FORM FRM4894/1

CTU Protocol

NHS Blood and Transplant

SONAR

Surveillance Of arteriove Nous fistul Ae using ult Rasound

A prospective observational cohort study to determine whether ultrasound surveillance can reliably predict arteriovenous fistulae failure in patients with chronic kidney disease.

Version: 1.0
Date: 20/06/2018

ISRCTN: [Insert Number]
REC: [Insert number]

NHSBT CTU Ref: 17/99

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS Foundation Trust

Approved by:

Name	Role	Signature	Date
Gavin Pettigrew	Chief Investigator		
Helen Thomas	Principal Statistician		
Alison Deary	Head of Operations		
Renate Hodge	Clinical Data Services Manager		

General Information

This document was constructed using the National Health Service Blood and Transplant Clinical Trials Unit (NHSBT CTU) Protocol Template FRM4894 Version 1.0, which is based on the SPIRIT guidelines 2013 (1, 2). It describes the SONAR study, coordinated by the NHSBT CTU and provides information about procedures for entering patients/participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the study, but sites entering participants for the first time are advised to contact the Trial Manager to confirm they have the most up to date version.

Compliance

The study will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2013), the Principles of Good Clinical Practice (GCP), the UK Data Protection Act, the General Data Protection Regulation, the UK Policy Framework for Health and Social Care Research and any other applicable national regulations.

Sponsor

Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge is the primary study sponsor and has delegated responsibility for the overall management of the SONAR study to the NHSBT CTU. Queries relating to the sponsorship of the study should be addressed to the R&D Office, block S Level 4, Addenbrooke's Hospital, Cambridge, Hills Road, CB2 0QQ.

Funding

This study is funded by the NIHR Health Technology Assessment Board, grant number 17/27/11.

Authorisations and Approvals

This study was approved by the National Institute of Health Research and is therefore part of the Clinical Research Network portfolio.

Trial Registration

This study will be registered with the ISRCTN Clinical Trials Register.

Trial Administration

Please direct all enquiries to the Trial Manager in the first instance. Clinical queries will be passed to the Chief Investigator via the Trial Manager.

CTU Details

NHSBT CTU NHS Blood and Transplant Long Road Cambridge CB2 0PT	Administration Office:	01223 588088
	Fax:	01223 588136
	Email:	SONAR@nhsbt.nhs.uk

Coordinating CTU Staff Details

Trial Manager	Anna Sidders	Tel:	01223 588915
		Email:	anna.sidders@nhsbt.nhs.uk
Data Manager	Valerie Hopkins	Tel:	01223 588188
		Email:	valerie.hopkins@nhsbt.nhs.uk
Statistician	Cara Hudson	Tel:	01179 757432
		Email:	cara.hudson@nhsbt.nhs.uk
Project Manager	Claire Foley	Tel:	01223 588151
		Email:	claire.foley@nhsbt.nhs.uk

Chief Investigator

Professor/Dr	Mr Gavin Pettigrew	Tel:	07841004696
Department	University Department of Surgery	Email:	gjp25@cam.ac.uk
Institution	University of Cambridge		
Address Line 1	Box 202, Level E9		
Address Line 2	Cambridge Biomedical Campus		
City	Cambridge		
County, Post Code	CB2 0QQ		
Country	UK		

Co-Investigators

Mr Ayaz Hossain	Cambridge University Hospital, Hills Rd, Cambridge
Mr Vasilis Kosmoliaptsis	Cambridge University Hospital, Hills Rd, Cambridge
Mr Dom Summers	Cambridge University Hospital, Hills Rd, Cambridge
Mr James Richards	University of Cambridge, Cambridge
Ms Emma Aitken	Cambridge University Hospital, Hills Rd, Cambridge
Mr Matthew Slater	Department of Vascular Studies, Cambridge University Hospital
Dr Edward Wilson	Cambridge Centre for Health Services Research, University of Cambridge, Cambridge
Ms Alison Deary	NHSBT, Bristol
Mrs Helen Thomas	NHSBT, Bristol
Mrs Cara Hudson	NHSBT, Bristol
Dr Thomas Hiemstra	Cambridge University Hospitals, Cambridge
Mr Rajesh Sivaprakasam	The Royal London Hospital, Whitechapel Rd, London
Miss Kate Crawford	Vascular Studies Unit, The Royal London Hospital, London
Mr Nicholas Barnett	Guy's Hospital, Great Maze Pond, London
Mr Abbas Ghazanfar	St Georges Hospital, Blackshaw Rd, Tooting London
Dr Subash Somalanka	St Helier Hospital, Wrythe Lane, Sutton Surrey
Mr Atul Bagul	Leicester General Hospital, Gwendolen Rd, Leicester
Mr Simon Knight	Churchill Hospital, Old Road, Headington, Oxford
Mr Andrew Tambyraja	Edinburgh Royal Infirmary, 51 Little France Cres, Edinburgh
Mr Sam Turner	Southmead Hospital, Bristol, B10 5NB
Mr James Hunter	University Hospital Coventry & Warwick, Coventry
Mr Jeremy Crane	Hammersmith Hospital, Shepherd's Bush, London
Mr Sam Dutta	Nottingham University Hospital, Hucknall Rd, Nottingham
Mr Zia Moinuddin	Manchester Royal Infirmary, Oxford Rd, Manchester
Mr Paul Gibbs	Queen Alexandra Hospital, Southwick Hill Rd Portsmouth
Mr Reza Motallebzadeh	Royal Free Hospital, Pond St, Hampstead, London
Mr Matthew Bartlett	Vascular Studies Unit, The Royal Free Hospital, Pond St, London

For full details of Trial Committees, please refer to Section 13.

Study Synopsis

Scientific title of clinical study	Surveillance of arteriovenous fistulae in haemodialysis
Public title of clinical study	Surveillance of arteriovenous fistulae in haemodialysis
Protocol Short Title/Acronym	SONAR - Surveillance Of arterioveNous fistulAe using ultRasound
Protocol Version and Date	v1.0, 20th June 2018
Primary Sponsor	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
Funder	NIHR Health Technology Assessment
Primary Clinical Trials Registry number	ISRCTN
Date Study Registered	
Study design	A prospective observational cohort study
Health Condition(s) or Problem(s) Studied	Patients in whom the creation of an arteriovenous fistula (AVF) is clinically indicated: this includes those patients either with established (dialysis dependant) or approaching End Stage Renal Disease (ESRD).
Key inclusion and exclusion criteria	***Inclusion criteria*:** 1. The participant is an adult, aged 16 years or older 2. The participant has end-stage renal disease and either requires haemodialysis or is likely to do so imminently. 3. The participant is due creation of an arm AVF (either wrist or elbow) including the following types of fistula: radiocephalic, ulno-basilic, brachiocephalic and brachiobasilic (one or two stage) fistula with a minimal acceptable threshold of 2 mm venous diameter at whatever site chosen. 4. The participant provides full informed consent to participate. ***Exclusion criteria:*** A patient will not be eligible for this study if he/she fulfils one or more of the following criteria: 1. Attempted formation of proximal neo-anastomosis at the forearm cephalic and basilic venous systems following failure of a standard radiocephalic or ulnobasilic fistula. 2. Participants with known central venous stenosis (including those who undergo simultaneous central venous angioplasty / stenting and AVF creation). 3. Participants in whom it is anticipated that it will not be possible to perform serial ultrasound scanning.

CTU Protocol

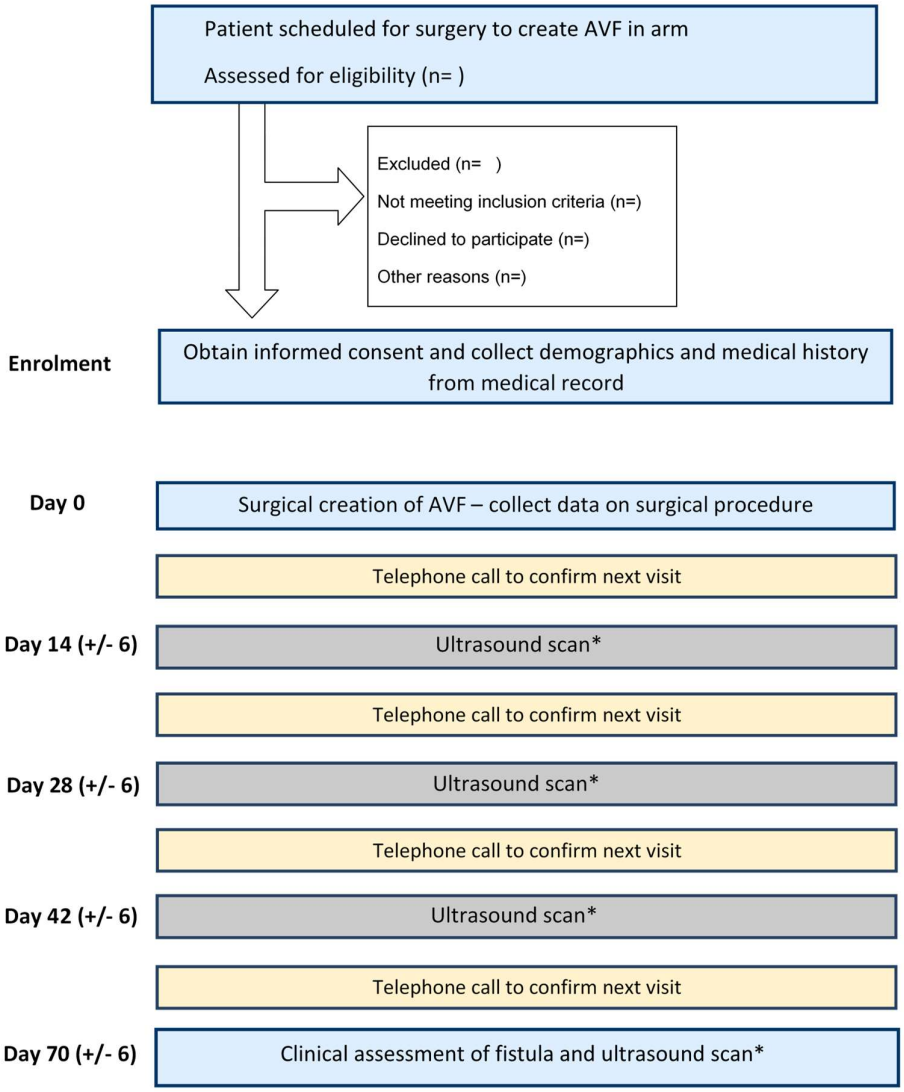
Setting	UK hospitals providing vascular access surgery and haemodialysis.
Interventions to be compared	For this prospective observational cohort study there will be no formal interventional comparison. Consenting participants who are enrolled will be observed for 10 weeks following creation of their AV fistula and will undergo Doppler ultrasound scans during weeks 2, 4, 6 and 10. Routine clinical examination will be undertaken as per local policy with a final clinical examination at week 10 to evaluate the success of the fistula formation.
Study hypothesis	Doppler ultrasound surveillance can reliably predict failing nascent AV fistulas by identifying potentially-correctable anatomical defects.
Primary outcome measure(s)	1. Primary fistula patency by week 10 according to surrogate ultrasound parameters (wrist fistula: minimum venous diameter 4mm, with flow >400 mls/min; elbow fistula: minimum venous fistula diameter 5mm, with flow >500mls/min (3)).
Key Secondary outcome measure (s)	Major secondary outcome measure(s): 1. For those patients established on dialysis, successful use of the fistula for dialysis on three successive occasions. 2. Clinical suitability for dialysis based on examination alone, 10 weeks after fistula creation. 3. Formation of a new fistula (including fashioning of proximal neoanastomosis) or radiological salvage procedure. 4. Fistula thrombosis. 5. Secondary fistula patency 6. Patient acceptability based on the proportion of patients that complete their scans.
Duration of Study	Set up: 3 months Recruitment: 18 months Close out: 3 months
Countries of recruitment	UK
Target Sample Size	347 participants
Date of first enrolment	Expected August 2018
Recruitment Status	Pending: participants are not yet being recruited or enrolled at any site
Contact Details for Public Queries	Anna Sidders, Trial Manager Clinical Trials Unit NHS Blood and Transplant Long Road Cambridge CB2 OPT anna.sidders@nhsbt.nhs.uk 01223 588915

CTU Protocol

Contact Details for Scientific Queries	Mr Gavin Pettigrew, Chief Investigator: gjp25@cam.ac.uk
CTU Project Manager	Claire Foley Claire.foley@nhsbt.nhs.uk
Lay Summary of Study	The kidneys are required for excretion of excess fluid and harmful toxins. If a person develops kidney failure, then build-up of toxins and fluid can be fatal within a few days. Consequently, patients with kidney failure require either a replacement kidney (kidney transplant) or for the excess fluid and toxins to be removed from the body by a process known as dialysis. Most patients who develop chronic kidney failure will need dialysis at some point. Two-thirds of patients with kidney failure (around 20,000 patients a year in the UK) receive regular dialysis through a machine (haemodialysis). Attachment to the machine requires either the placement of semi-permanent 'lines' (plastic tubing) into one of the big veins in the patient's chest, or the surgical creation of an 'arterio-venous fistula', in which one of the small arteries in the arm is joined directly to one of the veins. The vein becomes gradually bigger allowing for a greater flow of blood. The fistula vein can then have two needles inserted into it (''be needled'') to enable connection with the dialysis machine. The increased rate of blood flow within the fistula vein, coupled with the increased size and wall thickness of the vein, allow for successful, and repeated needling. Fistulas are the best option for most patients, as the risks of a life-threatening blood infection are about ten times less common than for patients who dialyse via their 'line'. Unfortunately, the creation of an arterio-venous fistula is not an exact science and up to half of them fail within a year of being created, despite a successful join at the time of surgery. The reasons why this happens and how we can prevent it are largely unknown. Our study will examine whether we can use 'Doppler ultrasound' (a non-invasive scan that uses high-frequency sound waves to create a picture of the blood flow in the fistula) to identify early problems with a fistula that may lead to it failing. To test whether ultrasound helps predict which fistulas will fail, we will recruit patients who need to have a fistula created. We will perform a series of scans in the weeks after the operation but we will not tell the patients or the clinicians the results. This should allow us to find out whether the scan helps to predict fistula failure or not, and when the best time is to perform the scan after the operation. If this study is able to show that we can use ultrasound to successfully identify fistulas that are not likely to mature, then we will proceed to undertake a second study, which does not form part of this protocol. This second study will evaluate whether it is possible to intervene at an early stage in those fistulas that are

	identified by ultrasound as unlikely to mature, and by doing so improve the longevity of the fistula (patency). There is still a great deal of debate about the role of ultrasound in predicting the chances that a fistula will mature successfully. This is important because the use of ultrasound is expensive, but also means that patients have additional scans that may not be needed. Our study, which will involve a number of large UK dialysis centres, will show clearly how effective or otherwise ultrasound is at predicting whether fistulas develop successfully, and whether this represents a good use of NHS funds. By doing so, we anticipate that our study will influence current dialysis practices here and abroad.

Study Schema



*The clinical team and the participants will be blinded to the results of the ultrasound scans.

Routine clinical assessments may be performed during the trial period, as per standard practice.

Contents

Abbreviations, Glossary and Definitions

AE	Adverse event
AR	Adverse reaction
AVF	Arteriovenous fistulae
BSA	Body Surface Area
CF	Consent form
CI	Chief Investigator
LCRN	Local Clinical Research Network
COM	Clinical Operations Manager
CRF	Case Report Form
CTU	NHSBT Clinical Trials Unit
CVC	Central Venous Catheter
DCF	Data Clarification Form
DH	Department of Health
DM	Data Manager
ERC	Endpoint Review Committee
ESRD	End stage renal disease
GCP	Good Clinical Practice
GP	General Practitioner
HE	Health Economics
HRA	Health Research Authority
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
IRAS	Integrated Research Application System
MRC	Medical Research Council
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NIHR	National Institute for Health Research
PALS	Patient Advice and Liaison Service
PI	Principal Investigator
PIS	Patient Information Sheet
PPV	Positive predictive value
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard operating procedure
SSI	Site Specific Information
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

Definitions

Primary patency: The interval between access creation to thrombosis event

Secondary patency: The interval between access creation to abandonment of the access including all radiological and surgical salvage procedures in between.

Clinical maturation: Suitability to cannulate based on clinical examination

Functional maturation: Ability for the access to achieve adequate dialysis

1. Background

1.1 Introduction

1.2 Summary of existing knowledge

The UK renal registry data highlights that the incidence of people commencing renal replacement therapy in the UK increased from 109 per million population (pmp) in 2013 to 115 pmp in 2014. This equates to some 7,500 patients each year, of whom approximately 70% receive haemodialysis as the first option, with as many as two thirds of these initially reliant on a central venous catheter (CVC) (5). As the population ages, it is anticipated that there will be a 5 to 10% increase in the UK dialysis population per annum.

Arteriovenous fistulas (AVFs) are considered the best modality for providing haemodialysis care in patients with end stage renal disease (ESRD). Compared to dialysis via an AVF, haemodialysis via a CVC is associated with an increased risk of catheter-related bloodstream infection, with an estimated incidence of 1.2–2.5 per 1000 patient-days (6-10). This results in increased hospitalisation and additional costs (11, 12). Patient mortality for patients dialysing via a CVC is ~40% higher than for patients dialysing via an AVF (13). There is therefore a clear incentive to form AVFs in patients requiring haemodialysis and current UK tariffs for haemodialysis have been deliberately set to incentivise dialysis via an AVF.

However, only 20% of UK dialysis centres currently achieve the 80% Renal Association target for dialysis of their prevalent population via definitive access, and many fall well short (5, 14). The reasons why such a small proportion of the prevalent dialysis population achieve dialysis via an AVF are multifactorial, but the relatively poor maturation rate, with as many as 50% of fistulas failing to mature, undoubtedly contributes. Although this failure may reflect inherent problems with arterial inflow to the fistula that are difficult to correct, at least in some cases, stenosis due to venous intimal hyperplasia is thought responsible. These may be identifiable by ultrasound surveillance and once detected, are potentially correctable by either radiological or surgical intervention. If so, the improved assisted primary fistula patency is likely to increase AVF usage substantially, as well as save money by avoiding the need to create a further AVF and to dialyse via a CVC. Increased AVF usage would also likely result in improved patient survival by avoiding CVC-related complications, and by preserving precious venous ‘capital’ for future fistula formation four to six weeks after fistula formation. It may be possible that assessment at these earlier time points is predictive of outcome.

The literature relating to the use of ultrasound surveillance to salvage failing arteriovenous fistula is however conflicting, and a consensus strategy has not been reached. This may reflect variations in: the type of surveillance adopted; the type of fistula under surveillance, and the precise ultrasound scanning method. Ultrasound can reliably identify fistulas that have successfully matured (15, 16), and although the precise ultrasonic characteristics that constitute a mature fistula continue to be debated (17), adoption of a surrogate ultrasound definition of maturity avoids exclusion of pre-dialysis patients from dialysis trials. We will adopt a similar approach for the current proposal. Few studies have attempted to use ultrasound to characterise early maturation, immediately after fistula creation, but those that do suggest that successful fistula maturation is associated with rapid increase in fistula blood flow, even by the first day after formation (3, 18). Fistula vein diameter may also increase rapidly (3). Thus, assessment at these earlier time points may be predictive of later values. In a study of 153 patients, Itoga et al. performed early duplex ultrasound on newly-formed fistulas (4-8 weeks after creation) (19). A flow limiting stenosis was detected in 40% of

patients, in whom 81% underwent subsequent radiological intervention. Assisted primary patency of the fistulas in this group (compared to the cohort without detectable ultrasound abnormality) was 83 vs 96% at six months and 64% vs 89% at one year. There was no control cohort (patients who did not undergo routine surveillance), but the assisted patency reported for the entire study population would appear to be better than generally reported following fistula creation. One randomised study to date (20) has evaluated routine early ultrasound surveillance (2, 4 and 8 weeks after fistula creation, 150 patients), and reported a 13.6% fistula failure / non-maturation rate in the surveillance group, compared to 25.4% in the control group in whom ultrasound was performed on the basis of a perceived clinical indication. This difference did not reach statistical significance, but notably, the study was powered for a 20% difference in maturation. Our proposed study is powered for a 10% difference, with a corresponding increase in numbers of enrolled patients.

1.3 Rationale for Study

Fistula surveillance is costly and given the paucity of evidence suggesting surveillance increases rates of dialysis via the fistula, it is not surprising that there is significant heterogeneity in practice across the UK.

This study aims to define if there is any benefit of a structured ultrasound-based surveillance programme in predicting whether AVFs can be used successfully for haemodialysis.

1.4 Study Design

The overall aim of this programme of research is to determine whether US surveillance of newly-formed AVFs can be used to identify failing fistulas and subsequent salvage intervention can be then used to maintain patency.

When after fistula creation should ultrasound surveillance be performed?
Although one year unassisted fistula patency (primary) is approximately 55%, about 60% of these failures will occur within the first three months after creation (21, 22), and it is likely that failures in the first year relate to individuals whose fistula had never developed optimally (23, 24).

We feel that for a trial to demonstrate that ultrasound surveillance improves patency rates for newly created fistula, two conditions must be met:

1. Ultrasound can effectively distinguish those newly-formed fistulas that are unlikely to mature.
2. Salvage interventions performed on those ‘at-risk’ fistulas are effective.

These questions will be answered in two phases:
Phase 1: A prospective observational cohort study to firstly determine whether US surveillance can reliably predict fistula failure.

Phase 2: A prospective randomised trial that examines one-year fistula patency and compares US surveillance against standard clinical assessment.

The outputs of phases 1 and 2, will form the primary inputs into a decision model predicting the incremental cost effectiveness of US surveillance versus standard clinical assessment.

This study protocol covers only phase 1 of the study. We will only move on to phase 2 if ultrasound is found to be effective at identifying ‘at-risk’ AVFs and this will be covered by a separate protocol and application.

Phase 1 will recruit patients who are either pre-dialysis or already established on haemodialysis via a central venous catheter (see study scheme). Consenting patients will undergo serial US scanning at weeks 2, 4, 6 and 10 after fistula formation in addition to standard care (such as regular clinical assessment) as per local centre policy. The US findings will be blinded, i.e. not be relayed to the participant or to the participant's clinical team.

The only acceptable reasons for unblinding are:

The participating centres' local standard of care requires a scan, or a clinical need for a scan is identified. In which case the centre will have access to study scan data for that timepoint (but not the other study scans) to avoid unnecessary additional scans being scheduled.

Or:

During a trial scan, the AVF is seen to be thrombosed, in which case this information would be shared with the clinical care team to enable appropriate care to continue. In such cases, no further study scans would be required. Clinical outcome data will still be collected at week 10.

1.5 Potential benefits and risks of study

The only direct benefit to the patient of the study is the possible early detection of thrombosis in a newly created fistula that may not be reviewed until a later clinic follow up date. Other than this there are no other direct benefits to participating in this observational study apart from contributing to further understanding of the use of ultrasound surveillance in identifying potentially failing arteriovenous fistulae.

Doppler ultrasound is a low risk form of imaging, as it does not use ionizing radiation. This is an observational study with very low risk to participants.

Acoustic power output and duration of exposure to ultrasound should not exceed those of a typical diagnostic examination, with exposure kept as low as reasonably achievable (25). While no patient injury has been recorded from non-contrast enhanced ultrasound at diagnostic levels, bioeffects including significant heating and cavitation have been demonstrated at higher intensities.

Infection control practices must be adhered to for all ultrasound examinations. Equipment (including the examination couch, probe, gel bottle and all surfaces of the ultrasound machine) will be disinfected after every use. Hand hygiene is essential. Where surgical wounds from the fistula procedure remain or the skin is otherwise damaged, sterile gel and probe covers must be used.(26)

1.6 Hypothesis

Doppler ultrasound surveillance can reliably predict failing nascent AV fistulas by identifying potentially-correctable anatomical defects.

2. Study Setting

Participating sites, must regularly perform arteriovenous fistula surgery and have capability to both collect data and capacity to scan participants according to the specified protocol.

Participating sites include:

1. Cambridge University Hospital, Cambridge.
2. The Royal London Hospital, London.
3. Guy's Hospital, London.
4. St Georges Hospital, London.
5. St Helier Hospital, Surrey.
6. Leicester General Hospital, Leicester.
7. John Radcliffe Hospital & Churchill Hospitals, Oxford.
8. Edinburgh Royal Infirmary, Edinburgh.
9. Bristol Royal Infirmary, Bristol.
10. University Hospital Coventry & Warwick, Coventry.
11. Hammersmith Hospital, London.
12. Nottingham University Hospital, Nottingham.
13. Manchester Royal Infirmary, Manchester.
14. Queen Alexandra Hospital, Portsmouth.
15. Royal Free Hospital, London.

3. Selection of Participants

There will be no exceptions to eligibility requirements at the time of enrolment.
Participants will be considered eligible for enrolment in this study if they fulfil all the inclusion criteria and none of the exclusion criteria detailed below.

3.1 Participant Inclusion Criteria

1. The participant is an adult, aged 16 years or older
2. The participant has end stage renal disease and either requires haemodialysis or is likely to do so imminently.
3. The participant is due creation of an arm AVF (either wrist or elbow) including the following types of fistula: radiocephalic, ulno-basilic, brachiocephalic and brachiobasilic (one or two stage) fistula with a minimal acceptable threshold of 2 mm venous diameter at whatever site chosen.
4. The participant provides full informed consent to participate.

3.2 Participant Exclusion Criteria

A patient will not be eligible for this study if he/she fulfils one or more of the following criteria:
1. Attempted formation of proximal neo-anastomosis at the forearm cephalic and basilic venous systems following failure of a standard radiocephalic or ulnobasilic fistula.
2. Participants with known central venous stenosis who undergo simultaneous central venous angioplasty / stenting and AVF creation.
3. Participants in whom it is anticipated that it will not be possible to perform serial US scanning.

3.3 Co-enrolment Guidelines

Participation in other studies would not exclude participation in the SONAR study. Co-enrolment is possible upon agreement with the TMG.

4. Screening procedures and Consent and pre-enrolment investigations

It will be the responsibility of the local clinical team (which may include the local researcher(s)) to identify eligible patients scheduled to have a newly created AV fistula and invite them to participate. Potentially eligible participants will be screened against the inclusion and exclusion criteria, given study information verbally and be provided with the approved patient information sheet. They will have time to consider their involvement and ask any questions. If they wish to participate, they will be fully consented using the approved study consent form.

A screening log will be completed to record all potentially eligible patients considered for entry to the study.

A unique ID will be assigned for each participant enrolled, denoted by site code and sequential number e.g. XXX_001.

Some participants' fistulae will fail, and it is acceptable to re-enrol these participants with a different unique ID number, if they have another fistula created as per the inclusion/exclusion criteria.

There will be no mandatory pre-enrolment investigations.

5. Study Outcomes

5.1 Primary Outcome Measure(s)

1. Primary fistula patency by week 10 according to surrogate ultrasound parameters (wrist fistula: minimum venous diameter 4mm, with flow >400 mls/min; elbow fistula: minimum venous fistula diameter 5mm, with flow >500mls/min (3)).

5.2 Secondary Outcome Measures

1. For those patients established on dialysis, successful use of the fistula for dialysis on three successive occasions.
2. Clinical suitability for dialysis 10 weeks after fistula creation based on examination alone according to local practice
3. Formation of a new fistula (including fashioning of proximal neoanastomosis) or radiological salvage procedure
4. Fistula thrombosis
5. Secondary fistula patency
6. Patient acceptability based on the proportion of patients that complete their scans

6. Assessments and Follow-up

6.1 Study Assessment Schedule

TIMEPOINT*	Screening	Enrolment	AVF Surgery Study Day 0	Week 2 Study Day 14 (+/- 6 days)	Week 4 Study Day 28 (+/- 6 days)	Week 6 Study Day 42 (+/- 6 days)	Week 10 Study Day 70 (+/- 6 days)
Eligibility Screen	X						
Informed Consent□		X					
Collect demographics and medical history		X					
Collect operative data			X				
ASSESSMENTS							
Doppler Ultrasound Scan of AVF^				X	X	X	X
Clinical Assessment of suitability of AVF for dialysis							X
Routine Assessment of AVF	**(as per participating centre standard of care)**						

*All timepoints are measured from the date of AVF creation.
□ Informed consent should be obtained prior to any trial procedures (see protocol section 4 for full details on consent procedure).
^Participants found to have a thrombosed AVF will require no further study scans.

6.2 Procedures for Assessing Efficacy

Data collection will be the responsibility of the local clinical team led by the local PI and research personnel at each site. Data will be recorded in a standard Case Report Form (CRF), which will be provided by the CTU. Three participant identifiers (Participant ID allocated at enrolment, initials and age at enrolment) will be captured on the CRF.

Assessments will be performed according to the schedule in the study schema (p10). Overall responsibility for collating data from all centres will reside with the Trial Manager. All data will be pseudo anonymised with participants assigned a unique participant ID number at enrolment by the local research team, who will hold the key. A copy of the consent forms will also be filed in the participant's hospital notes, investigator site file and a copy will be given to the participant. Completed consent forms will not be sent to the CTU.

6.2.1 Procedures at enrolment

Enrolment will occur as soon as possible after screening and informed consent for entry into the study has been given. Background data (participant characteristics) will be collected and include; participant age, gender, heart rate and blood pressure, medical history to include ischaemic heart disease, hypertension, diabetes as well as current dialysis status (No dialysis, Peritoneal or Haemodialysis). Anticoagulants such as Aspirin, Clopidogrel,

Dipyridamole, Warfarin or Non-Vitamin K Anticoagulants will also be noted. A vascular access history will also be necessary, which will include previous CVC insertions, and AVFs creation. It will also be important to know whether the patient has had a formal pre operative ultrasound scan. Operative details will include date of surgery and type of fistula (Radiocephalic, ulnabasilic, brachiocephalic or brachiobasilic).

6.2.2 Procedures during week 2

- Ultrasound assessment
- Flow characteristics as defined by scanning protocol
- Routine clinical examination (if applicable as per local policy)
- Recording of first detection of “at risk” fistula – either by clinical examination or (US)
- Recording of time-point at which a fistula is no longer patent on US.
- Recording of the formation of a new AVF
- Recording of reported fistula thrombosis

6.2.3 Procedures at week 4

- Ultrasound assessment
- Flow characteristics as defined by scanning protocol
- Routine clinical examination (if applicable as per local policy)
- Recording of reported fistula thrombosis

6.2.4 Procedures at week 6

- Ultrasound assessment
- Flow characteristics as defined by scanning protocol
- Routine clinical examination (if applicable as per local policy)
- Recording of reported fistula thrombosis

6.2.5 Procedures at week 10

- Clinical assessment of fistula function
- Number of successful/unsuccessful dialysis visits within 10-week period
- Secondary fistula patency at week 10- defined as the interval from the time of access placement until access abandonment, thrombosis, or the time of patency measurement including surgical or endovascular interventions (including the formation of a proximal neo-anastamosis) in order to re-establish functionality in thrombosed access.
- Recording of first detection of “at risk” fistula – either by clinical examination or (US)
- Recording of time-point at which a fistula is no longer patent on US.
- The number of fistula operations and radiological salvage interventions (number, nature and timing) reported up to week 10
- Flow characteristics as defined by scanning protocol
- Recording of the formation of a new AVF
- Recording of reported fistula thrombosis
- Recording number of days dialysed via a central venous catheter (CVC), and CVC-related septic complications

6.3 Blinding of Assessments

The ultrasound findings will be blinded, i.e. not be relayed to the participant or to the participant's clinical team.

The only acceptable reasons for unblinding are:

The participating centres' local standard of care includes a scan, or a clinical need for a scan is identified. In which case the centre will have access to study scan data for that timepoint (but not the other study scans) to avoid unnecessary additional scans being scheduled.

Or

During a trial scan, the AVF is seen to be thrombosed, in which case this information would be shared with the clinical care team to enable appropriate care to continue. In such cases, no further study scans would be required. Clinical outcome data will still be collected at week 10.

Patients who discontinue the study early will not be replaced.

6.4 Study Closure

The study will be closed after the last 10-week appointment of the last recruited patient is completed, and all data have been received, cleaned and the database is locked. Once the study is closed, participating centres will be contacted, and may be visited, to ensure that all documentation is filed and ready for archive.

7. Safety reporting

This is an observational study using Doppler ultrasound, to which there are no known adverse reactions. No adverse event data will be collected in this study.

8. Quality Assurance and Control

Data will be managed in accordance with the NHS Blood and Transplant Clinical Trials Unit's Management Process Descriptions.

8.1 Risk Assessment

A risk assessment has been conducted which acknowledges the potential risks to the study. This section provides an overview of the Quality Assurance (QA) and Quality Control (QC) measures that will be put in place to ensure the study is performed and data generated and recorded in accordance with the principles of ICH GCP.

8.2 Central Monitoring at CTU

The CTU data managers will review all data received for errors and missing data points.

8.3 On-Site Monitoring

The frequency, type and intensity for routine monitoring and the requirements for "for cause" monitoring will be detailed in a separate study specific monitoring plan.

8.3.1 Direct access to patient records

Participating investigators should agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patient consent must be obtained for this.

8.3.2 Confidentiality

The data will be handled in accordance with the principles of the UK Data Protection Act and any subsequent data protection legislation.

8.4 Auditing

In addition to potential GCP inspections or audits by the host R&D department, NHSBT CTU reserves the right to conduct site audits, either as part of its on-going audit programme, or in response to adverse observations during monitoring visits.

9. Statistical Considerations

9.1 Method of Generating Allocation Sequence

No randomisation is required.

9.2 Outcome Measures

See Section 5.

9.3 Sample size

We have estimated that 20% of fistulas fail early and that early ultrasound has a positive predictive value (number of true positives/number of predicted positives, PPV) of 72% for predicting non-maturation. To estimate this with ±10% precision (i.e. the 95% confidence interval is from 62% to 82%), 78 predicted failures are required. We estimate that US predicts failure in 25% of fistulas, therefore, 312 fistulas overall are required. Allowing for 10% dropout, 347 fistulas are required. We anticipate that two models to predict primary fistula patency will be required and therefore we will have two PPVs- one for wrist fistulas and one for elbow fistulas. Assuming a ratio of 50:50 for wrist to elbow fistulas, the precision confidence interval will be from 55.3% to 85.2%.

9.4 Interim Monitoring and Analyses

The feasibility of recruitment will be assessed based on data between month 3 and month 9 of the recruitment period. Our stop-go criteria for expanding to complete the full first phase study will be: 1) stop if fewer than 80 patients have been recruited; (2) Recruit additional centres if between 80-120 patients have been recruited; (3) Continue the trial as planned if recruitment rates are as predicted.

9.5 Analysis Plan (Brief)

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

9.5.1 Analysis of primary and secondary outcomes

The primary fistula patency rate by week 10 will be calculated alongside an exact 95% confidence interval based on all participants enrolled. It will also be calculated based on participants whose fistulas did not fail early.

The secondary outcomes will be presented using descriptive summary statistics.

Mixed multivariable logistic regression will be used to model primary fistula patency by 10 weeks to develop a model, which can be used as a risk-score calculator in the phase 2 trial (not part of this protocol). Two models will be built, one for wrist fistulas and one for elbow fistulas. Measurements taken from the first scan performed at week 2 will be considered as parameters in the model initially and further parameters from either the second scan or the third scan will then be considered. The choice of second or third scan will be based on the best fitting parameters, as assessed by significance level. A random effect for patient will be included in the models to account for multiple scan data per participant. The aim will be to build parsimonious models, which contain the minimum number of measurements, required to effectively predict primary fistula patency. A receiver operating characteristic

(ROC) curve analysis of the developed risk scores will be used to assist decisions regarding an appropriate cut-off for an indicator for when intervention is required for both wrist and elbow fistulas. The PPV will be calculated alongside an exact 95% confidence interval for the chosen risk-score cut-off.

9.5.2 Analysis Population and Missing Data

All recruited participants will be included in the analyses, where possible.

Data management will regularly review the data and missing/anomalous data will be queried with the sites.

It is anticipated that some participants will not attend all scans and therefore some scan data will be missing. Levels of missing data will be summarised for each of the scan time points and will be considered when choosing which scan results to use in the final model. Any missing primary and secondary outcome data will not be imputed. Missing data for parameters in the modelling of primary fistula patency will be imputed using multiple imputation if the level of missing data is greater than 10%.

10. Ethical and Regulatory Issues

10.1 Compliance

This study complies with the Declaration of Helsinki (2013). It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the UK Data Protection Act, the General Data Protection Regulation and the UK Policy Framework for Health and Social Care Research.

10.1.1 Site Compliance

The site will comply with the above regulations and guidelines. An agreement will be in place between the site and NHSBT, setting out respective roles and responsibilities.

The site will inform the CTU as soon as they are aware of a possible serious breach of compliance, so the CTU can report the breach if necessary, within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a serious breach is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

10.1.2 Data Collection and retention

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 10 years after the end of the study. During this period, all data should be accessible to the competent authorities and the Sponsor with suitable notice.

10.1.3 Access to Data

Custody of the final data set will reside with the Chief Investigator and NHSBT CTU (for audit purposes). Access to the final data set for additional analyses will be permitted under the agreement of the Trial Steering Committee, according to the publication policy in

10.2 Ethical Conduct of the Study

10.2.1 Ethical Considerations

Before initiation of the study at each clinical site, the protocol, all informed consent forms and any information to be provided to the prospective participant will be submitted to a Research Ethics Committee for ethical approval. Any subsequent amendments will be submitted to, and approved by, the same Research Ethics Committee.

As the study is observational with a small likelihood of direct benefit to participants, their involvement will be mainly altruistic. This will be made clear during discussions with potential participants, and in the patient information sheet. Participants may be inconvenienced by the additional hospital visits for the study, and so their travel expenses will be reimbursed.

10.2.2 Consent or assent

The rights of the patient to refuse to participate in the study without giving a reason must be respected. After the participant has entered into the study, the clinician must remain free to treat the patient according to best standards of care, irrespective of their involvement in the study. The participant will remain within the study for the purposes of follow up and for data analysis. Similarly, the participant must remain free to change their mind at any time about the protocol and study follow up without giving a reason and without prejudicing his/her further treatment.

10.3 Confidentiality

Study specific data which is non-identifiable, will be collected at each site on the Case Report Form (CRF). Each participant will have a unique ID allocated to them which will be recorded on the CRF for reporting purposes. Only study sites will have access to the identifiable information to maintain participant confidentiality. CRF data will be submitted to NHSBT CTU at pre-specified intervals and logged into the regulatory compliant, secure MACRO™ database. Only authorised personnel at NHSBT CTU will have password protected access to the study database.

10.4 Other approvals

The protocol will be submitted by those delegated to do so to the HRA for approval. A copy of the HRA approved Patient Information Sheet and Consent Form on local headed paper should be provided to the CTU before any participant is entered onto the study.

The protocol will also be submitted by those delegated to do so to the relevant R&D department of each participating site. A copy of the respective NHS Trust capacity and capability assessment should be provided to the CTU before any patient is entered onto the study.

11. Indemnity

The NHS indemnity scheme applies to this trial when it is being conducted in the UK. Section 4 of the non-commercial clinical trial agreement 2008 describes the indemnity arrangements as follows:

As both Sponsor and site are NHS bodies, i.e. NHS bodies/NHS Foundation Trusts in England, Wales or Northern Ireland and are indemnified by the same Indemnity Scheme (being one of the NHS Litigation Authority clinical negligence or the Welsh Risk Pool or the Clinical Negligence Fund in Northern Ireland) and the Party incurring any loss can recover such loss under one of the Indemnity Schemes, then such Party shall rely on the cover provided by the Indemnity Scheme and not seek to recover the Loss from the other Party(ies). Where the other Party(ies) caused or contributed to the Loss, it undertakes to notify the relevant Indemnity Scheme(s) to take this into account in determining the future levies of all Parties in respect of the indemnity schemes.
If:

- The Parties are members of the same Indemnity Scheme in England, Wales or Northern Ireland and the Party incurring the Loss is not indemnified for that Loss by its Indemnity Schemes; or
- All Parties are NHS bodies in Scotland; or
- The Parties are NHS bodies/Foundation Trusts established in different jurisdictions within the United Kingdom;

Then the Parties shall apportion such Loss between themselves according to their respective responsibility for such Loss. Should the Parties be unable to agree the apportionment the matter shall be resolved in accordance with clause 16.5.
If one or more Parties are NHS Foundation Trusts and the Party incurring the Loss is not responsible for all or part of the Loss and is not indemnified in respect of the Loss by one of the Indemnity Schemes, then the Party incurring the Loss shall be entitled to recover the Loss from the other Party (ies) pursuant to the provisions of this Agreement.

The Chief Investigator is an employee of the University of Cambridge, who have provided the following indemnity cover:

The University Insurance Office has advised that subject to the study being approved by the relevant Ethics Committee, insurance for negligent and non-negligent harm to research subjects under the University's Clinical Trials and/or Human Volunteer Studies policy can be arranged. The insurers are Newline Syndicate 1218, the insurance policy reference is B0823Q31000177/WD1600523 and the Limit of Indemnity is £10m for each and every claim.

12. Finance

12.1 Funding

This study is funded by the NIHR Health Technology Assessment board, grant reference: 17/27/11 Surveillance of Arteriovenous Fistulae in Haemodialysis.

Funding arrangements will be provided in the NHS Trust agreements with the Sponsor, Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

12.2 Declaration of interests

None of the individuals named in this protocol have any competing interests to declare. The NHSBT CTU requires serving members of all Oversight Committees to sign a declaration of interests form on appointment and to declare any competing interests which may develop during the conduct of the study at the start of every meeting.

13. Oversight and Trial Committees

There are a number of committees involved with the oversight of the study. These committees are detailed below.

13.1 Trial Management group (TMG)

A Trial Management Group (TMG) comprising the Chief Investigator, other lead investigators and members of the CTU. The TMG will be responsible for the day to day running and management of the study. It will meet at least four times a year, more often during set up and close down phases of the study.

13.2 Trial Steering Committee

The Trial Steering Committee (TSC) has membership from the TMG and independent members, including the Chair. The role of the TSC is to provide overall supervision for the study and provide advice through its' independent Chair. The ultimate decision on continuation of the study lies with the TSC.

13.3 Data Monitoring Committee

The CTU has a core independent Data Monitoring Committee (DMC) for all of its trials. The group will act as DMC to this study, provide advice to the Chair of the TSC and can recommend premature closure of the study. For the purposes of this study, the core DMC will be joined by an independent member who can provide expert disease specific advice.

13.4 Role of Study Sponsor

As Sponsor, Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge are responsible for the initiation and management of the study. Activities are delegated to NHSBT CTU as appropriate.

13.5 Role of Study Funder(s)

The NIHR Health Technology Assessment board will continually monitor the progress of the study. Regular progress reports will be submitted as required.

14. Publication

14.1 Dissemination

The final study data set will be analysed and results published as soon as possible following completion of study follow up, final data checks and database lock. Individual Clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of publications

Study findings will be presented to academic and non-academic groups. The PPI group will play an important part in disseminating the study findings into the public domain. Dissemination to non-academic audiences including service users, commissioners, clinicians and service providers will be facilitated through the use of existing networks e.g. email lists, social media.

All research teams and PPI members involved in the study will be invited to a close out meeting to discuss the findings of the study and to consider the implications for progression to the phase 2 main study.

Open access, peer reviewed academic outputs and research reports together with associated summaries and key findings will be produced for funders, policy makers and NHS audiences and held on the study website.

Any publications arising from this study will adhere to the NIHR funding and support outputs guidance.

14.2 Authorship

Authorship for any publications arising from this study will follow the rules set out by the International Committee of Medical Journal Editors definitions of Authorship and Contributorship, http://www.icmje.org/ethical_1author.html

14.3 Approvals

Study results will be embargoed and not disseminated until authorised by the CI and TSC. Final manuscripts and presentations will be approved by the CI and TSC prior to publication. Similarly, any subsequent sub-study analysis will require authorisation by the CI and TSC prior to publication. Sub-study manuscripts must not be published prior to the publication of the main study.

14.4 Identification

A trial identifier should be included on all presentations and publications (e.g. the ISCRTN)

14.5 Timing

It must be made clear that no data may be made public before publication and never without agreement from the CI.

14.6 Acknowledgements

For the main report of this study submitted for publication, together with associated methodology and health economic papers or posters/presentations, we will use the

International Committee of Medical Journal Editors definitions of Authorship and Contributorship http://www.icmje.org/ethical_1author.html). The members of the TSC and IDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication and the support of the NHSBT Clinical Trials Unit, and Funder acknowledged in all publications/presentations.

15. Protocol Amendments

Revision History:

Version	Author	Date	Reason for revision

16. References

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