior Clinical Trials Pharmacist R&D Clinical Research & Development NHS Greater Glasgow & Clyde West Glasgow Ambulatory Care Hospital Dalnair Street Glasgow, G3 8SJ Tel: +44 (0) 141 232 1792 E-mail: elizabeth.douglas@ggc.scot.nhs.uk

CONTENTS

List of abbreviations....6
Study synopsis....8
Study flow chart....9
Study visits chart....10
1 BACKGROUND....11
1.1 Evaluation of the potential kidney transplant recipient....11
1.2 Vascular mapping before access creation....11
1.3 Vascular access surveillance....11
1.4 Associations between cardiac function and vascular access....12
1.5 Markers of endothelial dysfunction....12
1.6 Ferumoxytol enhanced Magnetic Resonance Angiography (FeMRA)....13
2 RATIONALE....14
3 STUDY OBJECTIVES....15
3.1 Primary objectives....15
3.2 Secondary objectives....15
4 STUDY HYPOTHESES....15
5 STUDY DESIGN....17
5.1 Data collection and study procedures....17
5.2 Imaging studies and blood tests....18
5.2.1 Ultrasound vascular mapping....19
5.2.2 Ferumoxytol enhanced magnetic resonance angiography....19
5.2.3 Blood processing and storage....21
5.3 Study visits....21
5.4 Duration of participation....22
6 STUDY POPULATION....22
6.1 Inclusion criteria....22
6.2 Exclusion criteria....22
6.3 Informed consent....23
6.4 Potential risks and benefits....24
6.5 Withdrawing from the study....25
6.6 Confidentiality....25
7 STUDY OUTCOMES....25
7.1 Primary outcome....25
7.2 Secondary outcomes....26
8 DATA COLLECTION & MANAGEMENT....26
8.1 Data collection....26
8.2 Data storage....26
9 STATISTICAL CONSIDERATIONS....27
10 STUDY CONDUCT RESPONSIBILITIES....28

10.1 Protocol amendments....28
10.2 Protocol violations and deviations....28
10.3 Study record retention....28
10.4 Study auditing....28
10.5 End of study....28
10.6 Archive....29
11 REPORTS, DISSEMINATION OF FINDINGS....29
11.1 Authorship policy....29
11.2 Reports....29
11.3 Publication....29
11.4 Peer review....29
12 PHARMACOVIGILANCE....29
12.1 Definition of adverse events....29
12.2 Adverse event recording....30
12.3 Serious adverse events and serious adverse reactions recording and reporting....30
12.4 Reporting of SARs and SAEs to the Ethics Committee....30
12.5 Annual progress reports....31
12.6 Reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA)...31
13 REFERENCES....32
TABLE 1....34
TABLE 2....35
TABLE 3....36

List of abbreviations

AR: adverse reaction
AVF: arteriovenous fistula
AVG: arteriovenous graft
CI: chief investigator
CI-AKI: contrast-induced acute kidney injury
CKD: chronic kidney disease
CMR: cardiovascular magnetic resonance imaging
CRF: clinical research file
CT: computed tomography
CTA: computed tomography angiography
CTIMP: clinical trial of an investigational medicinal product
CVS: central vein stenosis
DCE: dynamic contrast enhanced
DSA: digital subtraction angiography
ESRD: end stage renal disease
FeMRA: Ferumoxytol enhanced magnetic resonance angiography
FSH: follicle stimulating hormone
FTM: failure to mature
HD: haemodialysis
HRT: hormone replacement therapy
hs-CRP, high sensitivity C-reactive protein
hs-TNI, high sensitivity troponin I
ICAM-1, intercellular adhesion molecule 1
IDA: iron deficiency anaemia
IL-1, interleukin-1
IL-6, interleukin-6
LV: left ventricular
MCP-1, monocyte chemoattractant protein-1
MHRA: Medicines and Healthcare Products Regulatory Agency
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
NSF: nephrogenic systemic fibrosis
PAI-1, plasminogen activator inhibitor-1
PACS: picture archive and communication system
PI: principal investigator
PIS: patient information sheet
PTFE: polytetrafluoroethylene
PV: pharmacovigilance

R&D: research and development
REC: research ethics committee
RV: right ventricular
SAE: serious adverse event
s-IL2R, soluble interleukin-2 receptor
SMC, smooth muscle cell
TGFß, transforming growth factor beta
TLR-4, Toll-like receptor 4
TNF-a, tumor necrosis factor-a
tPA, tissue plasminogen activator
USPIO: ultrasmall superparamagnetic iron oxide
VCAM-1, vascular cell adhesion molecule 1
vWF, von Willebrand factor

Study Synopsis

Background – The usually employed methods for non-invasive cardiovascular imaging using Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) carry potential risks for kidney disease patients. An alternative contrast agent is needed to optimise imaging results while minimising risks in this vulnerable patient group. Ferumoxytol originally developed as a MRI contrast agent and is currently licensed in the USA and Canada for iron-replacement therapy primarily in patients with kidney disease, still has excellent potential as MRI contrast agent in assessing the heart, central and peripheral vessels.

Objectives - To determine the quality and clinical yield of Ferumoxytol-enhanced Magnetic Resonance Angiography (FeMRA) use in cardiovascular assessment of patients with late-stage chronic kidney disease (CKD) compared with current standard-of-care imaging techniques.

Study Design - Single centre comparative prospective cohort study.

Setting and Participants - Patients with late-stage kidney disease undergoing conventional cardiovascular imaging as part of pre-operative kidney transplant candidacy assessment and haemodialysis vascular access creation or surveillance will be enrolled from the Glasgow Renal and Transplant Unit and followed up for up to 2 years.

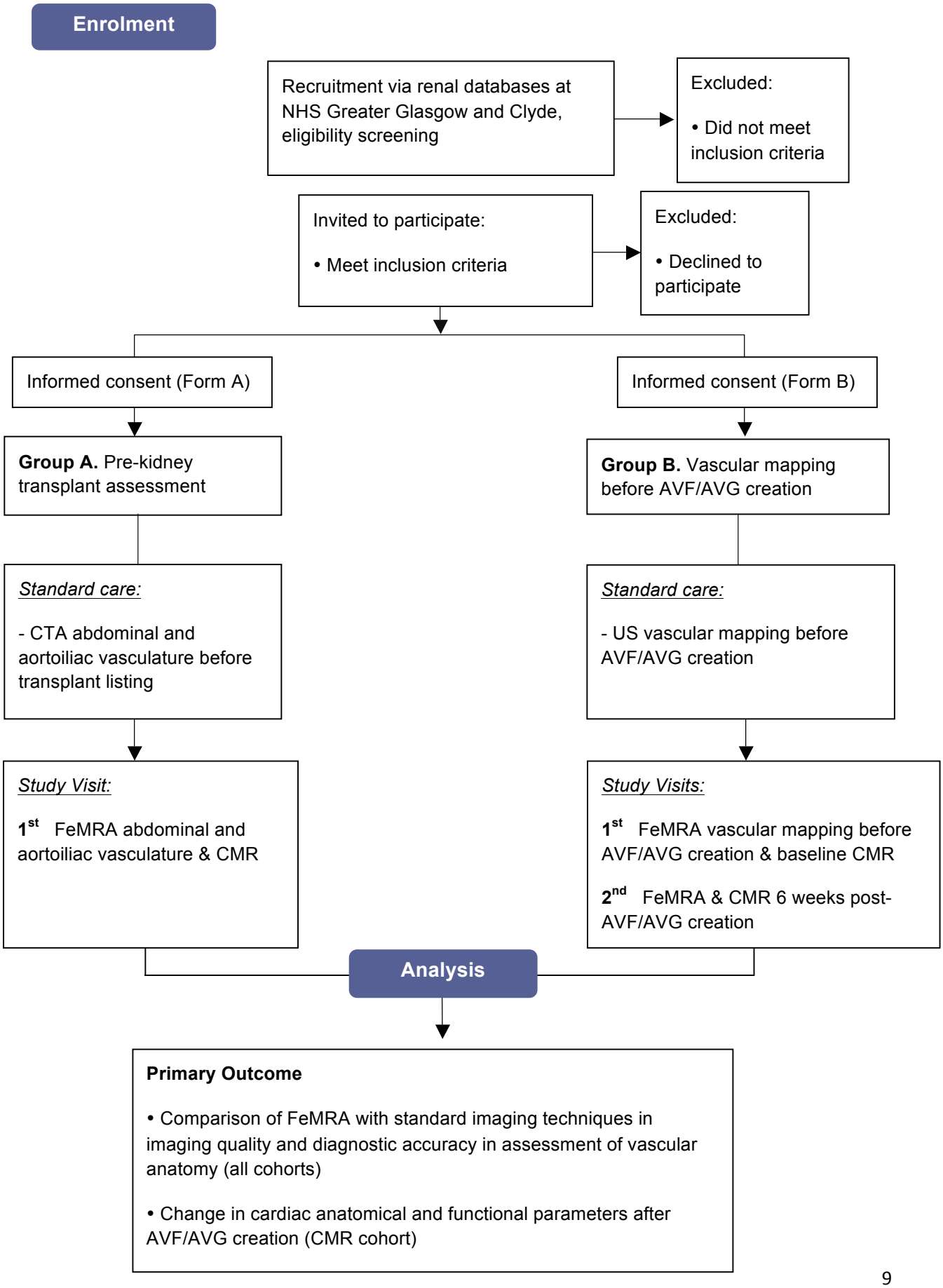
Interventions – Cardiovascular magnetic resonance angiography using 3mg/kg body weight of Ferumoxytol as intravenous contrast agent for enhancement as part of cardiovascular assessment.

Main Outcome Measures – Head-to-head comparisons of imaging quality and diagnostic accuracy of FeMRA compared with standard imaging techniques.

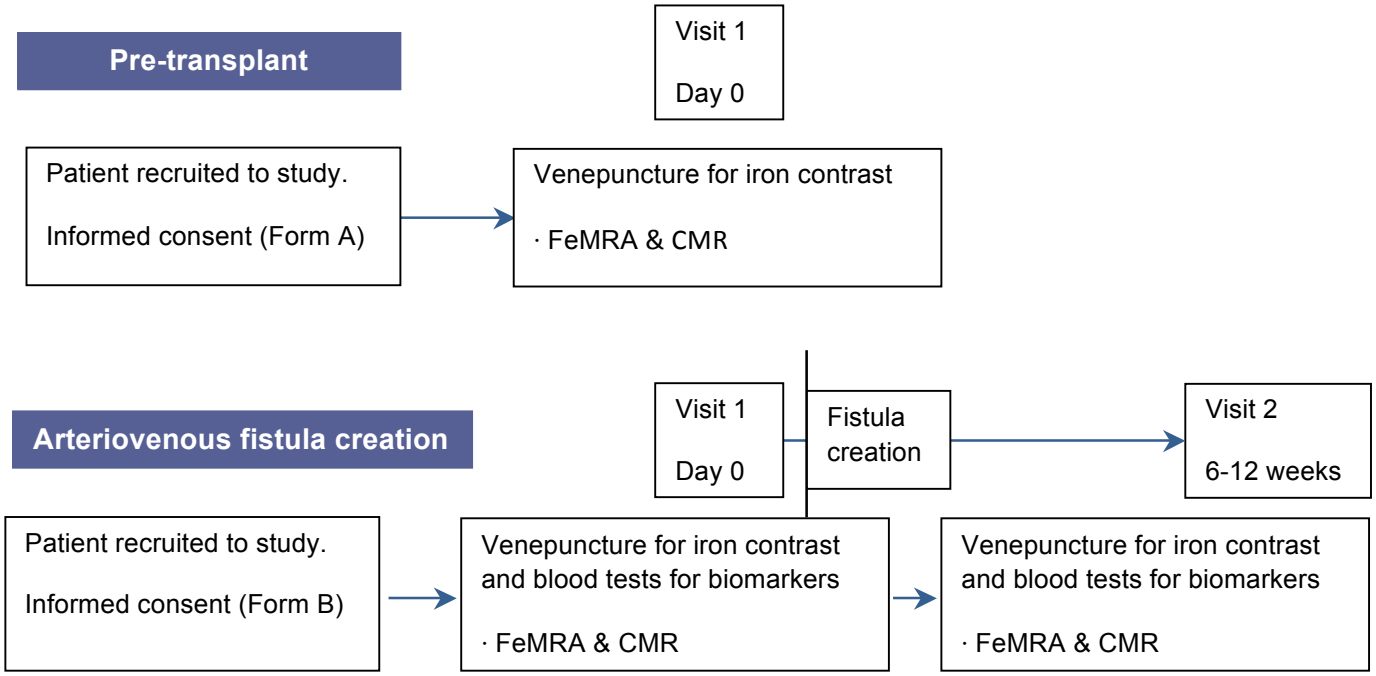
Limitations - Single centre design. The separation of investigations in time will allow certain findings to evolve and become more or less apparent.

Conclusions - The FeMRA in CKD Study will be of sufficient size and scope to 1) evaluate the quality and diagnostic utility of FeMRA in late-stage CKD, and 2) establish the most appropriate imaging modality for cardiovascular assessment in patients with late-stage CKD.

Study flow chart



Study visits chart



1. Background

Conventional vascular imaging techniques are often either contra-indicated or only used with caution in chronic kidney disease (CKD) patients due to their relative invasiveness, risks and cost. Computed tomography angiography (CTA) requires radiation and nephrotoxic iodinated contrast which may precipitate significant worsening of renal function and even prompt the need for institution of dialysis. Similarly, in patients receiving maintenance haemodialysis (HD), contrast administration has the potential risk of accelerating a decline in residual kidney function. Additionally, CT has reduced accuracy for arterial diagnosis in the presence of arteriosclerotic calcification which is extremely common in these patients. Magnetic resonance angiography (MRA) in patients with end-stage renal disease (ESRD) using linear chelate gadolinium-based contrast agents has been associated with the rare disease 'nephrogenic systemic fibrosis'[1]. Alternative imaging methods also have drawbacks: for example, this frail patient group has a higher risk of complications from conventional invasive catheter-based angiography and calcification interferes with duplex ultrasound assessment of the peripheral arterial vasculature. Other tests such as non-contrast MRA methods are less accurate and ultrasound is often not appropriate for evaluation of the deep vessels of the thorax, abdomen and pelvis.

1.1 Evaluation of the potential kidney transplant recipient

Kidney transplantation is the treatment of choice for most patients with ESRD. A large number of potential kidney transplant recipients with established renal failure have peripheral vascular disease and need additional tests to characterise the vessels before placement of a kidney graft. CTA of the aortoiliac vasculature for identification of calcifications of the iliac arterial sector allows better recipient selection and accurate planning for the vascular anastomosis and placement of the renal graft[2].

Until now, the widespread use of CTA in the workup of the potential renal transplant recipient has been limited because of concerns of contrast-induced acute kidney injury (CI-AKI), especially in predialysis patients. In addition, CTA can be limited by arterial calcification and also does not robustly evaluate venous anatomy.

1.2 Vascular mapping before access creation

Doppler ultrasound is routinely used to allow proper selection of a target vessel with adequate luminal diameter to improve access outcome. This is readily available and cheap but has a major limitation which is the relative inability to assess central vein patency. Central vein stenosis (CVS) occurs in over 40% of patients with previous percutaneous line insertions for dialysis[3] and digital subtraction angiography (DSA) is the gold standard for patients at risk of CVS. However, for optimum results DSA requires bilateral venous cannullation with good caliber cannulas to allow rapid injection of contrast to opacify the central veins, and this can be challenging in CKD patients.

1.3 Vascular access surveillance

Doppler US may be useful for surveillance of arteriovenous fistulas (AVF)[4]. In a systematic review, 4 randomised trials evaluated access flow-based monitoring in native AVFs[5]. Although access blood flow screening with Doppler US prevented access thrombosis in AVFs, it did not reduce the risk of access loss or extent of resource use. Despite limited data, Doppler US has become the standard of

practice for fistula surveillance with an increasing number of HD centres implementing fistula surveillance programs.

Polytetrafluoroethylene (PTFE) grafts are used for HD in patients with limited options for a native access. Their survival is similar or even better compared to AVFs with 1-year patency of approximately 70%[6] though they are typically complicated by thrombosis requiring multiple procedures to restore patency. Different methodologies are currently being used for surveillance and monitoring depending upon local practice and expertise. Doppler ultrasound is probably the most reproducible and accurate arteriovenous graft (AVG) surveillance method but has low accuracy of identifying central vein stenotic lesions. Graftogram with DSA which is the conventional angiography technique has the advantages of high spatial and temporal resolution and the ability to intervene but is invasive with the risk of vascular injury and stroke, does not provide a three–dimensional representation of what can be complex anatomy, and requires the use of iodinated contrast and ionising radiation.

1.4 Associations between cardiac function and vascular access

Cardiovascular disease is a well-known predictor of fistula failure to mature (FTM)[7] but the role of a low cardiac output state before fistula creation has not been investigated sufficiently. An inability of the heart to increase the cardiac output following fistula creation may lead to hypotension, reduced fistula flow and subsequent failure of maturation.

On the other hand, it is well established that creation of arteriovenous access for dialysis has significant effects on both systolic and diastolic function. The fistula or graft adds a low resistance, high-compliance venous compartment to the central arterial system. It is associated with increased blood flow, pulmonary hypertension, and cardiac output. Although usually clinically insignificant, the increased cardiac output and blood flow may be so great at times that they result in overt cardiac failure[8, 9]. This is particularly true if the patient has underlying heart disease and/or the access has flows greater than 2000 mL/min[10].

1.5 Markers of endothelial dysfunction

In HD patients, complex coagulation abnormalities occur, ranging from bleeding to thrombosis. On the one hand, the enhanced bleeding tendency in these patients is primarily based on functional platelet abnormalities and defective adhesion to the vessel wall[11]. On the other hand, a variety of coagulation abnormalities contribute to an increased thrombotic tendency.

Cytokines and pro-inflammatory factors have been shown to play central roles in the activation of acute and chronic vascular responses to injury[12]. For example, thrombin secreted by activated platelets adhering to the injured endothelium triggers the release of fibroblast growth factors, stimulating smooth muscle cells (SMC) mitogenesis and chemotaxis. Transforming growth factor beta (TGFß), a pleiotropic cytokine, promotes intimal hyperplasia by augmenting neointimal cell proliferation, inducing SMC migration and stimulating the secretion of fibrotic extracellular matrix proteins[13]. Patients with renal disease undergoing HD have a raised inflammatory profile with significantly increased high sensitivity C-reactive protein (hs-CRP), serum tumor necrosis factor-a (TNF-α), interleukin-1 (IL-1), soluble interleukin-2 receptor (s-IL2R), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1) and intercellular

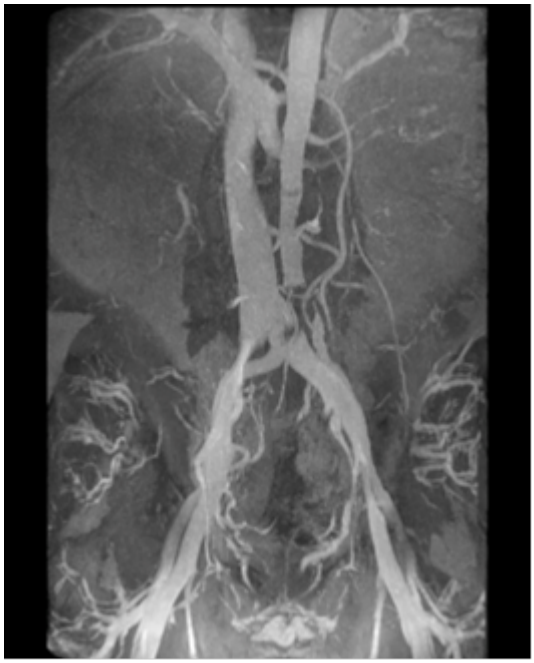
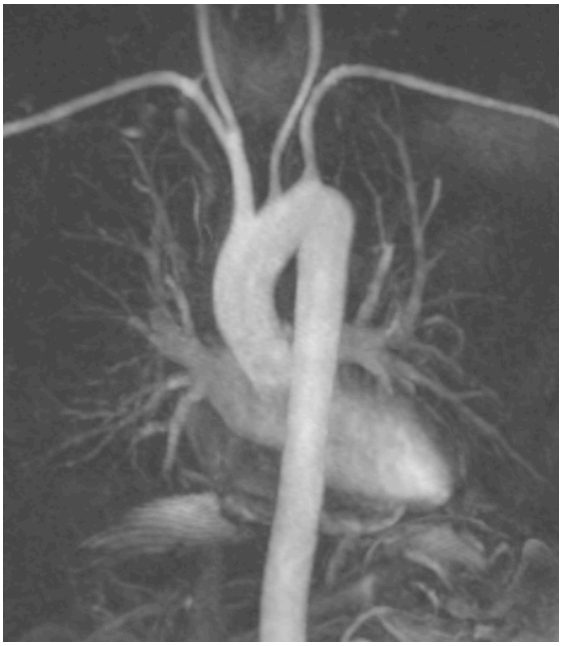
adhesion molecule 1 (ICAM-1), as well as increased expression of the pro-inflammatory receptor Toll-like receptor 4 (TLR-4)[14-18].

1.6 Ferumoxytol enhanced Magnetic Resonance Angiography (FeMRA)

Ferumoxytol is an ultrasmall superparamagnetic iron oxide (USPIO) particle encapsulated by a semisynthetic carbohydrate with properties that can be used for diagnosis and therapy. Ferumoxytol was initially developed as a MRI contrast agent and filed for patent as this on March 8th 2000 (patent published 2003)[19]. However, interest in Ferumoxytol as a therapeutic agent for the treatment of iron deficiency anaemia (IDA) eclipsed its use as magnetic resonance (MRI) contrast agent. During the last decade, the identification of the association of nephrogenic systemic fibrosis (NSF) with linear chelate gadolinium-based contrast agent administration to patients with advanced kidney disease has led to renewed interest in Ferumoxytol as a contrast agent due to its superparamagnetic properties[20-22].

Ferumoxytol is licensed in the USA and Canada for treating IDA in the setting of CKD [23] but not for clinical diagnostic imaging. It has gained appeal as a MRI contrast agent in patients with estimated glomerular filtration rates <30mL/min/1.73m^2 in whom other imaging modalities are contraindicated or can only be used with caution and there are reports in the literature for its safe use and utility in both adult[24] and pediatric[25] patients with CKD. Ferumoxytol metabolism is not dependent on kidney function, but rather is removed from the circulation by the reticuloendothelial system of the liver, spleen, and bone marrow. Additionally, the prolonged intravascular half-life (>14 hours) of Ferumoxytol allows for longer image acquisition and repeat imaging, if necessary[21, 26, 27].

The typical dose used for imaging is 15-40% that for iron replacement, therefore the safety profile for imaging is more attractive than for iron replacement. Ferumoxytol has been licensed in the USA and Canada for use in patients with kidney failure and this has important implications in clinical practice since the agent can be used in patients with compromised renal function where there is a pressing clinical question but no other viable angiographic option. We, and others, have studied vascular iron MRA using Ferumoxytol as contrast for clinically indicated scans[28] (examples of our scans below).

Left - Iliac vessels with iron MRA in a transplant recipient. **Right -** Iron MRA of central vessels.

2. Rationale

Use of conventional contrast agents, both iodinated or gadolinium based, in patients with late-stage CKD are limited by the risks for additional acute kidney injury and NSF, respectively, that must be balanced by the critical nature of the radiologic study for the well-being of the patient. In addition, current techniques have reduced accuracy for arterial diagnosis in the presence of arteriosclerotic calcification or have limitations in assessing central vein patency. In these patients, Ferumoxytol is an alternative agent for cardiovascular assessment, including vessel patency and course.

We are proposing to apply novel techniques with MRA using intravenous iron whilst planning transplantation or haemodialysis for renal replacement therapy. The "Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage chronic kidney disease (FeMRA in CKD) study" is a single centre prospective cohort study designed to compare routinely used imagining techniques with FeMRA in patients with severely impaired renal function.

Study participants undergoing standard imaging tests as part of their clinical care will also have FeMRA. We will compare outcomes of interest including quality of image and diagnostic accuracy in a head-to-head design. The additional information gained will determine if Ferumoxytol-based vascular imaging has the potential to offer a practical solution to both gadolinium-based and iodinated contrast agents when assessing vessel anatomy in patients with late-stage CKD.

3. Study Objectives

The FeMRA in CKD study is designed to compare standard with novel imaging techniques for cardiovascular assessment in late-stage CKD with the objective to provide a better imaging modality.

3.1 Primary objectives

1. Vascular anatomy before implantation of a kidney graft using routine and novel imaging techniques.

2. Vascular anatomy before and after fistula creation using routine and novel imaging techniques.

3. Vascular anatomy before and after synthetic graft creation using routine and novel imaging techniques.

3.2 Secondary objectives

1. Assessment of cardiac anatomy, function, and myocardial perfusion before implantation of a kidney graft using novel imaging techniques.

2. Anatomical predictors of US-based fistula maturation using routine and novel imaging techniques.

3. Assessment of cardiac anatomy, function, and myocardial perfusion before and after fistula creation using novel imaging techniques.

4. Assessment of cardiac anatomy, function, and myocardial perfusion before and after synthetic graft creation using novel imaging techniques.

5. Assessment of cardiac morphology, coronary blood supply, microvascular perfusion, and tissue characterisation using novel imaging techniques (sub-study).

4. Study Hypotheses

These hypotheses will be tested:

A. <u>Vascular anatomy</u>

1. FeMRA is superior to CTA for characterisation of abdominal and aortoiliac anatomy (pre-transplant assessment) before implantation of a kidney graft.

2. FeMRA is superior to Doppler US for characterisation of upper limb vascular anatomy (vascular mapping) before fistula creation.

3. FeMRA is superior to Doppler US for characterisation of upper limb vascular anatomy (vascular mapping) before synthetic graft creation.

4. FeMRA is superior to Doppler US for characterisation of upper limb vascular anatomy (vascular mapping) before fistula creation in patients with suspected CVS.

5. FeMRA is superior to Doppler US for characterisation of upper limb vascular anatomy (vascular mapping) before synthetic graft creation in patients with suspected CVS.

6. FeMRA is superior to Doppler US for characterisation of fistula arm vascular anatomy (surveillance) at 6 weeks after fistula creation.

7. FeMRA is superior to DSA graftogram for characterisation of graft arm vascular anatomy (surveillance) at 6 weeks after synthetic graft creation.

B. Anatomical predictors of outcomes

1. Anatomical characteristics of vessels such as diameter or anatomical lesions prior to fistula (or graft) creation are determinants of fistula (or graft) outcomes.

2. Early post-operative changes in vessel diameter predict fistula (or graft) outcomes.

3. FeMRA is superior to Doppler US for identification of pre-operative subtle anatomical lesions (vascular mapping) associated with fistula (or graft) outcomes.

4. FeMRA is superior to Doppler US for identification of pre-operative subtle anatomical lesions (vascular mapping) associated with fistula (or graft) outcomes in patients with suspected CVS.

5. FeMRA is superior to Doppler US for assessment of fistula lumen, inflow artery diameter, and average draining vein diameter as surrogates for fistula maturation and usability.

6. FeMRA is superior to Doppler US for identification of early post-operative subtle anatomical lesions (surveillance) associated with fistula outcome.

7. FeMRA is superior to DSA graftogram for identification of early post-operative subtle anatomical lesions (surveillance) associated with graft outcome.

C. Cardiac imaging

1. FeMRA is useful in rapid MRI assessment of cardiac anatomy, function, and myocardial perfusion.

2. FeMRA has the advantage of complete cardiovascular assessment (heart, central, and peripheral vasculature) using a single imaging modality when used for pre-transplant assessment.

3. Low cardiac output state before fistula (or graft) creation is a predictor of fistula (or graft) outcomes.

4. Successful fistula (or graft) creation is associated with high-output cardiac failure.

5. Successful fistula (or graft) creation is associated with a favorable effect in cardiac microcirculation kinetics (pre-conditioning hypothesis).

6. Patients who have unsuccessful fistula (or graft) operation exhibit no recordable changes in cardiac microcirculation.

7. FeMRA is useful in assessment of cardiac morphology, coronary blood supply, microvascular perfusion, and tissue characterisation (sub-study).

D. Implications in clinical practice

1. FeMRA is the imaging modality of choice for characterisation of abdominal and aortoiliac anatomy (pre-transplant assessment) before implantation of a kidney graft.

2. FeMRA is the imaging modality of choice for characterisation of vascular anatomy (vascular mapping) before fistula (or graft) creation in patients with suspected CVS.

3. FeMRA is the imaging modality of choice for characterisation of vascular anatomy (surveillance) early post-operatively after synthetic graft creation.

5. Study Design

5.1 Data collection and study procedures

Pre-operative procedures

- Eligibility screening
- Informed consent
- Baseline clinical data collection
  - Demographics
  - Comorbidities
  - Medications
  - Dialysis history
  - Vascular access history
- Provide patient alert card

- Pregnancy test before Ferumoxytol administration for women of child-bearing potential
- Vascular mapping
  - Ultrasound vascular mapping *or* DSA for patients with suspected CVS *(standard care)*
  - FeMRA fistula (or graft) arm/central veins & CMR *(study visit 1)*
  - Blood samples for biomarkers (*study visit 1)*
- Pre-transplant assessment
  - CTA abdominal and aortoiliac vasculature *(standard care)*
  - FeMRA abdominal/aortoiliac vasculature & CMR (*study visit 1)*
  - Blood samples for biomarkers (*study visit 1)*

Post-operative procedures

- Pregnancy test before Ferumoxytol administration for women of child-bearing potential
- Fistula surveillance
  - 6-week ultrasound fistula arm *(standard care)*
  - 6-week FeMRA fistula arm/central veins & CMR *(study visit 2)*
  - Blood samples for biomarkers *(study visit 2)*
- Graft surveillance
  - 6-week DSA graftogram *(standard care)*
  - 6-week FeMRA graftogram/central veins & CMR *(study visit 2)*
  - Blood samples for biomarkers *(study visit 2)*
- Imaging surrogates for fistula usability
- Vascular access complications and fistula procedures data collection
- Fistula use and abandonment data collection

Sub-study (optional)

- Cardiac 4D MRA *(no additional study visit required)*

5.2 Imaging studies and blood tests

Pre-operative and post-operative FeMRAs will be performed by trained personnel using standardised protocols. FeMRAs will be reviewed by the study radiologists who will be blinded to other investigations. Standard care imaging studies will also be reviewed by the study radiologists who will be blinded to the FeMRA findings. An independent radiologist that is not directly involved in the study will also review images. All discrepancies will be resolved by mutual consensus between the radiologists.

We will not alter our routine clinical practice which involves CTA for pre-transplant assessment when indicated, ultrasound vein mapping (or invasive angiography) for all patients before vascular access creation, US Doppler for fistula surveillance, and DSA graftogram for graft surveillance. All these tests are part of our standard care, and results will be available for clinical use. However, FeMRAs will not be made available to clinicians or study investigators unless there is a finding that threatens the participant's health (e.g. impending rupture of pseudoaneurysm).

The imaging studies will serve multiple functions including characterising the natural history of fistula maturation and delineating temporal changes that reflect physiological responses to fistula (or graft) creation. The 6-week ultrasound (and FeMRA) will be used to predict imaging-based

anatomical maturation as a potential surrogate for clinical maturation. One study objective is to determine if FeMRA is superior to ultrasound in characterisation of blood vessel anatomy and demonstration of subtle arterial and venous changes prior to these having haemodynamic significance. Another objective is to determine the utility of fistula luminal diameter, inflow artery diameter, and average draining vein diameter as composite surrogate outcomes for fistula maturation and usability.

5.2.1 Ultrasound vascular mapping

The patients will receive bilateral upper extremity US vascular mapping with both vein and arterial components. Vein-US mapping involves measurement of vein diameters at the following locations: cephalic and basilic veins at the proximal upper arm, mid-upper arm, distal upper arm, and antecubital fossa; cephalic vein at the proximal forearm, mid-forearm, distal forearm, and the wrist. Compressibility and presence of thrombus as well as continuity to the upper arm deep venous vasculature will be assessed. Vein-US examinations will be performed with the patient supine at ambient temperature and a rubber tourniquet in place. Specific arterial-US examination components include: diameter of the brachial artery at the antecubital fossa, diameter of the radial artery at the wrist, level of brachial artery bifurcation relative to the antecubital fossa, results of the US Allen's test, and arterial waveform tracing at the antecubital fossa brachial artery and the wrist radial artery. The US Allen's test will be performed as described by the American Institute of Ultrasound in Medicine (AIUM) Practice Guidelines[29] by occluding the radial artery near the wrist and placing the US probe distal to the occlusion. Retrograde flow indicates a positive Allen's test and a patent palmar arch. Lack of flow indicates a negative Allen's test and an incomplete palmar arch.

Findings on vascular mapping that would be against fistula creation include cephalic or basilic vein <2.5mm, vein not continuous to upper arm, radial or brachial artery <2.0mm, an incomplete palmar arch by US Allen's test, blunted radial artery waveforms, and brachial artery bifurcations above the antecubital fossa. The overall plan for the site of fistula creation will be based on both vascular mapping findings and clinical judgment as opposed to hard arterial anatomic criteria alone.

5.2.2 Ferumoxytol enhanced magnetic resonance angiography

Patients will undergo MRA with Ferumoxytol administered in an appropriate setting under supervision of trained medical personnel with appropriate monitoring and resuscitation facilities immediately available.

We are proposing to perform FeMRA to assess central and peripheral vessels, and the heart depending on the indication. Images will be acquired while the patient remains supine in the MRI system (3T Prisma at Glasgow Clinical Research Facility on Queen Elizabeth University Hospital campus) with local phased array imaging coils. The scan will last for approximately 45 minutes.

We will place an intravenous cannula during the course of the research scan for administration of the dilute Ferumoxytol infusion. Blood samples will be obtained at the time of cannula placement. The cannula will only be in place for an hour or less, thus rendering negligible any potential complications relating to infection.

The patient will be monitored by medical and radiographic staff at baseline, during, and for a minimum period of 30 minutes following termination of infusion. Patients will be instructed to immediately alert the operator should they have any feelings of discomfort at any time. Patients will be continuously monitored by pulse oximetry while in the MRI scanner and will have blood pressure and pulse measured before and after infusions. Administration of other medications that could potentially cause serious hypersensitivity reactions and/or hypotension, such as chemotherapeutic agents or monoclonal antibodies will not be administered for at least 30 minutes after administration of Ferumoxytol. In order to avoid the situation that patients will have completed their scanning and would experience a reaction after leaving the imaging suite, we will require subjects to remain under observation for a minimum period of 30 minutes following injection even if they are already out of the scanner. Once out of the scanner, patients will remain in a reclining or semi-reclining position. Observation for the full 30 minutes following the contrast injection, i.e., both while the patient is in the scanner and following that will be done by the doctors directly involved in the study who are aware of the study protocol, and who are trained on procedures to be followed in the event of any reaction. The same precautions will be taken for each scan, even if no hypersensitivity reaction occurred after the first scan. Should the patient experience signs or symptoms of hypersensitivity they will be observed until clinically stable.

The imaging protocol will be similar to that of standard MRA studies with gadolinium-based contrast agents. Imaging will be performed on a 3T Prisma (Siemens) clinical MRI system. A maximum dose of 3mg of Ferumoxytol/kg of patient weight will be delivered (not to exceed 300mg). In all cases Ferumoxytol will be diluted to a concentration no greater than 1 part Ferumoxytol to 4 parts 0.9% sodium chloride. Ferumoxytol administration is controlled by a sophisticated MRI compatible infusion pump for precise control over infusion rate. When given for treatment of IDA, the licensed dose of Ferumoxytol is an initial 510mg dose administered as an intravenous infusion in 50-200mL 0.9% sodium chloride or 5% Dextrose over at least 15 minutes, followed by a second 510mg dose 3 to 8 days later. When administered for imaging, Ferumoxytol will be given in a continuous infusion of diluted agent over at least 15 minutes to comply with the FDA recommendations, though the diagnostic dose is less than half the therapeutic dose (210mg for a 70kg patient). A 20ml saline flush will be injected following administration of the full dose of Ferumoxytol. Patients will be divided into 13 dose bands according to body weight using increments of 5kg. The dose given within each weight group will be rounded up to the dose required for the upper limit of the group. The average rounding is a 6% increase in dose (range 4-13%) compared to actual dose at the lowest weight of the band. For patients exceeding 100kg, a total dose of 300mg will be administered irrespectively of weight. Details of the total dose and infusions volumes to be administered for each dose band are shown in Table 1.

Patients will be asked if they wish to have a second scan at the same day as part of a sub-study. This is optional and will not affect patients' participation in the main study. In this sub-study, we will acquire additional cardiac MRI scans at our University MRI site (Glasgow Cardiovascular Research Centre, British Heart Foundation Centre of Excellence). This additional scan will give us information about the status of epicardial coronary vessels and provide a detailed 4D magnetic resonance angiography dataset (3D coronary vessel tree in multiple ECG phases). This method was developed by our collaborators at the Cedars Sinai Hospital, USA, and will allow us to have a complete, non-invasive assessment of the heart morphology and different levels of function: from the patency of

the coronary blood supply, microvascular perfusion, tissue characterisation using T1/T2/T2* mapping to wall motion, and feature tracking analysis of myocardial strain. The protocol will include localisers, T1/T2 and T2* maps, self-navigated 4D MRA sequence and 4D flow assessment.

At time of consent, patients will be asked if they wish to have the additional coronary 4D MRA scan at the British Heart Foundation scanner (following their FeMRA scan at the Queen Elizabeth University Hospital). No additional contrast administration is required for the 4D coronary MRA scan which will last for approximately 60 minutes. Patients that will consent will be offered lunch and transport to the University site. The 4D MRA scan will take place 2-4 hours after the FeMRA scan. This scan will also be supervised by the doctors directly involved in the study who are aware of the study protocol, and who are trained on procedures to be followed in the event of any reaction.

5.2.3 Blood processing and storage

Venous blood will be collected at baseline and at 6 weeks after fistula (or graft) creation. Venous blood will be analysed for vascular biomarkers, which may include TGFß, high sensitivity troponin I (hs-TNI), pentraxin 3, ICAM-1, von Willebrand factor (vWF), tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1). Novel biomarkers of endothelial function continue to emerge and we shall seek the permission of research participants for stored blood samples to be analysed in the future.

The total amount of research blood taken at each visit will be no more than 30ml. Samples will be anonymised in the laboratory. No identifiable details will be collected with the samples. If agreement is given for potential novel biomarkers, 10ml of blood will be anonymously stored – any subsequent analysis of these samples will be subject to approval of a Research Ethics Committee prior to analysis. On the completion of this study, the blood samples will be transferred and retained to the NHS Greater Glasgow & Clyde biorepository. This will enable the samples to be stored and used within a suitable research governance framework.

5.3 Study visits

Each patient will have one (if assessed as a potential kidney transplant recipient) or two (if planned for vascular access creation) study visits. We are proposing to perform FeMRA at 6 weeks following fistula creation as at that point it is generally apparent whether a fistula will mature without additional intervention[30, 31].

Participants will be provided with a patient information sheet (PIS) and given at least 24 hours to consider their response before consent is taken and a screening visit is performed to check their eligibility by all the criteria. Standard imaging tests will take place as part of the routine clinical care. The FeMRA scan will be requested and scheduled at a suitable date and time - usually the scan will be within two weeks after they sign the consent form. For practical reasons, the scans will be booked in different dates. There is not a minimum elapsed time recommended between the two scans as they are using different contrast agents that are not interfering with each other's imaging quality, but we will ensure they will occur at least 48 hours apart to have enough time to monitor for potential unexpected adverse events. We will also schedule all scans on non-dialysis days for those patients who are on dialysis.

All study investigations will take place at the Queen Elizabeth University Hospital. For patients that will consent to have the cardiac 4D MRA scan in addition to the FeMRA scan as part of the sub-study, this will take place at the University MRI site (Glasgow Cardiovascular Research Centre, British Heart Foundation Centre of Excellence) the same day. Travel expenses will be provided for study visits. In addition, lunch and transport to the University site will be offered for the patients having the cardiac 4D MRA scan.

5.4 Duration of participation

The participant would only be in the study in person up to the completion of the study investigations. This means one day for the patients in group A (for the day of their MRI scan and blood samples) and 6 weeks for the patients in group B (up until their second MRA scan and blood samples).

Unless they withdraw from the study, the patients will remain in the study for the entire duration of the follow up for up to 2 years. Follow up involves regular review of the medical records for identification of any outcomes of interest. Their imaging would remain available for review after the end of the study. As the clinicians should be blinded to the results of the investigational scan (unless there is a finding that threatens the participant's health), we will ensure that the FeMRA scans will be reported no sooner than 6 weeks after they are performed. The images will be uploaded to the Scottish National Picture Archive and Communication System (PACS) immediately after the scans are carried out.

6. Study Population

The study is expected to enroll 40 participants undergoing imaging for pre-transplant candidacy assessment and 60 undergoing creation of new fistula (or graft) for dialysis.

6.1 Inclusion criteria

1. Planned surgical creation of an autogenous upper-extremity fistula or synthetic graft.
   AND
   Current treatment with maintenance haemodialysis or anticipated treatment with maintenance haemodialysis within 6 months after planned fistula or graft creation surgery.

   OR
   Planned imaging of abdominopelvic vasculature as part of pre-transplant assessment.

2. Anticipated ability to comply with study procedures.

3. Ability to provide informed consent.

6.2 Exclusion criteria

1. Life expectancy ≤6 months.

2. Frail, elderly patients with multiple or serious co-morbidities (doctor's discretion).

3. Pregnancy, lactation or women of child-bearing potential not willing to use effective contraception for the duration of the study.

   Childbearing potential is defined as women who have experienced menarche and who have not undergone successful surgical sterilisation or who are not post-menopausal (irregular menstrual periods, or amenorrhoea >12 months, with serum follicle stimulating hormone (FSH) >35mIU/ml; women taking hormone replacement therapy (HRT)).

   Women of childbearing potential will be eligible if they are willing to use effective contraception (combined oral contraceptives, progesterone only contraceptives, intrauterine device, and barrier methods) or they are abstinent due to lifestyle choice or their partner is sterile (vasectomy).

4. Standard contra-indications to MRI: the presence of certain metallic objects in the body (e.g. non-MRI compatible cardiac pacemaker, artificial joints, previous cranial surgery with ferromagnetic clips, metal fragments in eye, etc.) and severe claustrophobia.

5. History of allergic reaction to any intravenous iron product, known hypersensitivity to excipients, asthma, eczema, atopy, patients with immune or inflammatory conditions (e.g. systemic lupus, rheumatoid arthritis), any conditions associated with iron overload (e.g. haemochromatosis, chronic liver disease, or blood disorders requiring frequent blood transfusions), and known history of drug allergy.

6. Any other reason considered by a study physician to make subject inappropriate for inclusion.

6.3 Informed consent

The chief investigator (CI) will be responsible to explain the nature and purpose of the study to the patient prior to study entry. A detailed PIS will be given to the patient and written informed consent obtained before study entry. A period of at least 24 hours will be given for the patient to consider entry to the study prior to obtaining written consent and all efforts will be made to ensure that patients understand the commitment required to fulfill the study requirements. Patients will also be made aware that participation is voluntary and that they can leave the study at any time without their standard care being affected.

The participant will be informed and must agree to their medical records being inspected by regulatory authorities, research ethics committee (REC) and monitors but it will be explained that their name will not be disclosed outside the study site.

Participants will be given an alert card to be carried at all times whilst they are participating in the study containing details of the study drug and contacts.

6.4 Potential risks and benefits

Ferumoxytol is specifically licensed for the treatment of IDA in patients with CKD. This is currently used in the USA and Canada but not in Europe as the company has withdrawn the drug from the market purely for commercial reasons. Nonetheless, Ferumoxytol is still available in the UK and is used as an unlicensed medicine for imaging purposes. As with any medicinal compound there is potential for adverse reactions, though the rates of these in clinical trials and post-marketing safety data on therapeutic use of Ferumoxytol are very low[23, 32-34]. The main concern has been reported cases of 'anaphylactic' type reactions with therapeutic bolus injections of undiluted compound leading to the recent recommendations for controlled infusion of dilute Ferumoxytol. Rather than true allergy it is thought this is a chemotoxic phenomenon related to high concentrations of the iron compound when infused rapidly interacting with mast cells in the vascular wall[35].

We propose to use only a fraction of the therapeutic dose (approximately a quarter of the full dose for a 70kg adult), much-diluted and slowly infused to avoid the risk of reaction. We will undertake careful monitoring of patients during the infusions and following scans patients will undergo a period of close observation.

We have experience with the use of Ferumoxytol in a study investigating a different imaging property in greater than 600 subjects. No serious adverse events were recorded. We have also undertaken clinically indicated MRI scans using Ferumoxytol as contrast agent in an expanding cohort of patients with advanced renal failure in whom other imaging methods have proven problematic. Other centres performing similar MRI work have seen no instances of this type of acute adverse reaction in large (>100) cohorts of patients. A recent survey (05/2015) of all sites using Ferumoxytol world-wide found that there had been about 3,000 imaging-related administrations without any serious adverse events reported. Other investigators have shown the safety and utility of Ferumoxytol in its use for clinical diagnostic imaging in pediatric patients with CKD[25].

It is important to note that the above risks have parity with the other commonly administered intravenous radiological contrast media (whether iodine or gadolinium-based). Patients will therefore not be exposed to disproportionate risk.

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic haemosiderosis though this is unlikely to occur with the very small doses of iron used for imaging. These patients have regular monitoring of serum iron, ferritin and transferrin bound iron as part of their routine clinical care. The results of the above tests will be retrieved and reviewed by the study investigators.

Administration of Ferumoxytol may transiently affect the diagnostic ability of MRI and alteration of MRI studies may persist for up to 3 months following infusion. This is the case when the higher therapeutic doses are used for iron supplementation. We are not expecting this effect with the much lower doses we are proposing to use for imaging purposes.

In any case, anticipated MRI studies should be conducted prior to the administration of Ferumoxytol. If MRI is required within 3 months after Ferumoxytol administration, use of T1- or proton density-

weighted MR pulse sequences to minimise the Ferumoxytol effects will be performed; MRI using T2*-weighted pulse sequences for iron estimation purposes will not be performed earlier than 4 weeks after the administration of Ferumoxytol.

In any case, Ferumoxytol may affect the appearances only of certain organs (e.g. liver or bones) and this is not different of what happens when intravenous iron (any preparation) is administered for therapeutic purposes. The information of iron administration as a contrast agent will be available to the clinicians to avoid any misinterpretation of future MRI scans. Ferumoxytol does not interfere with any other imaging modalities available for diagnosis. There is no direct benefit to the research participant. They will have the knowledge that their participation is helping to develop new methods to investigate disease in patients such as themselves in future.

6.5 Withdrawing from the study

The patient can withdraw or should be withdrawn under the following conditions:

- The patient is free to withdraw from the study at any point without giving reason.
- The patient can be withdrawn at any point in time where the CI or PI believes it is in their best interest.
- The patient is unable to adhere to the study e.g. attending for MRI scan.
- The patient has an adverse reaction to Ferumoxytol.

Data from patients who withdraw will be included in the final analysis with their consent. If they prefer they can choose to have all previously collected data destroyed.

6.6 Confidentiality

Data (e.g. MRI scans) will be anonymised with only a study code identifying data for the purposes of research analysis on university network storage. Each patient will have a clinical research file (CRF) created with the link to this held in a locked office in BHF Cardiovascular Research Building.

All referrals for imaging are made through password-protected software. The referrals can only be read by password-protected software. The imaging data obtained from the study is recorded on computers within a building with secure access. These computers, and the imaging software on them, are also password-protected. Images and reports subsequently transferred to the Scottish National PACS are also only accessible via password-protected software for those involved in patient care.

7. Study Outcomes

7.1 Primary outcome

The primary outcome is comparison of FeMRA with standard imaging techniques in assessment of vascular anatomy. Multiple cross sections of various vascular beds obtained with currently used imaging techniques will be compared with matched sections obtained with FeMRA in a blinded fashion (Table 2). The emphasis is generally on imaging quality and diagnostic accuracy on identification of clinically significant anatomic characteristics or lesions (Table 3).

7.2 Secondary outcomes

1. Anatomical predictors of ultrasound-based anatomical fistula maturation at 6 weeks after creation.

   Criteria of ultrasound-based fistula maturation include:

   - AVF lumen diameter >4mm *and*
   - AVF blood flow >500mL/min

2. Fistula or graft complications: stenosis, thrombosis, hand ischaemia, aneurysm or pseudoaneurysm, infiltration, fistula bleeding, and infection.

3. Fistula or graft procedures: surgical revision, angioplasty, stent placement, thrombolysis or thrombectomy, ligation of accessory veins, superficialisation of vein, transposition of vein, central venous catheter use, and placement of new arteriovenous access.

4. Utility of FeMRA in assessment of cardiac anatomy, function and microcirculation kinetics before listing for kidney transplantation.

5. Association between cardiac function and fistula (or graft) outcomes assessed by FeMRA.

6. Effect of successful fistula (or graft) creation on cardiac function assessed by FeMRA.

7. Utility of FeMRA to characterise changes in cardiac microcirculation kinetics following formation of a dialysis fistula or graft (ischaemic pre-conditioning hypothesis).

8. Utility of FeMRA in assessment of cardiac morphology, coronary blood supply, microvascular perfusion, and tissue characterisation (sub-study).

8. Data collection & management

8.1 Data collection

The data will be collected by the research fellow (CI) on paper with subsequent transcription to electronic form. The medical notes will act as source data for demographics, past medical history, medications and blood results.

8.2 Data storage

Anonymised data will be stored on University of Glasgow computers and hardware encrypted hard drives, accessed by members of the primary research team only. Each patient will have a CRF created with the link to this held in a locked office in BHF Cardiovascular Research Building. Clinical imaging data will be stored on the National PACS and will remain stored on this password-protected system for as long as imaging on any patient in Scotland is stored. Access is available to any healthcare professional with credentials that allow access to PACS within the ethical boundaries of Good Medical Practice as defined by the General Medical Council.

The CI will have control of and act as the custodian for the data generated by the study.

9. Statistical Considerations

The general analytical approach will be to estimate accuracy (95% CI), sensitivity (95% CI) and specificity (95% CI) of FeMRA and standard imaging techniques. In addition, Cohen's κ with 95% CI will be computed to compare arterial sections that can be assessed with both imaging techniques (i.e. FeMRA vs. CTA/US) and quantify the agreement between the FeMRA and standard imaging findings. A value of κ>0.7 indicates a high level of agreement. For venous sections that can only be assessed with FeMRA (i.e. central veins in thorax, veins in lower limbs) percentages and confidence intervals will be used.

Because multiple image locations from each patient will be used for the statistical evaluation (at least 20 vascular cross sections from each scan), the interdependence of each location for a given patient examination will be assessed by use of a κ statistic. A value of κ<0.4 indicates weak or no interdependence.

We initially aimed to recruit 30 patients in each group (60 patients in total). If we assume that FeMRA will identify 10% more clinically significant vascular anatomic characteristics compared with CTA/US, then one would need to study 180 vascular sections in total to show a significant difference between tests using chi-squared test, assuming power of 80% and probability of type 1 error of 5%.

We reviewed the data from the first 17 patients to ensure our sample size of 60 patients would be sufficient to confirm our study hypothesis. From these patients, 8 were in group A, and 9 were in group B.

A total of 340 vascular sections were assessed by one observer. Image quality on steady-state acquisitions was scored as grade 4 in 260 of 340 (76.5%, 90% confidence interval 72-79%) and grade 3 in 80 of 340 (23.5%) vascular sections (at least diagnostic quality) when assessing the arterial and venous vasculature with FeMRA. There were no arterial anatomic characteristics or lesions of clinical significance that were identified on CTA and not on FeMRA (and vice versa) in group A. In group B FeMRA identified 2% more significant arterial stenoses compared with US. There was very good agreement on assessment of image quality in arteries between FeMRA and CTA (kappa=0.85) and moderate agreement between FeMRA and US (kappa=0.65). On assessment of the venous vasculature, 5% more anatomical characteristics of significance (i.e. stenosis, occlusion, aneurysm, presence of thrombus) were identified with FeMRA compared with standard imaging methods (which cannot assess venous vasculature).

Based on these preliminary findings, we aim to increase the number of participants (40 in group A, 60 in group B) to ensure adequate power to reject a false null hypothesis, as FeMRA can identify 3-5% more clinically significant vascular anatomic characteristics compared with CTA/US (rather than 10% that was initially assumed).

To evaluate associations between anatomical predictor variables and outcomes, multiple linear and logistic mixed-effects regression models will be used. Associations of fistula and graft outcomes with predictors will be treated as uniform across all anatomical configurations unless there is strong statistical or biological evidence to suggest otherwise. Based on data from a retrospective study performed in our centre[36] we assume a fistula failure rate of 30% (40% for patients on dialysis and 20% for pre-dialysis patients).

10. Study conduct responsibilities

10.1 Protocol amendments

Any changes to the final approved protocol will require an amendment. The CI will liaise with the sponsor to determine whether an amendment is substantial or non-substantial. Amendments to the protocol will be submitted in writing to the Sponsor for approval prior to being submitted to the appropriate REC, Regulatory Authority and local NHS Research and Development (R&D) for approval. All approvals will be in place prior to participants being enrolled into an amended protocol. All amended versions of the protocol will be signed by the CI and the sponsor representative.

10.2 Protocol violations and deviations

The CI will not implement any deviation from the protocol without agreement from the Sponsor, appropriate REC, Regulatory Authority and without local NHS R&D approval, except where necessary to eliminate an immediate hazard to trial participants.

In the event that any study investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented in a Breaches & Deviations Log and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, Regulatory Authority and local NHS R&D for review and approval as appropriate.

10.3 Study record retention

As the data from this study does not form part of an application for a Marketing Authorisation all study documentation, including medical case notes, will be kept for at least 5 years.

10.4 Study auditing

The study will be subject to auditing by the sponsor, depending on the sponsor's risk assessment and audit schedule. The CI will permit trial related monitoring, audits, REC review, and regulatory inspections. In the event of an audit, the CI agrees to allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records and source documentation.

10.5 End of study

The study will conclude after the last participant's last visit.

The CI has the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor, REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor, REC and Regulatory Authority within 1 year of the end of the study.

10.6 Archive

On completion of the study, the protocol, data, and report will be archived in the sponsor archives. Data will be stored anonymously and for a period of 5 years.

11. Reports, Dissemination of findings

11.1 Authorship policy

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

11.2 Reports

Annual reports will be submitted to the approving ethical committee and the sponsor. A final report will also be issued to these groups. No patient identifiable data will be included.

11.3 Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

Patients will be provided with a summary in lay language of the results of the study in the form of a simple letter including thanks/acknowledgment of participation.

11.4 Peer review

Peer review of the protocol will occur via the Sponsorship Committee and of the resulting publication by the referees of the journal to which the paper (and its protocol) will be submitted.

This study will be submitted for further funding and peer review to the NHS GG&C Research Endowment Fund Allocation and British Renal Society.

12. Pharmacovigilance

12.1 Definition of adverse events

The following definitions will be used.

- **Adverse Reaction (AR):** any untoward and unintended response in a subject to a research product which is related to any dose administered to that subject.
- **Serious Adverse Event Reporting:** a Serious Adverse Event (SAE) is defined as an untoward occurrence that: (a) results in death; (b) is life-threatening; (c) requires hospitalisation or prolongation of existing hospitalisation; (d) results in persistent or significant disability or incapacity; (e) consists of a congenital anomaly or birth defect; or (f) is otherwise considered medically significant by the investigator.

12.2 Adverse event recording

AEs must be recorded, assessed, reported, analysed and managed in accordance with the Research Governance Framework for Health and Community Care and the study protocol. All AEs must be assessed for seriousness.

12.3 Serious adverse events and serious adverse reactions recording and reporting

Where an SAE requires recording, full details should be documented including the nature of the event, start and stop dates, severity, relationship to research product and/or procedures. Outcome will be recorded in the patient's CRF and medical notes. These events will be monitored and followed up until satisfactory resolution and stabilisation. SAEs must be assessed to determine if related to the research procedures (includes administration of research products) and expectedness.

- **Related:** that is, it resulted from administration of research products or any of the research procedures.
- **Expectedness for SAR:** that is, the expectedness of an adverse reaction to administered research products is assessed against the prescribing information available for Ferumoxytol injection.
- **Expectedness for SAEs**: is assessed against the research procedure events listed in the study protocol as an expected occurrence.

All SAEs and SARs must be reported to the pharmacovigilance (PV) office immediately (within 24 hours) using the generic non-clinical trial of an investigational medicinal product (CTIMP) SAE form which is available from http://www.glasgowctu.org/data/SAE_non-CTIMP.pdf. The SAE form should be completed and signed by appropriately delegated staff. The form should be faxed or e-mailed to the PV Office (pharmacovig@glasgowctu.org) and a copy placed in the Study Site File. If necessary a verbal report can be given by contacting the PV Office on 0141 330 4744. This must be followed up as soon as possible with a signed written (or electronic) report.

If all of the required information is not available at the time of initial reporting, the CI (or designee) must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow up information for a previously reported event.

12.4 Reporting of SARs and SAEs to the Ethics Committee

Reports of SARS and SAEs should be submitted within 15 days of the CI becoming aware of the event, using the 'report of serious adverse event form' for non-CTIMPs published on the Health Research Authority web site: http://www.hra.nhs.uk/documents/2015/02/safety-report-form-non-ctimp.docx. The form should be completed in typescript and signed by the CI.

12.5 Annual progress reports

The CI must also provide an annual progress report to the REC. A report on the safety of participants will be included as part of this report.

12.6 Reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA)

Whilst there is no statutory requirement to report to the MHRA, adverse reactions to Ferumoxytol may be reported to the MHRA YellowCard Scheme (www.mhra.gov.uk/yellowcard).

13. References

1. Collidge, T.A., et al., *Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort.* Radiology, 2007. **245**(1): p. 168-75.
2. Andres, A., et al., *Helical computed tomography angiography is the most efficient test to assess vascular calcifications in the iliac arterial sector in renal transplant candidates.* Transplant Proc, 2003. **35**(5): p. 1682-3.
3. Taal, M.W., L.J. Chesterton, and C.W. McIntyre, *Venography at insertion of tunnelled internal jugular vein dialysis catheters reveals significant occult stenosis.* Nephrol Dial Transplant, 2004. **19**(6): p. 1542-5.
4. Tonelli, M., et al., *Screening for subclinical stenosis in native vessel arteriovenous fistulae.* J Am Soc Nephrol, 2001. **12**(8): p. 1729-33.
5. Tonelli, M., et al., *Ultrasound monitoring to detect access stenosis in hemodialysis patients: a systematic review.* Am J Kidney Dis, 2008. **51**(4): p. 630-40.
6. Munda, R., et al., *Polytetrafluoroethylene graft survival in hemodialysis.* JAMA, 1983. **249**(2): p. 219-22.
7. Lok, C.E., et al., *Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I).* J Am Soc Nephrol, 2006. **17**(11): p. 3204-12.
8. Pandeya, S. and R.M. Lindsay, *The relationship between cardiac output and access flow during hemodialysis.* ASAIO J, 1999. **45**(3): p. 135-8.
9. Sandhu, J.S., et al., *Hemodynamic effects of arteriovenous fistula in end-stage renal failure.* Ren Fail, 2004. **26**(6): p. 695-701.
10. Basile, C., et al., *The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients.* Nephrol Dial Transplant, 2008. **23**(1): p. 282-7.
11. Castillo, R., et al., *Defective platelet adhesion on vessel subendothelium in uremic patients.* Blood, 1986. **68**(2): p. 337-42.
12. Igata, M., et al., *Adenosine monophosphate-activated protein kinase suppresses vascular smooth muscle cell proliferation through the inhibition of cell cycle progression.* Circ Res, 2005. **97**(8): p. 837-44.
13. Pardali, E., M.J. Goumans, and P. ten Dijke, *Signaling by members of the TGF-beta family in vascular morphogenesis and disease.* Trends Cell Biol, 2010. **20**(9): p. 556-67.
14. Milburn, J.A., et al., *Thrombin-anti-thrombin levels and patency of arterio-venous fistula in patients undergoing haemodialysis compared to healthy volunteers: a prospective analysis.* PLoS One, 2013. **8**(7): p. e67799.
15. Smits, J.H., et al., *Coagulation and haemodialysis access thrombosis.* Nephrol Dial Transplant, 2000. **15**(11): p. 1755-60.
16. Papayianni, A., et al., *Circulating levels of ICAM-1, VCAM-1, and MCP-1 are increased in haemodialysis patients: association with inflammation, dyslipidaemia, and vascular events.* Nephrol Dial Transplant, 2002. **17**(3): p. 435-41.
17. Lobo, J.C., et al., *Is there association between uric acid and inflammation in hemodialysis patients?* Ren Fail, 2013. **35**(3): p. 361-6.
18. de Graaf, R., et al., *Human heat shock protein 60 stimulates vascular smooth muscle cell proliferation through Toll-like receptors 2 and 4.* Microbes Infect, 2006. **8**(7): p. 1859-65.

19. Prince, M.R., et al., *A pilot investigation of new superparamagnetic iron oxide (ferumoxytol) as a contrast agent for cardiovascular MRI.* J Xray Sci Technol, 2003. **11**(4): p. 231-40.
20. Chalouhi, N., et al., *The emerging role of ferumoxytol-enhanced MRI in the management of cerebrovascular lesions.* Molecules, 2013. **18**(8): p. 9670-83.
21. Bashir, M.R., et al., *Emerging applications for ferumoxytol as a contrast agent in MRI.* J Magn Reson Imaging, 2015. **41**(4): p. 884-98.
22. Hasan, D., et al., *Early change in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm: a pilot study.* Stroke, 2012. **43**(12): p. 3258-65.
23. Macdougall, I.C., et al., *A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD.* Clin J Am Soc Nephrol, 2014. **9**(4): p. 705-12.
24. Mukundan, S., et al., *Ferumoxytol-Enhanced Magnetic Resonance Imaging in Late-Stage CKD.* Am J Kidney Dis, 2016.
25. Nayak, A.B., et al., *High-resolution, whole-body vascular imaging with ferumoxytol as an alternative to gadolinium agents in a pediatric chronic kidney disease cohort.* Pediatr Nephrol, 2015. **30**(3): p. 515-21.
26. Bremerich, J., D. Bilecen, and P. Reimer, *MR angiography with blood pool contrast agents.* Eur Radiol, 2007. **17**(12): p. 3017-24.
27. Ersoy, H., et al., *Blood pool MR angiography of aortic stent-graft endoleak.* AJR Am J Roentgenol, 2004. **182**(5): p. 1181-6.
28. Walker, J.P., et al., *Ferumoxytol-enhanced magnetic resonance angiography is a feasible method for the clinical evaluation of lower extremity arterial disease.* Ann Vasc Surg, 2015. **29**(1): p. 63-8.
29. American Institute of Ultrasound in, M., R. American College of, and U. Society of Radiologists in, *AIUM practice guideline for the performance of ultrasound vascular mapping for preoperative planning of dialysis access.* J Ultrasound Med, 2012. **31**(1): p. 173-81.
30. Asif, A., P. Roy-Chaudhury, and G.A. Beathard, *Early arteriovenous fistula failure: a logical proposal for when and how to intervene.* Clin J Am Soc Nephrol, 2006. **1**(2): p. 332-9.
31. Ferring, M., J. Henderson, and T. Wilmink, *Accuracy of early postoperative clinical and ultrasound examination of arteriovenous fistulae to predict dialysis use.* J Vasc Access, 2014. **15**(4): p. 291-7.
32. Hetzel, D., et al., *A Phase III, randomized, open-label trial of ferumoxytol compared with iron sucrose for the treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy.* Am J Hematol, 2014. **89**(6): p. 646-50.
33. Vadhan-Raj, S., et al., *Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron.* Am J Hematol, 2014. **89**(1): p. 7-12.
34. Auerbach, M., et al., *Safety and efficacy of total dose infusion of 1,020 mg of ferumoxytol administered over 15 min.* Am J Hematol, 2013. **88**(11): p. 944-7.
35. Bircher, A.J. and M. Auerbach, *Hypersensitivity from intravenous iron products.* Immunol Allergy Clin North Am, 2014. **34**(3): p. 707-23, x-xi.
36. Stoumpos, S., et al., *Predictors of sustained arteriovenous access use for haemodialysis.* Am J Nephrol, 2014. **39**(6): p. 491-8.

Table 1. Infusion protocol				
Weight (kg)	**Ferumoxytol Dose (mg)**	**Volume of Ferumoxytol injection required to prepare infusion (ml)** (1ml of solution contains 30mg iron as ferumoxytol)	**Volume of 0.9% sodium chloride required to prepare final infusion (ml)**	**Final prepared Ferumoxytol infusion volume (ml)**
40-45	135	4.5	18.0	22.5
46-50	150	5.0	20.0	25.0
51-55	165	5.5	22.0	27.5
56-60	180	6.0	24.0	30.0
61-65	195	6.5	26.0	32.5
66-70	210	7.0	28.0	35.0
71-75	225	7.5	30.0	37.5
76-80	240	8.0	32.0	40.0
81-85	255	8.5	34.0	42.5
86-90	270	9.0	36.0	45.0
91-95	285	9.5	38.0	47.5
96-100	300	10.0	40.0	50.0
≥100	300	10.0	40.0	50.0

Table 2. Vessel locations to be assessed		
Pre-transplant assessment	**Vascular mapping**	**Fistula (or graft) surveillance**
Arterial vasculature	***Vein mapping (peripheral veins)***	Inflow artery proximal to the fistula or graft
Abdominal aorta	Cephalic vein at the proximal upper arm	Inflow artery distal to the fistula or graft
Coeliac artery	Cephalic vein at the mid-upper arm	Anastomotic sites (fistula has one site, graft has two sites)
Superior mesenteric artery	Cephalic vein at the distal upper arm	Puncture sites
Inferior mesenteric artery	Cephalic vein at the antecubital fossa	Outflow vein proximal to the fistula or graft
Renal arteries	Cephalic vein at the proximal forearm	Outflow vein middle to the fistula or graft
Common iliac arteries	Cephalic vein at the mid-forearm	Outflow vein distal to the fistula or graft
External iliac arteries	Cephalic vein at the distal forearm	External jugular veins
Internal iliac arteries	Cephalic vein at the wrist	Subclavian veins
Venous vasculature	Basilic vein at the proximal upper arm	Axillary veins
Inferior vena cava	Basilic vein at the mid-upper arm	Brachiocephalic veins
Renal veins	Basilic vein at the distal upper arm	Superior vena cava
Common iliac veins	Basilic vein at the antecubital fossa	
External iliac veins	***Vein mapping (central veins)***	
Internal iliac veins	External jugular veins	
Common femoral veins	Subclavian veins	
Superficial femoral veins	Axillary veins	
Profunda femoral veins	Brachiocephalic veins	
Greater saphenous veins	Superior vena cava	
Popliteal veins	***Arterial mapping***	
	Brachial artery at the antecubital fossa	
	Radial artery at the wrist	
	Level of brachial artery bifurcation relative to the antecubital fossa	

Table 3. Anatomical characteristics or lesions to be assessed
Artery diameter
Vein diameter
Stenosis
Occlusion
Vessel irregularity
Luminal narrowing
Wall thickening
Calcification
Aneurysm/pseudoaneurysm
Presence of thrombus
Fistula (or graft) specific
Vein depth from skin surface
Fistula (or graft) diameter
Fistula (or graft) stenosis
Fistula (or graft) thrombosis
Inflow stenosis
Outflow stenosis
Length of straight segment for cannulation
Blood flow rate