NHS
Health Research Authority

Anaesthesia Choice for Creation of Arteriovenous Fistulae (**ACCess** Study)

PROTOCOL

Version 1.0 23rd November 2020

This protocol has regard for the HRA guidance and order of content

ISRCTN: 14153938

Sponsor: NHS Greater Glasgow and Clyde

Sponsor's Protocol No: GN19RE456

REC/IRAS No: 290482

Funder: National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme 130567

University of Glasgow

NHS Greater Glasgow and Clyde

FUNDED BY

NIHR | National Institute for Health Research

FULL/LONG TITLE OF THE TRIAL

Anaesthesia **C**hoice for **C**reation of Art**e**riovenou**s** Fi**s**tulae

A multicentre observer-blinded randomised controlled trial comparing 1-year primary unassisted patency of primary radio-/brachio-cephlic arteriovenous fistulae created under regional anaesthesia (ultrasound-guided supraclavicular or axillary block 1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine with epinephrine (final concentration 1 in 400,000) compared to local anaesthesia (1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine).

SHORT TRIAL TITLE / ACRONYM

Anaesthesia **C**hoice for **C**reation of Art**e**riovenou**s** Fi**s**tulae (ACCess study)

PROTOCOL VERSION NUMBER AND DATE

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RESEARCH REFERENCE NUMBERS

IRAS Number:	290482
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SIGNATURE PAGE

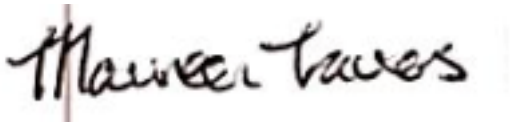
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:



23/11/20

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Position: Research Co-ordinator, Clinical Research & Development, NHS Greater Glasgow and Clyde

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Signature: Date:

23/11/20

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Clinical queries should be directed to the principal investigator at site in the first instance. The Chief Investigator can be contacted for clinical queries also. All other queries should be directed to the ACCess Trial Team at the Project Management Unit.

FOR RANDOMISATIONS

Online at *[WEBSITE]* (24 hours)

i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

AAGBI	Association of Anaesthetists of Great Britain and Ireland
AE	Adverse Event
AVG	Arteriovenous graft
AVF	Arteriovenous fistula
BBF	Brachiobasilic fistula
BCF	Brachiocephalic fistula
BNF	British National Formulary
CHI	Community Health Index
CI	Chief Investigator
CKD	Chronic kidney disease
COMET	Core Outcome measures in Effectiveness Trials
CPMS	Central Portfolio Management System
CRF	Case Report Form
CTU	Clinical Trials Unit
CVC	Central venous catheter
DANA	Dialysis Access Nurses Association
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EQ-5D	EuroQOL Health Questionnaire Quality of Life Tool
ERA-EDTA	European Renal Association- European Dialysis and Transplant Association
ESRD	End stage renal disease
ESVS	European Society of Vascular Surgery
GA	General anaesthesia
GCP	Good Clinical Practice
HD	Haemodialysis
HR-QoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICHOM	International Consortium for Health Outcomes Measurement
IRAS	Intergrated Research Application System
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive web response system
KDQOL-SF	Kidney Disease Quality of Life Short Form

LA	Local anaesthesia
LVLS	Last visit last subject
MAGIC	Managing Access by Generating Improvements in Cannulation
NHS	National Health Service
NHSGGC	NHS Greater Glasgow and Clyde
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute of Health Research
NRS	Numerical Rating Scale
PD	Peritoneal dialysis
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
Pre-D	Pre-dialysis
PROM	Patient related outcome measure
PSSRU	Personal and Social Services Resource Unit
QALY	Quality Adjusted Life Year
RA	Regional anaesthesia
RAP	Rapid Assessment Procedures
RA-UK	Regional Anaesthesia- United Kingdom
RCB	Robertson Centre for Biostatistics
RCF	Radiocephalic fistula
RCoA	Royal College of Anaesthetists
RCT	Randomised Control Trial
R&D	Research and Development
REC	Research Ethics Committee
RREAL	Rapid Research Evaluation and Appraisal Lab
RRT	Renal replacement therapy
RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SHTG	Scottish Health Technologies Group
SmPC	Summary of Product Characteristics
SONG-HD	Standardising Outcomes in Nephrology- Haemodialysis
SONAR	Surveillance Of arterioveNous fistulAs using ultRasound
SOP	Standard Operating Procedure
SSI	Site Specific Information
SWAT	Study Within A Trial
TCVC	Tunnelled central venous catheter
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UK	United Kingdom
UKRR	United Kingdom Renal Registry

UKRTN	United Kingdom Renal Trials Network
USS	Ultrasound
VASQOL	Vascular Access Specific Quality of Life Tool
VA	Vascular access
y.o.	Years old

iii. TRIAL SUMMARY

Trial Title	Anaesthesia Choice for Arteriovenous Fistulae
Short title	ACCess study
Trial Design	A multicentre observer-blinded randomised controlled trial (RCT) with internal pilot and embedded process evaluation study.
Phase	IV
Research Question	Does regional (RA) compared to local anaesthesia (LA) improve unassisted functional patency at 1 year and/or cost-effectiveness in patients undergoing primary radiocephalic (RCF) or brachiocephalic (BCF) fistula creation?
Trial Participants	Adult patients with end stage renal disease (ESRD) who require primary radio- (RCF) or brachio-cephalic fistula (BCF) creation.
Planned Sample Size	566 participants
Intervention	Regional anaesthesia: ultrasound (USS)-guided supraclavicular or axillary block): 1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine with epinephrine (final concentration 1 in 400,000).
Comparator	Local anaesthesia: 1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine.
Recruitment Period	24 months
Follow-up Period	12 months
Primary Outcome Measure	Unassisted functional arteriovenous fistula (AVF) patency at 1 year
Secondary Outcome Measures*	Vascular access complications (e.g. infection, stenosis, steal, thrombosis, bleeding) Re-operation/ re-intervention Alternative accesses Cannulation difficulties Mortality Dialysis and access modality Access-related hospitalisation HR-QoL Cost-effectiveness Efficacy and safety of anaesthesia * measured at 3 and 12 months

iv. SCIENTIFIC SUMMARY

Research question: Does regional (RA) compared to local anaesthesia (LA) improve unassisted functional patency at 1-year and/or cost-effectiveness in patients undergoing primary radio- (RCF) or brachio-cephalic (BCF) fistula creation?

Background: Arteriovenous fistulae (AVF) are the "gold standard" vascular access for haemodialysis, however universal usage is limited by a high early failure rate. Several small studies, including our own single-centre randomised controlled trial (RCT), previously demonstrated better early patency rates for AVF created under RA versus LA. The mechanistic hypothesis is that sympathetic blockade causes vasodilatation and increased blood flow through the new AVF. Despite this, considerable variation in practice exists in the UK. A high quality, adequately powered, multicentre RCT is required to definitively inform practice.

Aims and Objectives:

- Compare functional patency for AVF created under RA vs. LA
- Assess efficacy, safety and acceptability of RA and LA
- Compare rates of re-intervention, complications and need for alternative accesses between RA and LA
- Evaluate the cost-effectiveness of RA vs. LA for primary AVF creation

Methods: A multicentre, single-blinded RCT comparing RA (ultrasound-guided supraclavicular or axillary block with 1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine, with epinephrine (final concentration 1 in 400,000)) and LA (local infiltration with 1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine) in patients undergoing primary RCF or BCF creation. 566 patients will be recruited from up to 20 UK centres. An internal pilot with stop/go checkpoint after 4 months (95 patients) will ensure the ability to recruit.

The primary end point is unassisted functional patency at 1-year (defined as the ability of the access to uninterruptedly deliver the prescribed dialysis without intervention). In pre-dialysis patients, this will be defined both clinically (assessment by a blinded dialysis nurse) and ultrasonographically (4mm diameter and access flow >500ml/min). Secondary outcomes include: access-related complications e.g. infection, thrombosis; re-interventions to maintain/ re-establish patency; hospitalisation; alternative accesses; mortality; safety, efficacy and acceptability of anaesthetic technique and health-related quality of life measures (EQ-5D, KDQOL-SF and VAS-QoL (a novel vascular access specific tool). These will be assessed at 3 and 12 months. Intention-to-treat and per protocol analyses will be performed as well as health economic evaluation. A rapid feedback evaluation study will run in parallel to the main trial collecting qualitative data on recruitment and retention. Findings will be shared with the trial team on a regular basis to inform trial delivery.

Timeline for delivery: The trial will commence in May 2021. Recruitment will take two years. Follow-up will take one year. Results anticipated November 2024.

Anticipated impact and dissemination: Results will have direct implications for patient care across a range of medical specialties (surgery, anaesthesia, nephrology, dialysis nursing). They will be presented at international scientific conferences and published in a high impact peer-reviewed medical journal. It is anticipated that results will provide NICE level evidence to influence NHS commissioning and that recommendations be incorporated into the Renal Association's next 'Vascular Access for Haemodialysis' guideline.

v. PLAIN ENGLISH SUMMARY

Many patients with kidney failure need dialysis to remove toxins from the bloodstream. During dialysis, blood from the patient is taken into the dialysis machine, cleaned and then returned back to the patient. This requires entry and exit 'access' points into patients' blood vessels. The best form of access is called a fistula (an artificial connection between the artery and vein made with a small operation in the arm).

Unfortunately, fistula creation is not an exact science. Up to half fail within a year of being created. The reason why fistulas fail and how we can prevent it are largely unknown.

The fistula operation can be performed under local anaesthetic (i.e. injection of anaesthetic into the wrist or elbow to numb the area where the surgeon will operate) or anaesthetic 'block' (i.e. injection of anaesthetic around the nerves in the neck or armpit to numb the entire arm for many hours). We know that the 'block' also improves blood flow to the arm. Theoretically this could improve the success of a fistula operation but we are not sure. Currently in the UK there is no agreement on what to do and each unit chooses based on local preference and resources.

This study aims to compare the success of fistulas created under local anaesthetic versus an anaesthetic 'block'.

Patients requiring fistula creation will be randomised (like tossing a coin) to have their fistula made under local anaesthetic or 'block'. After the surgery most patients will be able to go home on the same day. They will be reviewed twice afterwards (3 and 12 months following surgery) to assess how they, and their fistula, are getting on.

Recent research has shown that patients consider fistula function rather than simply bloodflow is most important when determining the success of a procedure. Therefore we will judge success if a fistula can deliver dialysis without the need for any additional procedures or surgery. This will be easy to assess in patients receiving dialysis. However, we anticipate that about half of study participants will not have started dialysis yet. In these patients the fistula will be assessed by ultrasound (jelly scan) instead. We will compare the number of patients with a successful fistula at 12 months in each group to determine which anaesthetic technique (if either) is better.

We will also collect information about complications (infections, blockages, needling problems), additional procedures, hospital visits or 'lines' (plastic tubes inserted to allow dialysis if the fistula isn't working properly). Finally, patients will be asked to complete some short questionnaires to evaluate general wellbeing. One of the questionnaires has been recently designed by doctors specifically to look at the effect of the 'access' on patient lifestyle. This information will allow us to determine if the treatments are good value for money.

Wherever possible, patients will be followed-up in their dialysis units to avoid additional hospital visits and only hospitals that already offer both local anaesthetic and 'block' within their current practice will be eligible to participate. In this way we will keep down costs of running the trial and draw on existing relationships to make everything run efficiently.

We anticipate that the results of this trial will be used to influence the decision-making of NHS funders and ensure that, in the future, the best treatment option is available for every patient with kidney failure in the UK.

vi. FUNDING

The trial is funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme Reference Number 130567

vii. ROLE OF TRIAL SPONSOR AND FUNDER

The trial is sponsored by NHS Greater Glasgow and Clyde (NHS GGC) (Reference Number GN19RE456).

The sponsor is responsible for ensuring that proper arrangements are in place to initiate, manage, monitor and finance the study in line with the Research Governance Framework and Good Clinical Practice.

Specifically, the sponsor is responsible for ensuring that:

- the trial is appropriately assessed and resourced
- the trial is conducted to the required standards and conforms with regulatory requirements
- there is adequate provision for compensation and indemnity in the event of harm to research participants.

Some of these responsibilities will be delegated to the Chief Investigator (CI), Glasgow Clinical Trials Unit or Robertson Centre for Biostatistics (RCB), University of Glasgow:

The sponsor will maintain oversight for all aspects of the trial and will be directly responsible for, financial contracts, maintenance of the Trial Master file (TMF) and archiving.

The funder is responsible for monitoring trial progress through annual reports and minutes of the TSC.

viii. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee

The Trial Steering Committee (TSC) will provide overall supervision of the trial and ensure that the conduct of the trial is in line with standards set out in the EU Good Clinical Practice (GCP) Guideline [1]. The TSC will formally report to the sponsor.

The TSC will specifically consider patient safety (including failed blocks); trial progress; adherence to the protocol and statistical analysis plan; new information that may come to light during the trial; dissemination of results; and complaints procedure/ compensation for participants.

The TSC will comprise of the following members: an independent TSC chair; an independent expert in the field of access surgery; an independent expert in the field of nephrology; an independent expert in the field of regional anaesthesia; an independent statistician; CI; lead anaesthetist and patient representative. A sponsor's representative, trial statistician and representative of the funder will also be invited to attend all TSC meetings. The CI will propose membership of the TSC to the funder who will agree final membership.

The TSC will meet on six occasions during the trial: prior to trial commencement (to approve protocol); 4-5 months (to evaluate recruitment in the pilot study); 16 months (end of follow-up for pilot phase); 24

months (end of recruitment); 36 months (end of follow-up); end of trial. Additional meeting may be called as required by either the Independent Chair of the TSC, CI or sponsor.

Data Monitoring Committee

The Data Monitoring Committee (DMC) is responsible for monitoring data emerging from the trial, in particular as they relate to the safety of participants, and to advise the TSC on whether there are any reasons for the trial not to continue. The DMC is the only body involved in the trial that will have access to the unblinded comparative data during the trial.

The DMC will be completely independent of the trial and any institutions involved in the trial. It will consist of an expert clinical trialist (chair); expert in the field of vascular access and expert statistician. The funder will approve membership of the DMC.

The DMC will meet annually during the recruitment and follow-up phases of the trial aiming to coincide with the following specific time points: 4 months (end of recruitment phase of pilot study); 16 months (end of follow-up for pilot/ midpoint of recruitment for main trial); 30 months (all participant completed 3 month follow-up). Additionally the CI can request a meeting if there are concerns that require addressed.

The Robertson Centre for Biostatistics (RCB) will prepare a report for each DMC meeting. The unblinded statistician may be invited by the Chair to attend the closed session to discuss the data; otherwise, no one involved with the trial or TSC will be present at the DMC closed session when unblinded data are presented.

Following each meeting, a written report will be made by the Chair of the DMC to the TSC and CI, advising whether the trial should continue or be stopped or modified. If the DMC recommends that the trial should be stopped at any point, the funding body will be notified. Ultimate responsibility in deciding whether or not to act upon recommendations from the DMC or a decision for early termination lies with the TSC in conjunction with the sponsor and funder.

Trial Management Group

Day-to-day management of the trial is the responsibility of the CI and other co-Investigators. A separate Trial Management Group (TMG) will assist with site set-up and closure (the responsibility of individual PIs), day-to-day running, recruitment, randomisation, delivery, adherence to protocol, follow-up, data management and analysis. The TMG will meet 3-monthly via teleconference. Additionally two face-to-face Investigator's meetings will be convened to bring collaborators together, ensure that the practical details of the trial are working well and everyone within the trial understands them.

ix. KEY WORDS:

Arteriovenous fistula

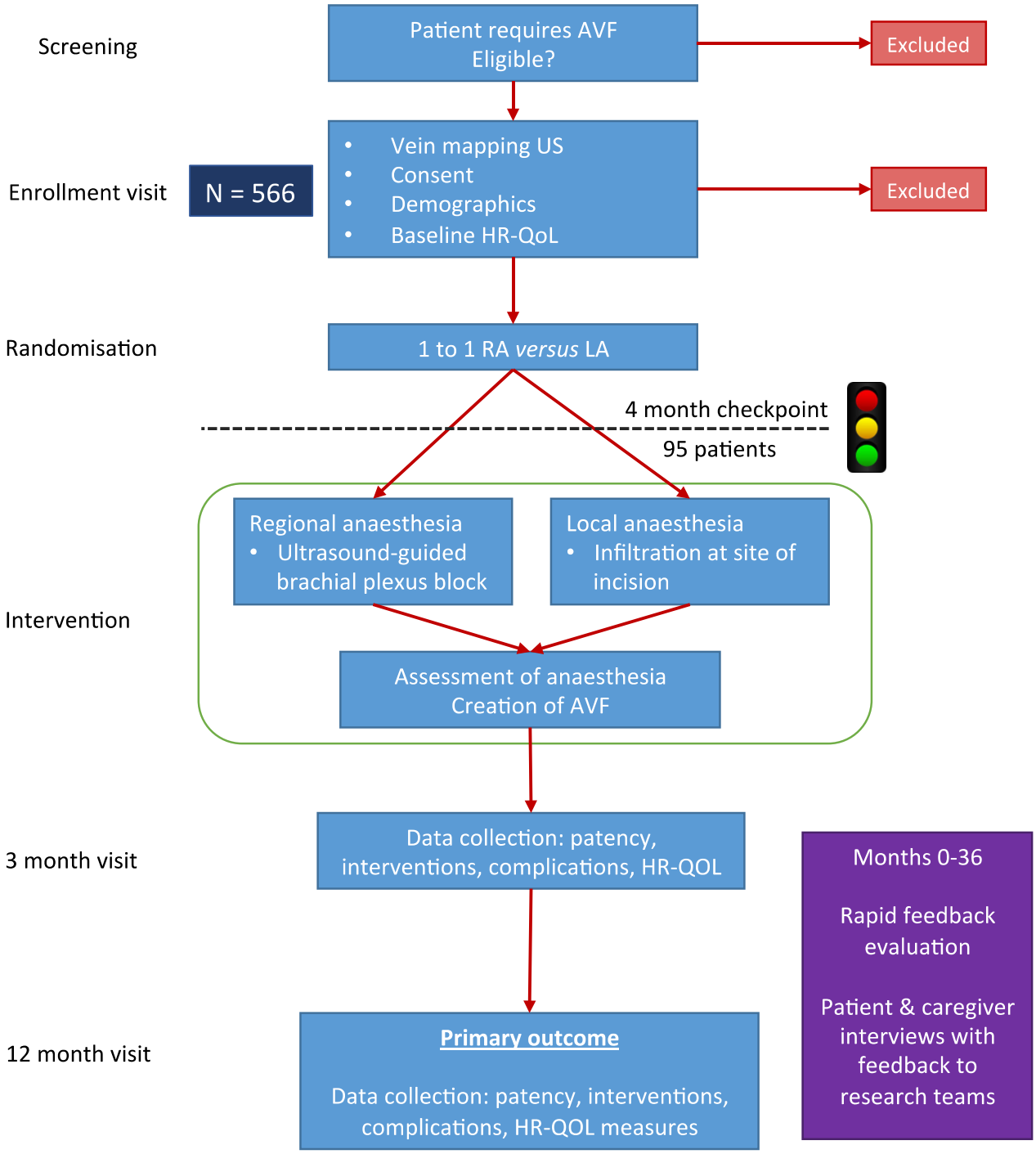
Regional anaesthesia

Local anaesthesia

Vascular access

End stage renal disease

x. TRIAL FLOW CHART



1 BACKGROUND

The incidence of end stage renal disease (ESRD) has increased exponentially over the last 30 years [2]. Over 25,000 people in the UK are currently on haemodialysis (HD), with this number increasing by 2.5% year-on-year [3].

Kidney disease has a significant impact on both longevity and quality of life. Survival from ESRD is worse than most cancers. In Scotland, a 25-year old diabetic commencing dialysis has only 50% chance of living beyond 5 years [2]. The disease also places considerable demand on healthcare resources: 11.7 in-patient bed days are required each year for patients on HD [4]. Frequent hospitalisation, coupled with the cost of renal replacement therapy (RRT) (out-patient HD costs ~£35000/patient/year), means that 3% of the NHS budget intended for a population of 65 million is expended on kidney failure services for just 50,000 patients [5].

Vascular access is the “key modifiable risk factor to improve patient experience and outcome on HD” [6].

Arteriovenous fistulae (AVF) are the preferred method of vascular access, with fewer infective and thrombotic complications than the alternative (central venous catheters (CVCs)) [6]. AVF deliver better quality dialysis and improve patient survival compared to other forms of vascular access [7]. Patients dialysing via AVF are three times less likely to be admitted to hospital than their counterparts with CVCs [6]. Frequent hospitalisations have a negative impact on health-related quality of life (HR-QoL) [8].

Unfortunately the universal adoption of AVF remains suboptimal. The most recent UK Renal Registry (UKRR) 2016 Multisite Dialysis Access Audit highlighted that nearly 80% of dialysis units in England, Wales and Northern Ireland (43 of 54 centres) still fall short of Renal Association targets recommending that 60% of incident patients receive HD via AVF or arteriovenous graft (AVG) [3,9]. Significant improvement in autologous access rates is urgently required.

The principal hindrance to widespread AVF usage is “failure to mature”, with early failure rates approaching 50% [10,11]. It follows that any intervention to improve AVF maturation would confer significant benefit to patient health and wellbeing; reduce surgical workload; and deliver cost savings.

Several small studies, including our own single-centre randomised controlled trial (RCT) [10], have demonstrated better early patency rates for AVF created under regional (RA) compared to local anaesthesia (LA). The mechanistic hypothesis is that sympathetic blockade causes vasodilatation, improved tissue oxygenation and increased blood flow through the new AVF [10,12]. Similarly, a recent meta-analysis (n=286) found a strong signal for lower AVF failure rates with RA [13]. All four of the included studies were single-centre and, according to the authors, suffered from a range of methodological flaws. The authors of the meta-analysis called for a large definitive trial.

Limited evidence has emerged since the meta-analysis [13]. An American retrospective cohort study (n=3,199) demonstrated better short-term term AVF outcomes, lower re-operation rate and shorter duration of hospital stay in patients with AVF created under RA [14]. It should, however, be noted that the principal comparator group in this study was general anaesthesia (GA). Only 7% of patients received a regional technique. Similarly, an Australian observational study (ACTRN12615000393550), conducted across seven hospitals (n=168), also found a signal favouring AVF creation under RA compared to GA (Raymond Hu, personal communication). These investigators now intend embarking on a pilot feasibility study investigating the effects of GA vs. RA on AVF patency (n=50) in early 2020

(ACTRN12619001769178). The conclusions of this study will have limited applicability to UK practice, where GA is rarely employed for AVF creation due to concerns about cardiovascular co-morbidity and blood pressure labiality in patients with ESRD [15].

Assessment of secondary outcomes from our original single-centre RCT has subsequently demonstrated enduring benefit in 1-year functional patency for AVF created under RA (68% vs. 49%; OR 2.1, P<0.01) [16]. Health economic analysis was performed using HR-QoL data extrapolated from the literature as none was collected during the original trial. Net cost savings of £195.10/pt. at 1 year and an incremental cost-effectiveness ratio of approximately £12,900 per quality-adjusted life year (QALY) gained over a 5 year time horizon were found with RA. Both the European Society for Vascular Surgery (ESVS) and European Renal Association (ERA-EDTA) guidelines now recommend RA for all primary AVF [17,18].

2 RATIONALE

Despite recommendations from both the ESVS and ERA-EDTA, which support RA for all primary AVF [17,18], significant disparity regarding choice of anaesthesia for AVF creation persists around the UK. The absence of any British guidelines and failure to modify local practices, suggest persistent dubiety and deficiencies in the evidence base. Our recent survey of the Dialysis Access Nurses' Association (DANA) demonstrated that 37.5% of UK dialysis units (n=69) principally employ RA for primary AVF creation. The remainder use LA (response rate: 69.6%).

Whilst available data point towards RA providing better short-term AVF outcomes, there is scanty evidence as to whether or not any potential durable clinical benefit could be offset against the longer procedural times, need for a skilled anaesthetist and additional upfront costs that inevitably come with RA. Only a definitive, adequately powered, multicentre RCT with associated cost-effectiveness analysis will provide sufficient evidence to change practice and policy.

2.1. Equipoise

The pilot trial carried out by some of the ACCess investigators [10] was conducted within ideal conditions, with blocks performed by two expert RA enthusiasts. As highlighted in the meta-analysis, extrapolation of these results to everyday practice in other centres (or even to other anaesthetists within our own centre) may be limited [13]. The multicentre trial design in this trial addresses this issue and other criticisms of the original work, namely short follow-up, poor early functional patency rates and lack of HR-QoL data.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

To compare unassisted functional AVF patency at 1 year in patients undergoing primary RCF/ BCF creation under RA versus LA:

P **Population**- Patients undergoing primary RCF or BCF creation

I **Intervention**- Regional anaesthesia (USS-guided supraclavicular or axillary block -1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine, with epinephrine added to make final concentration 1 in 400,000.

C **Comparison**- Local anaesthesia (1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine)

O **Outcome**- Unassisted functional patency at 1 year

3.2 Secondary objectives

- To compare the efficacy (quality of anaesthesia) provided by LA and RA in patients undergoing primary RCF/ BCF creation
- To compare the safety of LA and RA in patients undergoing primary RCF/ BCF creation
- To compare the acceptability of LA and RA in patients undergoing primary RCF/ BCF creation
- To compare rates of re-intervention, access-related complications, hospitalisations and need for alternative access in patients undergoing primary RCF/ BCF creation under RA and LA
- To compare mortality in patients undergoing primary RCF/ BCF creation under RA and LA
- To compare dialysis and access modality utilised in patients undergoing primary RCF/ BCF creation under RA and LA
- To evaluate the cost-effectiveness of RA versus LA for primary RCF/BCF creation

3.3 Primary endpoint/outcome

Unassisted functional AVF patency at 1 year (defined as the ability of an access to uninterruptedly deliver the prescribed dialysis without intervention). In pre-D patients, this will be defined both clinically (assessment by an experienced, blinded dialysis nurse) and ultrasonographically (4mm diameter and access flow >500ml/min) [19].

3.4 Secondary endpoints/outcomes

All outcomes will be assessed at 3 and 12 months. Outcome measures have been chosen with two considerations: patient-centred care and to facilitate health economic analysis. They reflect the "standard CKD set" recommended by the International Consortium for Health Outcomes Measurement (ICHOM) CKD Working Group [20]. Key safety and efficacy outcomes for USS-guided regional nerve block outlined by the National Institute for Health and Clinical Excellence (NICE) [21] will also be recorded.

Access specific outcome measures:

- Patency (i.e. is the fistula running): defined clinically as the presence of a bruit
- Access complications (including infection, stenosis, thrombosis, steal, bleeding) (dates and nature)
- Re-operation/re-intervention to maintain or re-establish patency (revisional surgery, angioplasty, stenting or thrombectomy) (dates and nature)
- Alternative accesses e.g. CVCs (dates and access type)
- Time to first cannulation (date)
- Cannulation difficulties (including failure to establish two needle dialysis, infiltration, prolonged bleeding) (monitored in patient diaries and recorded at 3 and 12 months)

Patient specific outcome measures:

- Mortality (date and cause)
- Date commenced on HD
- Access modality at start of HD

- Change of RRT modality (dates)
- Change of access modality (dates)
- Access-related hospitalisation (dates and cause)

HR-QoL:

- EQ-5D-5L (EuroQol) [22]; Kidney Disease Quality of Life Short Form (KDQOL-SF) [23]; Vascular Access Specific Quality Of Life (VASQOL)

Safety outcome measures:

- Adverse events relating to anaesthesia e.g. systemic toxicity, pneumothorax, nerve damage, intravascular injection
- Technical difficulties delivering anaesthesia e.g. inability to identify structures, misplacement, paraesthesia

Anaesthesia:

- Pain score at incision, at 30 minutes and 1 hour postoperatively (NRS 0-10)
- Speed of onset/quality of motor and sensory block (as described in Rodriguez et al, 2004 [24])
- Need for anaesthetic supplementation/"failed block"
- Volume of anaesthetic agent (mL)
- Time to administer anaesthetic (mins)

Other:

- Change in surgical plan e.g. switch from BCF to RCF
- Patient satisfaction (NRS 0-10)

3.5 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation
Primary Objective To compare unassisted functional AVF patency at 1 year in patients undergoing primary RCF/ BCF creation under RA versus LA	Unassisted functional patency (defined as the ability of an access to uninterruptedly deliver the prescribed dialysis without intervention). In pre-D patients, this will be assessed clinically (by a blinded dialysis nurse) and ultrasonographically (4mm diameter and access flow >500ml/min)	12 months
Secondary Objectives To compare the efficacy (quality of anaesthesia) provided by LA and RA in patients undergoing AVF creation	- Perioperative pain score (NRS 0-10)) - Speed of onset/quality of motor and sensory block - Need for anaesthetic supplementation/"failed block" - Volume of anaesthetic agent - Time taken to administer anaesthetic	Day 0
To compare the safety of LA and RA in patients undergoing AVF creation	- Adverse events relating to anaesthesia e.g. pneumothorax, intravascular injection, systemic toxicity - Technical difficulties delivering anaesthesia e.g. inability to identify structures, misplacement, paraesthesia	Day 0
To compare the acceptability of LA and RA in patients undergoing AVF creation	- Patient satisfaction scores (NRS 0-10)	Day 0
To compare rates of re-intervention, access-related complications and need for alternative access in patients undergoing AVF creation under RA and LA	- Access complications (inc infection, stenosis, thrombosis, steal, bleeding) - Re-operation/re-intervention to maintain or re-establish patency (revisional surgery, angioplasty, stenting or thrombectomy) - Alternative accesses e.g. CVCs - Access-related hospitalisation	3 and 12 months
To compare mortality in patients undergoing AVF creation under RA and LA	- Mortality (date and cause)	
To compare dialysis and access modality utilised in	- Date commenced on HD - Access modality at start HD - Change of RRT modality - Change of access modality	3 and 12 months

patients undergoing AVF creation under RA and LA To evaluate the cost-effectiveness of RA versus LA for AVF creation	- EQ-5D-5L - KDQOL-SF - VASQOL	3 and 12 months

4 TRIAL DESIGN

A multicentre observer-blinded, parallel group, RCT with internal pilot and embedded process evaluation study.

5 TRIAL SETTING

Operating theatres, outpatient clinics and dialysis units at NHS secondary and tertiary care institutions. 12-20 UK vascular access units with capacity for AVF creation under both RA and LA. A range of high (>150 cases per year) and medium-volume centres (>50 cases per year) will be selected for participation to ensure a representative sample of current UK practice.

Participating centres will include:

- Addenbrooke's Hospital, Cambridge
- Belfast City Hospital, Belfast
- Bradford Royal Infirmary, Bradford
- Dumfries and Galloway Royal Infirmary, Dumfries
- The Freeman Hospital, Newcastle-upon-Tyne
- Guy's and St Thomas' Hospital, London
- James Cook University Hospital, Middlesborough
- John Radcliffe Hospital, Oxford
- NHS Lanarkshire (Monklands and Hairmyres Hospitals), East Kilbride
- Leeds General Infirmary, Leeds
- Ninewells Hospital, Dundee
- Norfolk and Norwich University Hospital, Norwich
- Queen Elizabeth University Hospital, Glasgow
- The Royal Free Hospital, London
- The Royal London Hospital, London
- Royal Sussex Hospital, Brighton
- Stobhill Ambulatory Care Hospital, Glasgow

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- All adult patients (>18 years old) with ESRD on RRT or CKD stage IV or V referred for primary RCF or BCF creation

6.2 Exclusion criteria

General:

- Unable or unwilling to provide informed consent
- Patient preference for general or alternative anaesthesia
- Active infection at surgical or anaesthetic site

Access-specific:

- Previous ipsilateral AVF creation (a previous attempt at distal AVF creation which fails immediately is not considered a contraindication, however any distal access which has previously run sufficiently to mature the outflow vein or proximal revision of an existing AVF is considered a contraindication)
- Known ipsilateral cephalic arch or central venous stenosis (even if previously treated)
- USS evidence of stenosis in inflow artery
- Radial or brachial artery <1.8mm diameter and/or cephalic vein <2mm at wrist or <3mm at elbow (with tourniquet) on pre-operative USS [25]

Contraindications to anaesthetic agents/ technique:

- Allergy to LA or any excipient agents
- Acquired or inherited coagulopathy (including warfarin/ heparin/ novel oral anticoagulant use where it has not been possible to stop the anticoagulation in anticipation of surgery) and/or platelets <75 or INR > 1.4 [26]
- Significant pre-existing neurological disorder affecting upper limb
- Weight <45kg

Anti-platelet agents, including clopidogrel, will not be considered a contraindication. Contrary to historical guidance, the most recent Association of Anaesthetists of Great Britain and Ireland (AAGBI) and American Society of Regional Anaesthesia and Pain Medicine guidelines [26,27] affirm that clopidogrel is not an absolute contraindication to superficial plexus block. Audit of local practice within NHSGGC indicates that 21% of the local ESRD population takes clopidogrel. Therefore, in order to facilitate recruitment, the trial protocol permits RA in this patient cohort. The choice between supraclavicular and axillary block in this group of patients will be at the discretion of the trial anaesthetist taking into account “site, compressibility, vascularity and consequences of bleeding” in each individual patient [27].

Dialysis on the day of surgery will not represent a contraindication assuming minimal/ heparin free circuits are used and at least 4 hours has elapsed between heparin dose and anaesthetic administration.

Underlying pulmonary disease / impaired lung function is not a contraindication per se. Utilisation of an axillary nerve block minimises the risk pulmonary complications and it is acknowledged that, in patients with either bilateral pulmonary disease or unilateral lung pathology on the contralateral side to surgery, the clinical team will need to make a case-by-case decision regarding choice of block due to the small but finite risk with a supraclavicular block of pneumothorax or, more commonly, temporary phrenic nerve paralysis.

In line with NIHR guidance on equality, diversity and inclusion all people regardless of gender, sexual orientation, pregnancy, ethnicity, religion and socioeconomic status will be offered the same opportunity to participate. Hospital translators will be used where appropriate to obtain consent and

the HR-QoL tools employed are available in a large variety of languages. Where it may not be possible to provide a translated HR-QoL tool, this will not serve as a contraindication to participation should the patient wish to, rather this secondary outcome measure will be omitted from data collection.

6.3 Co-enrolment

Patients participating in another trial, whether observational or interventional (including IMP), can be enrolled into the ACCess study. Similarly, patients under follow-up in ACCess may subsequently be enrolled into another trial. It will not however be possible to enrol a patient into ACCess and another interventional trial of AVF maturation. Specifically, this means it will not be possible to enrol a patient into both ACCess and the HTA-funded Surveillance Of arterioveNous fistulAs using ultRasound (SONAR-2) study (17/27/11), unless the intervention is to be performed on a different, unrelated vascular access.

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Participant identification

The clinical referral pathway for AVF creation varies significantly between units with regards timing of referral, surgical review and pre-operative imaging. The protocol for screening and recruitment visits is intentionally flexible in order to maximise recruitment opportunities.

Potentially eligible participants will be identified from vascular access clinics and theatre waiting lists by the clinical care team at the time a decision is made to undertake RCF/ BCF creation.

7.1.2 Screening

Case note review of patients' past medical and vascular access history will be undertaken by the clinical team to determine if eligibility criteria are met. A vein mapping ultrasound (performed within the last 6 months either by radiologist, sonographer or trained member of the clinical team) will be necessary to ensure minimum vessel characteristics.

If a patient is screened but is not eligible for the trial, an anonymous record of the case will be kept in the screening log. The screening log will collect patient initials, age, gender, date of screen failure and reason for screen failure. The screening log will be kept in the ISF and a copy sent to the ACCess Trial Office on a 3-monthly basis. This screening log information will inform the TSC and updates to the funder on recruitment targets.

7.1.3 Payment

Reimbursement will be provided for reasonable travel expenses to any study visits necessary additional to standard care. This should ensure that no patients are prevented from participating for financial reasons.

7.2 Consent

The Principal Investigator (PI) will retain overall responsibility for the conduct of research at their site, which includes the taking of informed consent of participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the protocol, principles of Good Clinical Practice (GCP) and

Declaration of Helsinki. If delegation of consent is undertaken then details should be recorded within the delegation log of the ISF.

A member of the research team will obtain written informed consent prior to the undertaking any trial intervention. The exact timing for obtaining informed consent may vary between centres depending on local practice. It will either be obtained in the outpatient clinic or in hospital prior to AVF creation.

All patients will be provided with a written Patient Information Sheet and be given the opportunity to ask questions of both the clinical and research team as they choose. Written information will be provided at least 48 hours prior to obtaining informed consent, allowing potential participants to fully consider the information provided, ask questions and reflect as appropriate. However, the patient also has the right to make an immediate decision to consent.

All patients have the right to refuse participation without giving reasons. Participants remain free to withdraw from the trial at any time without giving reasons and without prejudicing his/her further treatment. If a patient declines to consent a record of this will be made within the patient notes and in the ACCess study screening log.

Once signed, a copy of the consent form should be given to the patient; the original kept in the local ISF, a copy placed in the patient notes and a copy sent to the ACCess Trial Office at the Glasgow CTU. The informed consent discussion should be recorded in the participant's medical notes including the version number of the PIS provided to the participant.

Patients recruited into the trial will be assigned a unique patient identifier allowing both site and participant to be identified i.e. XXX-001 on all future trial documentation. An enrolment log will be maintained in the ISF to permit identification of patient names against trial numbers for those recruited to the trial. The ISF will be retained at a secure location in each participating centre. The enrolment log is the only place where patient identifiable information will be recorded, is for internal use only and will not be shared with the ACCess Trial Office. Upkeep and security of the ISF is the responsibility of the PI. Each study participant who has provided informed consent will be recorded as a participant in the NIHR Central Portfolio Management System (CPMS).

7.2.1 Additional consent provisions for ancillary studies

Participants will be asked to provide consent for future data linkage studies via the Scottish Renal Registry (SRR) and UK Renal Registry (UKRR). Participants who decline will still be eligible to participate in the primary study.

7.3 Randomisation

A central randomisation facility (interactive web response system, IWRS) at the Robertson Centre for Biostatistics (RCB) will randomise patients 1:1 to the intervention group (RA) or comparator group (LA).

The randomisation list will be created by a computer-generated program, using a method of permuted blocks stratified by centre, dialysis status (pre-D/ HD) and site of AVF (RCF/BCF). Pre-dialysis status will include those that have a failing transplant or failing peritoneal dialysis who plan to switch to haemodialysis. Randomisation will take place at a patient, not centre, level to minimise bias from variation in surgical and dialysis practice.

The randomisation list, the program that generated it and the random seed used will be stored in a secure network located within the RCB, accessible only to those responsible for provision of the randomisation system.

7.4 Blinding

Due to the systemic effects of RA (motor blockade; visible venodilatation, etc.), which do not occur with LA, it will not be possible to blind the patients, surgical or anaesthetic teams. An unblinded member of the research team will enter these peri-operative data onto the eCRF. A “sham” anaesthetic procedure was considered, but rejected, as it would not create the required clinical picture to maintain blinding but would expose the patient to the potential risks of supraclavicular/ axillary injection. Dialysis staff and the trial team performing follow-up visits will be blinded to the intervention and USS will provide independent objective assessment of the AVF. The statisticians and health economist will also be blinded to the intervention until database lock at the end of the study.

7.5 Emergency Unblinding

Given that the patient, anaesthetist and surgeon are unblinded and anaesthesia is a one-off intervention, there is no need for emergency unblinding procedures.

7.6 Baseline data

The following baseline data will be collected:

Demographics:

- Age
- Gender
- Ethnicity
- Body mass index
- Blood pressure/ heart rate
- Dialysis status (pre-D/ HD/ failing transplant/ PD)
- Diabetes
- Hypertension
- Ischaemic heart disease
- Cerebrovascular accident
- Primary renal disease
- Antiplatelet/ anticoagulant medication

AVF planning:

- Previous AVF (left/ right; RCF/BCF/BBF; AVG)
- Previous TCVCs (left/ right; number)
- USS findings: radial/ brachial artery diameter (mm); cephalic vein at wrist/elbow diameter (mm)

AVF surgery:

- Side of surgery (left/ right)
- Site of surgery (RCF/BCF)
- Surgeon (anonymised identifier and grade)

- Change of operative plan

HR-QoL:

- EQ-5D-5L
- KDQOL-SF
- VASQOL (a separate VASQOL will be recorded for each access)

7.7 Trial assessments

Current pathways for AVF creation vary between units. The study protocol will standardise elements of care necessary to ensure validity of the trial, but will permit variation in the timing of screening, consent and randomisation, thus facilitating recruitment and best use of local resources. Trial participants will attend for 3 or 4 trial visits according to local practice. A Schedule of Events is outlined in Appendix 1.

The pathway below outlines the current standard care pathway for AVF creation:

1. *Patient identified as requiring vascular access creation*
2. *Referral to surgeon/vascular access team* (+/- USS vein mapping, +/- clinic review by surgeon/ nephrologist/ access nurse according to local practice)
3. *Wait list for surgery*
4. *AVF creation under either LA or RA* (both are provided as standard care)
5. *Post-operative follow-up to ensure maturation* (most, though not all, centres review patient in clinic post AVF creation)

Additional care provided during the trial will be as follows:

Screening visit (case note review):

- Clinical team will perform case note review to determine eligibility
- USS vein mapping to determine eligibility (may be performed at pre-operative or treatment visit as local procedure)
- Patient information sheet may be provided by post

Pre-operative visit (may be omitted depending on local procedures; outpatient clinic):

- +/- USS vein mapping
- +/- Consent (may be done on day of surgery depending on unit preference)
- +/- Randomisation (may be done on day of surgery depending on unit preference)

Treatment Visit- Day 0 (inpatient):

- +/- Consent
- +/- Randomisation
- eCRF completion (baseline demographics)
- Anaesthesia (LA/ RA)
- AVF surgery
- Assessment of block quality
- HR-QoL questionnaires
- Clinical examination- patency prior to discharge

Follow-up visits- Month 3 and 12 (+/- 28 days) (outpatient clinic/ dialysis unit):

- Clinical assessment of AVF
- Doppler USS of AVF
- eCRF completion (primary and secondary endpoints)
- HR-QoL questionnaires

Additionally patients will be asked to complete a patient diary documenting cannulation difficulties real-time with each dialysis session. These will be checked at 3 and 12 month follow-up visits.

Wherever possible study visits will be timed to coincide with existing clinic appointments in pre-dialysis patients, and conducted whilst the patient is on dialysis for those patients already established on HD. This should minimise the trial burden on an already heavily medicalised patient cohort. Similarly, conducting follow-up visits whilst patients are on HD should minimise the number of patients who are "lost to follow-up". Generally patients with ESRD comprise a relatively sedentary population, therefore it in anticipated that few patients will be "lost to follow-up"

7.8 Embedded process evaluation study

Qualitative research is used to inform various aspects of clinical trial design and delivery including identification of barriers to recruitment; problems with trial set-up and management; and potential difficulties with trial scale-up [28,29,30,31]. The Rapid Research Evaluation and Appraisal Lab (RREAL) at the Department of Targeted Intervention, University College London (UCL) has developed a rapid feedback evaluation approach to collect, analyse and share findings with trialists at a time when they can be used to inform within trial decision-making processes [32].

An embedded process evaluation study will run in parallel with the trial. The rapid feedback evaluation approach will combine qualitative data obtained from semi-structured interviews with patients, carers and staff and documentary analysis (reports, meeting minutes etc.) to:

- Explore staff views and experiences with different approaches to recruitment
- Examine patient and carer experiences of participating in the trial (understanding of trial literature; experience with treatment options; reasons for withdrawal)
- Examine patient and carer experiences of declining to take part in the trial
- Identify barriers and enablers to trial set-up, recruitment and delivery from the point of view of staff

Data collection

The study will run in parallel to the trial and will combine semi-structured interviews with patients, carers and staff and documentary analysis (reports, meeting minutes, etc.) in 3-4 NHS Trusts across the UK. The sample will include 10 interviews with patients/carers and 10 interviews with staff at each site for a total of 60-80 interviews (see sampling). The interviews with staff will focus mainly on documenting their experience setting-up or implementing the trial, the main barriers encountered during these stages and strategies used to overcome them. These experiences will be understood by taking into consideration the context of the each of the sites where the trial is delivered. The interviews with patients/carers who have decided to take part in the trial will focus on their experiences with the trial, their understanding of trial information, reasons why they decided to take part in a trial, reasons for withdrawal and experiences with treatment options. The interviews with patients/carers will take place at least 1 week after entering the trial to be able to capture a wide range of experiences. In the case of patients who decline the invitation to take part in the trial or decide to withdraw, the interview will take place right after decline/withdrawal. If the withdrawal happens after the interview

has been carried out, the researcher will carry out a short follow-up interview with the patient/carer to explore the reasons for withdrawal.

The interviews will be audio recorded and the researcher will also take notes during the interviews. The interviews will be carried out over the phone or face to face. Following rapid evaluation approaches, the interview notes will then be summarised and added to a Rapid Assessment Procedures (RAP) sheet to enable the sharing of emerging findings with the CI and TSC on a regular basis. One RAP sheet per site will be developed to facilitate cross-site comparisons.

Key documents from each site, including trial documentation, meeting minutes and other local reports will be collected throughout the study. These documents will be used to understand the strategies developed for trial set-up and implementation, changes in these plans over time, barriers to implementation and strategies used to overcome these.

Sampling

A purposive sample of 30-40 staff members and 30-40 patients and carers will be included in the study. Potential staff participants will include: staff from research office in charge of setting up the trial, research nurses, staff delivering treatment, Research team at primary site, research team at individual sites, vascular access nurses, surgeons, anaesthetists and nephrologists involved in delivering the trial and dialysis nurses. Patients will also be sampled purposively to reflect a balance in relation to gender, age, treatment arm, dialysis and pre-dialysis patients. In cases where patients do not agree to take part in an interview, carers might be approached.

Recruitment

For the staff interviews, potential participants will be identified by the local PI as agreeable in concept to participate in the process evaluation study. They will be contacted by the qualitative researcher via email and provided with a copy of the PIS. They will have at least 48 hours to discuss the PIS with the researcher and ask questions. If they decide to take part in the study, they will be asked to sign a consent form. Staff will be able to withdraw consent at any time before or during interviews. In the event of consent being withdrawn after the completion of an interview, the data provided prior to withdrawal will be deleted.

For the interviews with patients who have decided to take part in the trial, the clinical team will first approach them with information about the study and ask if they (or their carer) would like to be contacted by the qualitative researcher. If they agree, the researcher will contact them with a copy of the PIS. They will have at least 48 hours to discuss the PIS with the researcher and ask questions. If they decide to take part in the study, they will be asked to sign a consent form. They will be informed that they will be able to withdraw consent at any time before or during interviews. In the event of consent being withdrawn after the completion of an interview, the data provided prior to withdrawal will be deleted. They will also be informed that their decision to participate or not in the qualitative study will not have any impact on the care the patient will receive.

For the interviews with patients who have declined participation in the trial and/or their carers, the member of the clinical team approaching them to obtain consent for the trial will provide them with information about the qualitative study when they decline participation and ask them if they would like to be contacted by the qualitative researcher. If they agree, the researcher will contact them with a copy of the PIS. They will have at least 48 hours to discuss the PIS with the researcher and ask questions. If they decide to take part in the study, they will be asked to sign a consent form. They will

be informed that they will be able to withdraw consent at any time before or during interviews. In the event of consent being withdrawn after the completion of an interview, the data provided prior to withdrawal will be deleted. They will also be informed that their decision to participate or not in the qualitative study will not have any impact on the care the patient will receive.

Data analysis

Transcripts and key documents will be imported into NVivo and analysed using framework analysis [33]. The framework will be shaped by the research questions, published literature on qualitative research during trial implementation and additional topics emerging from the data. Data collection and analysis will be carried out in parallel as emerging findings will be shared with the trial team on a monthly basis to inform trial design and delivery.

7.9 Withdrawal criteria

Participants may voluntarily withdraw from the study at any time, however it is impossible to change the allocated treatment once the anaesthetic procedure has been performed.

Clear distinction will be made as to whether a participant is withdrawing from the trial but is still willing to be followed up on an intention-to-treat basis, or whether the participant refuses any follow-up. If a participant explicitly withdraws consent to have any further data recorded their decision will be respected and recorded. All communication surrounding the withdrawal will be noted in the patient's hospital records and trial database, and no further data will be collected for that participant.

If a participant decides after randomisation but prior to anaesthetic that (s)he does not wish to participate, (s)he may withdraw his/herself from the trial treatment. In this situation, if agreeable, the patient would continue to be followed-up on an intention-to-treat basis, and a further patient recruited in their place. Timing randomisation as close as possible to the procedure should minimise the number of post-randomisation withdrawals.

The physician responsible for the clinical care of a patient is also permitted to withdraw the patient from the trial (or certain aspects of the trial) for appropriate medical reasons, be they individual adverse events or new information gained about a treatment.

Should a patient lose capacity to provide continued consent, they will be assumed to wish to remain in the ACCess trial as there are no further procedures or invasive tests required.

7.10 End of trial

The study will be deemed complete following the last visit by the last subject (LVLS). The CI will notify the sponsor and funder of the end of the trial within 90 days of completion.

8 TRIAL TREATMENTS

8.1 Description of Trial Treatments

The choice of anaesthetic agents is influenced largely by the successful utilisation of these combinations in our previous study [8]; the ready availability of these drugs within the UK; acceptability to collaborating centres and the ability of the combination to provide both rapid onset and prolonged duration of block [15].

8.1.1. Intervention Arm: Regional Anaesthesia (RA)

Regional anaesthesia will be delivered as an ***USS-guided supraclavicular or axillary block using a 1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine, mixed with epinephrine (final concentration 1 in 400,000)***

It is recommended that this anaesthetic combination is achieved by mixing 10ml of 0.5% L-bupivacaine and 10ml of 1% lidocaine and then adding 0.05ml of 1:1,000 adrenaline (Appendix 2).

RA will be administered by a consultant anaesthetist trained in RA, or trainee practicing under direct supervision. USS guidance will be used at all times. A supraclavicular approach will be considered first-line, unless the anatomy or patient risk profile is unfavourable. In this situation an axillary block may be performed. In patients on antiplatelets or other anticoagulants, the choice between supraclavicular and axillary block will be at the discretion of the anaesthetist and take into account "compressibility, vascularity and consequences of bleeding" in each individual patient [27].

A 1:1 mixture of 0.5% L-bupivacaine, 1% lidocaine and epinephrine (mixed to 1 in 400,000 final concentration) will be utilised. Maximum dose limits: 2 mg/kg for bupivacaine and 7 mg/kg for lidocaine with epinephrine, recognising that the effects are additive.

Volumes of LA injected must take into account the weight of the patient and the maximum dose limits, whilst allowing spare LA for supplementation. In a study where the median patient weight was 66kg the ED95 for supraclavicular blocks was 27ml. A minimum volume of 25ml must be injected for patients over 60kg. This should be reduced to a minimum of 20mls in patients 51-60kg, and 15mls minimum for patients 45-50kg (Appendix 2). For supraclavicular blocks, a suggested technique is that a minimum of 25% of the LA will be deposited in the "corner pocket' between the 1st rib and the subclavian artery and the remainder will be deposited around the plexus posterolaterally, avoiding deliberate intracluster injection [34]. For axillary blocks, the same minimum volumes must be utilised, targeting 25% of the LA to the musculocutaneous nerve, with the remainder deposited around the ulnar, median and radial nerves (and the cutaneous nerves of the arm and forearm if these are visualised). These cutaneous nerves must be blocked directly or indirectly if axillary block is to be used for a brachiocephalic AVF.

Sensory and motor block of musculocutaneous, median, radial and ulnar nerves will be recorded every 5 minutes using previously validated 3-point scale [24]. Sensory blockade of the medial cutaneous nerve of the forearm and arm will also be recorded. Measurements will be continued until either sensory block is adequate or 30 minutes has elapsed, at which point the block may be supplemented by targeted USS-guided axillary or midhumeral injection as appropriate.

8.1.2. Comparator Arm: Local Anaesthesia (LA)

Local anaesthesia will be delivered as a ***1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine.***

A 1:1 mixture of 0.5% L-bupivacaine and 1% lidocaine will be infiltrated into the skin and soft tissues around the operative site by the operating surgeon prior to surgery commencing (Appendix 3). After 5 minutes, the adequacy of anaesthesia will be tested by application of a painful stimulus and additional local anaesthetic infiltration administered as required. Maximum dose limits of 2 mg/kg for bupivacaine and 3mg/kg for lidocaine will be observed, recognising that the effects are additive.

8.2. Management of a "failed block" (or failure of local anaesthesia)

A "failed block" will be defined as any block that (despite the targeted intervention described above) requires additional supplementation with LA, analgesia, conversion to GA or abandonment of surgery.

The incidence of “failed block” is anticipated to be low. Evidence from the published literature indicates that up to 8% of blocks may need supplementation either as an additional targeted block or LA infiltration [35]. Only one of the 63 patients (1.6%) from our previous single-centre RCT required LA supplementation [10]. Both intention-to-treat and per protocol analysis will be performed to account for “failed blocks”, however any confounding effect is anticipated to be minimal.

The algorithm for “failed block” or “failed LA” will be as follows:

1. Supplementation with LA (1% lidocaine) up to maximum cumulative LA dosage
2. Intravenous sedation and analgesia at the discretion of the anaesthetist
3. General anaesthesia (GA)
4. Abandonment of procedure: decision to be made following discussion between operating surgeon and anaesthetist if deemed unsafe to proceed with GA

The TSC/ DMC will monitor the number of failed blocks for patient safety and quality assurance throughout the study.

8.3. Pre-operative assessment and fasting

All patients will be assessed and prepared for surgery in accordance with standards set by the AAGBI [36]. Patients should be fasted as dictated by local guidelines. Unlimited clear fluids will be actively encouraged until 2 hours prior to the procedure [37].

8.4. Day case surgery

The new Best Practice Tariff for day case AVF surgery in England and Wales necessitates consideration in any vascular access cost-effectiveness study. In line with the government drive to have >80% of AVF created as day case procedures [38], the protocol will follow recently published AAGBI/ British Association of Day Surgery guidelines to define criteria for day surgery [39]. These guidelines state that fitness for a procedure should relate to the patient’s functional status rather than ASA physical status. Conditions such as obesity, diabetes and obstructive sleep apnoea are not necessarily contraindications to day surgery. Similarly, residual motor and/or sensory block are also not requirements for overnight observation. With appropriate supervision and arm protection, these patients may be discharged home with written instruction advising on their conduct until normal power and sensation return. Patients who live alone will not be deemed suitable for day surgery for surgical reasons due to the small risk of major post-operative haemorrhage. Failure to provide day case surgery within these criteria will not be considered a protocol breach however an explanation will be sought and documented. This will allow assessment of the feasibility of, and barriers to, day case AVF surgery.

8.5. Standardisation of surgical technique

A standardised surgical technique will be used throughout the trial to eliminate unwanted variation and potential confounding effects of operating surgeon/ centre.

The operating surgeon must be independently competent (i.e. beyond the learning curve) the perform AVF surgery as judged by themselves and the local PI (or suitably delegated senior surgeon if the PI is not a vascular access surgeon).

Microsurgical instruments will be used throughout. A standard approach to the vessels will be performed with transverse incision at, or just below, the elbow crease for BCF and longitudinal or

curvilinear incision at the wrist for RCF. The cephalic vein (or median cubital vein if suitable at the elbow) will dissected and skeletalised for a short length proximally and distally. Visible branches will ligated and divided. The vein will be divided, spatulated (where appropriate) and flushed with heparinised saline. The artery will be dissected and controlled with bulldog clamps or slings. The decision to utilise median cubital, perforating branch or true outflow cephalic vein for the anastomosis will be at the surgeon's discretion. Similarly the decision to create a proximal radial or ulno-cephalic fistula at the elbow will be at the surgeon's discretion, although these variables will be captured on the intra-operative eCRF. The size of the arteriotomy performed will be based on the risks and benefits for the individual patient (e.g. vessel quality, risk of steal etc.), however generally arteriotomies will between 3-5mm in length on the brachial artery and 7-10mm on the radial artery. An end-to-side anastomosis of vein to artery will be performed with continuous 6.0 (elbow) or 7.0 (wrist) Prolene.

Intra-operative findings and complications will be recorded on the eCRF. Minor deviations from the operative protocol will not be considered violations but will be recorded on the eCRF and any pattern of deviation evaluated by the DMC.

8.6. Perioperative Patient Safety

The Royal College of Anaesthetists (RCoA) "Stop Before You Block" checklist for correct site surgery [40] will be implemented in both study arms; full monitoring will be applied as outlined in AAGBI standards [41] and provisions made to follow AAGBI Severe Local Anaesthetic Toxicity Guideline [42] in the unlikely event of serious adverse reaction or toxicity. Following RA, patients will be supervised and monitored by an anaesthetist or "suitably competent health care worker" in line with Regional Anaesthesia-UK (RA-UK) guidance [43].

8.7 Known drug reactions and recognised adverse events

No adverse effects from either LA or RA were observed in our previous single centre RCT [10].

An NIHR-commissioned literature review of USS-guided regional anaesthesia [23] including 5 RCT, two non-randomised controlled trials, three case series and one case report including a total of 3,180 patients found no evidence of local anaesthestic toxicity or pneumothorax. Two patients (0.06%) had inadvertent intravascular injection of anaesthesia (one experienced seizures, the other had a prolonged block). 14 patients (0.4%) experienced accidental vascular puncture with no long-term sequalae reported and 4 patients (0.1%) experienced transiently prolonged paraesthesia or neurological symptoms, all of which had resolved by 6 weeks. Only 4 of these studies report outcomes in the upper limb and none make the distinction between axillary and supraclavicular block.

8.8 Assessment and management of risk

This trial is categorised as Type A = No higher than the risk of standard medical care

Both LA and RA are offered variably for AVF creation. As outlined in Section 8.7, the risks associated with both treatment arms are negligible and no greater than standard medical care.

No invasive tests are required during follow-up or for outcome assessment. A full risk assessment is outlined in Appendix 4.

8.8.1. Incidental findings

Incidental findings e.g. stenosis or aneurysm detected on USS or at follow-up visits will only be acted upon if clinically relevant. No intervention will be sought for asymptomatic stenoses detected outwith standard practice.

9 ADVERSE EVENT REPORTING

9.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a trail specific procedure has been administered, including occurrences which are not necessarily caused by or related to that trial specific procedure.

Serious Adverse Event (SAE)

Any adverse event or adverse reaction 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
f) Is otherwise considered medically significant by the investigator
g) Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above

Related Unexpected Serious Adverse Event (RUSAE)

Any SAE thought to be related to a trial specific procedure performed on that subject that is thought to be unexpected; that is the event is not listed within the protocol or would not be expected to occur when carrying out the trial specific procedure in normal clinical practice.

9.2 Recording and reporting of Adverse Events

All 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. Any AE meeting the regulatory definition of an SAE should also be assessed for causality and expectedness by the local investigators.

Adverse events should be recorded within the patient's case notes. SAEs should be recorded in the patient's case notes and reported via the eCRF.

9.3 Recording and reporting of Serious Adverse Events

In addition to events meeting the definition of SAE as outlined in Section 9.1, the following events must be also be recorded within the eCRF as SAEs within 24 hours of sites becoming aware of the event:

- Recognised perioperative complication of regional or local anaesthetic administration (including pneumothorax, inadvertent arterial puncture, inadvertent intraneural/intravascular injection, persistent neuropraxia, local anaesthetic toxicity)
- Any requirement for re-exploration or the abandonment of surgery

Full details including the nature of the event, start and stop dates, severity, actions taken, relationship to the trial specific intervention and the outcome of the event will be recorded in the patient's medical

notes and the eCRF. These events will be monitored and followed up until satisfactory resolution and stabilisation.

Causality of these events must be assessed by the PI or another authorised local investigator and will be assessed for expectedness by the CI or their delegate. This expectedness assessment will be based on the clinical judgement/experience of the CI with reference to section 9.4 and those SAEs listed as expected below in section 9.4.2

9.4 Expedited reporting of Related Unexpected Serious Adverse Events

Any SAE recorded within the eCRF that occurs between the date of randomisation and 30 days post-surgery that is thought to be both:

Related: that is, it resulted from administration of the anaesthetic or any of the research procedures,

And

Unexpected: that is, against the procedure events listed below as an expected occurrence

Will be reported to the Pharmacovigilance (PV) Office immediately (within 24 hours) via the eCRF.

The CI (or delegate) will review the RUSAE and provide their own assessment of causality. The CI will also perform an expectedness assessment.

9.4.1 Reporting of RUSAEs to the Ethics Committee

The PV office will report all RUSAEs to the ethics committee within 15 days of the PV office becoming aware of the event, via 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 Chief Investigator.

9.4.2 Expected Serious Adverse Events Related to the Administration of Anaesthesia

For expectedness assessment purposes, the following will be considered as expected serious adverse events:

- Pneumothorax
- Inadvertent arterial puncture/ haematoma
- Inadvertent intraneural/ intravascular injection
- Local anaesthetic toxicity (including seizures)
- Neuropraxia

For events considered related to the local anaesthetic agents, the expectedness of the event should be assessed against the relevant SmPC.

9.5 Reporting of non-expedited SAEs to the DMC and TSC

Glasgow CTU will report all SAEs to the DMC, the CI and the trial Sponsor, following a timetable outlined in the Trial Monitoring Plan (Section 9.6.1). The DMC will review the open, unblinded data for safety. Glasgow CTU will also report all SAEs to the TSC, blinded to treatment allocation, following a timetable agreed by the TSC prior to study commencement (approximately bi-annually).

9.6 Responsibilities

The following personnel will be responsible for activities outlined below:

Principal Investigator (PI):

1. Checking for adverse events when participants attend for treatment / follow-up.
2. Using medical judgement in assigning seriousness, causality and providing an opinion on whether any SAE was expected using the safety information outlined in section 9.4.2
3. Ensuring that adverse events are recorded in line with the requirements of the protocol.

Chief Investigator (CI):

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness to SAEs (in line with known safety information outlined in Section 9.3.2) where it has not been possible to obtain local medical assessment.
3. Immediate review of all RUSAEs
4. Review of SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

Sponsor (delegated to Glasgow CTU):

1. Central data collection and verification of adverse events according to the trial protocol onto a database.
2. Reporting safety information to the CI for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Notifying Investigators and REC of RUSAEs that occur within the trial.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.6.1. Trial Monitoring Plan

All SAEs will be reviewed by the CI (or nominated delegate) in line with the Trial Monitoring Plan outlined below:

- CI review of all RUSAEs within 1 week of their occurrence (blinded)
- CI review of all other SAEs on a monthly basis (blinded)
- Cumulative review of all safety information by the DMC on an annual basis (unblinded)

9.7 Notification of deaths

All deaths will be reported to the DMC, CI and sponsor for continuous safety review. A formal report will be prepared for the REC and DMC on an annual basis. Any death that is assessed to be caused (or possibly be caused) by the study treatment will be reported will be reported to the sponsor and REC immediately.

9.8 Pregnancy reporting

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

9.9 Overdose

An overdose will be defined as any excess in the maximum dose limits of local anaesthetic outlined in the protocol recognising that the effects are additive, irrespective of whether an (S)AR occurs as a result.

Any overdoses must be recorded as a protocol violation within the deviation log and reported to the Glasgow CTU within 24 hours of the local PI becoming aware of it.

These patients will continue to be followed-up on an intention-to-treat basis.

9.10 Reporting urgent safety measures

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

9.11 The type and duration of the follow-up of participants after adverse reactions.

It is anticipated that any adverse reaction to the trial intervention or comparator will occur in the immediate perioperative phase. Delayed reactions are not anticipated. No additional follow-up of SAEs beyond the duration of the trial is deemed necessary.

9.12 COVID-19

At the time of protocol writing, the COVID-19 epidemic is rapidly evolving. It is anticipated that, by the time recruitment commences, the situation will have normalised significantly however the trial team remain anxious to ensure that the clinical element of the trial be conducted at a time when stability and efficiency has returned to the operating theatre environment for two reasons:

1. Optimal recruitment requires maximal theatre throughput
2. The validity of secondary cost-effectiveness endpoints requires a trial environment representative of future clinical practice

Contingency plans will vary between centres (Appendix 6) but include bedside USS wherever possible to avoid additional hospital attendances; utilisation of a “block room” to optimise theatre throughput; and off-site operating.

Prior to commencement of recruitment, the ability of sites to recruit will be evaluated by the TSC and alternative sites substituted as required.

In the unlikely event of a major second wave, recruitment may need to be paused. Such a decision would be taken by the Sponsor in conjunction with the TSC, having first sought advice from the funder. In this case, follow-up of previously recruited patients would continue, either in person (when patients attends for HD) or via telephone (to minimise hospital contacts in pre-D patients).

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

566 subjects (283 per arm) will be required to detect a 15% difference in the primary outcome measure with 5% significance level and 90% power, assuming that 15% of subjects will be lost to follow-up, will change RRT modality or die.

15% is considered to be the minimum clinically importance difference between the two cohorts. It is a conservative estimate of the 19% difference in 1-year unassisted functional patency observed in the results from our single-centre RCT (65% RA vs. 46% LA; OR 2.1; P<0.01) [16] and is the magnitude of difference considered appropriate by experts in the field following independent review of the protocol by the UK Renal Trials Network (UKRTN). UKRR data indicates that 47% of incident patients are currently commencing HD via an AVF/ AVG (target: 60%) [3]. A 15% increase in functional patency would allow this target to be achieved. Similarly a 15% increase in AVF usage among prevalent HD patients would allow 95% of UK dialysis units to achieve the 80% prevalence target.

10.2 Planned recruitment rate

We anticipate that the recruitment rate will be relatively consistent throughout the duration of the trial. Initially, patients will be recruited from 12 centres during the pilot phase of the trial (Section 10.6), however may be increased up to 20 centres if recruitment is slower than anticipated.

Based on previous experience from the single centre study [10], we anticipate a screen failure rate of 25%.

To successfully complete on target, patients need to be recruited at a rate of 24 per month. We anticipate at least 12 centres (three high volume and nine medium volume) recruiting an average of 2 patients/centre/month. Conservatively estimating 25% recruitment at centres not participating in the HTA-funded Surveillance Of arterioveNous fistulAs using ultRasound (SONAR) study (17/27/11) and 15% recruitment from SONAR-participating centres, it would be possible to enrol 627 patients in 24 months. This estimate is in line with that observed in other HTA-funded trials (average: 1.96 patients/centre/month) [44] and the SONAR-1 study, which recruited 348 patients in 14 months (average: 1.5 patients/centre/month) (G Pettigrew, personal communication).

10.3 Statistical analysis plan

All statistical analyses will be carried out according to a detailed Statistical Analysis Plan, to be finalised prior to unblinding of treatment allocations and agreed by trial statisticians, the CI, and the TSC. All statistical programs will be developed and validated using dummy treatment codes.

Analyses will primarily be performed according to the intention-to-treat principle, i.e. by randomised group, rather than intervention received. However, additional analysis will be pre-specified to address “failed blocks” (e.g. per-protocol, as treated, and complier-average causal effects analyses).

10.3.1 Summary of baseline data and flow of patients

The flow of the patients in the study will be described according to CONSORT guidelines. The baseline characteristics listed in section 7.6 of this document will be summarised by randomised group without formal statistical comparison.

10.3.2 Primary outcome analysis

Unassisted functional patency will be analysed using a logistic regression model, adjusting for the stratification variables used at randomisation (centre, RRT modality, and site of AVF) and the treatment group assigned. The treatment effect will be reported with a 95% confidence interval for the Odds Ratio and p-value also reported. Time to loss of functional access will also be analysed using survival analysis regression methods.

10.3.3 Secondary outcome analysis

Similarly to the primary outcome, for each of the secondary outcomes, analyses will be conducted using appropriate regression methods reporting the treatment effects, 95% confidence intervals and p-values.

10.4 Safety analysis

Safety data including the number of adverse events and serious adverse events, including both the number of events and the number of subjects with events, will be reported overall and by study arm, where no formal statistical testing will be carried out.

10.5 Interim analysis and criteria for the premature termination of the trial

A 4-month internal pilot will be employed, principally to assess feasibility of recruitment. The following stop-go (traffic light) criteria for continuance to the full trial will be used:

- Red: Stop if <50 patients recruited or if <5 centres are open to recruitment
- Amber: Enrol more centres if between 48 and 95 patients recruited
- Green: Continue within existing parameters if >95 patients recruited

It is essential that pilot sites are representative; therefore the additional stop-go criterion of at least 5 sites recruiting by the end of the pilot has been introduced. Additionally if there is failure of adherence to trial protocol in >20% of participants or significant safety concerns raised by the Data Monitoring Committee (DMC) the trial will not progress beyond the pilot phase.

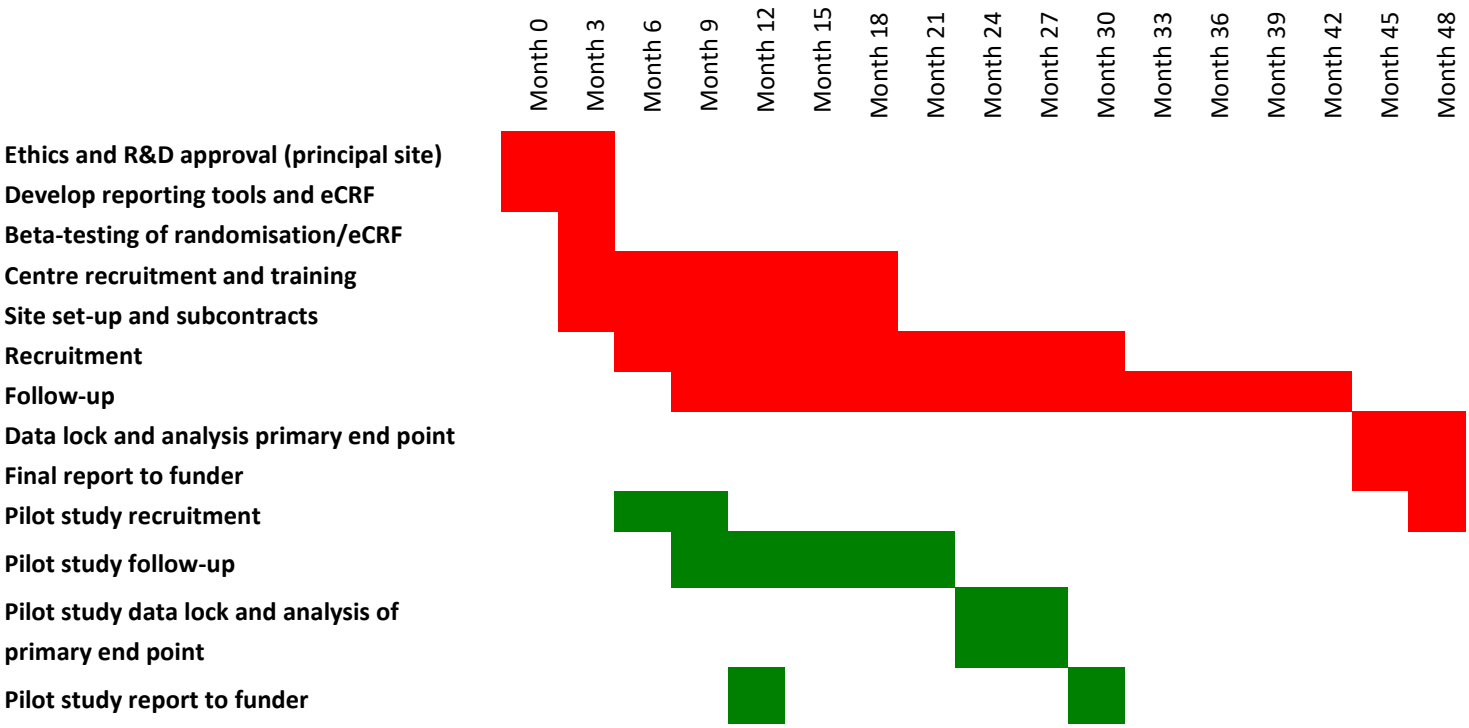
	Red	**Amber**	**Green**
% of Total Trial Recruitment	<50%	50-100%	100%
Recruitment rate/site/month	1	1-2	>2
Number of sites opened	<5	5-12	12
Total number of participants recruited	<48	48-95	>95
Failure of adherence to trial protocol	>20%	5-20%	<5%

In the event that the trial was to be terminated following the internal pilot, all patients would be followed up until the end of trial.

Otherwise, due to the relatively short duration and one-off trial intervention, no formal interim analysis will be undertaken unless requested by the DMC. In this case, analysis would be performed by blinded statisticians, with results only unblinded if evidence of overwhelming benefit or harm is demonstrated.

The GANTT chart below reflects the timeline for recruitment, follow-up and data-analysis, both of the

full trial (red) and in the event that only the pilot study (green) were to complete.



Additionally, the trial may be prematurely discontinued at any time on the basis of new safety information, lack of recruitment or upon advice of the sponsor, TSC, DMC or REC. The Trial Steering Committee (TSC), in discussion with the funder, will make the final decision regarding any premature trial termination. The Research Ethics Committee will be informed within 15 days of the early termination of the trial.

10.6 Procedure(s) to account for missing or spurious data

To determine the impact of uncertainty due to missing data in the study, this will be explored using multiple imputation methods.

10.7 Economic evaluation

The cost-effectiveness analysis will be conducted alongside the clinical trial so that data on costs and health outcomes will be available for each individual patient enrolled in the trial. The health outcomes for the cost-effectiveness analysis will be quality-adjusted life years (QALYs). Two complementary cost-effectiveness analyses will be performed:

1. A within- trial evaluation where cost and health effects of individual patients are limited to the one-year follow-up period in the trial
2. A decision model approach where cost and health effects are modelled to enable the incorporation of longer-term impacts of the intervention.

The primary outcome of the economic evaluation is the incremental cost-effectiveness ratio of regional compared to local anaesthesia in AVF creation expressed in £/QALY.

The economic analysis will be conducted from the perspective of NHS and personal social services (PSS). The computation of cost-effectiveness ratios from the point of view of society as a whole will also be explored.

10.7.1 Health economic data collection

All resource use data will be collected for each patient enrolled in the trial. This will be classified in intervention-related resource use (i.e. volume of anaesthetic agent, time required to perform procedure, need for anaesthetic supplementation, anaesthesia team composition including relevant NHS bands) and access-related resource use (i.e. access-related complications and hospitalisations, re-interventions, alternative access types created). Adverse events related to the intervention that result in resource utilisation will also be collected and included in the analysis.

Unit costs will be applied to all resource use estimates and will be informed where possible from standard UK sources such as the PSSRU, NHS Reference Costs, or the BNF for medicines-related costs. A bottom-up approach will be used to estimate the costs associated with the two anaesthesia procedures, by breaking down their respective resource use into medicines, medical equipment and staff time. Any initial capital outlays relating to specialised machinery/devices or multi-use products will be converted into equivalent annual costs based on the operational lifetime of the asset.

Effects will be captured at the individual patient level as part of the multi-centre controlled trial. Quality-adjusted life years will be derived by combining overall survival with utility weights derived from the EQ-5D questionnaire values obtained at the pre-operative time, at 3 months and 12 months after treatment.

10.7.2 Health Economic Analysis

10.7.2.1 Cost-effectiveness analysis alongside clinical trial (within-trial evaluation)

At the end of the clinical trial, cost and effects are available for each participating patient. Cost of an individual patient for the period from treatment until the end of the one-year follow-up will be estimated in both the intervention and comparator arms by taking into account the anaesthetic volume used and any supplementations, anaesthetic cost, staff costs and time taken to perform the procedure, adverse events-related to the intervention, as well as access-related complications, re-interventions and alternative access methods created across the follow-up of the study. The effect on individual patients will be their quality- adjusted life years measured as their EQ-5D value obtained at the end of the one-year follow- up. The point estimate of the incremental cost-effectiveness ratio (ICER) will be calculated as:

$$ICER = \frac{\overline{C_\iota} - \overline{C_c}}{\overline{E_\iota} - \overline{E_c}}$$

where $\overline{C_\iota}$ and $\overline{C_c}$ are the arithmetic mean costs among patients in the intervention arm and control arm respectively. Similarly $\overline{E_\iota}$ and $\overline{E_c}$ are the arithmetic mean quality-adjusted life years in the intervention arm and control arm.

The 1-year ICER may be assessed against an accepted cost-effectiveness threshold (national and international).

10.7.2.2 Decision analytic model analysis

In order to assess the long-term economic impact of the intervention, it is necessary to analyse cost, effects and to compute ICER over time intervals stretching beyond trial period. To study the long-term perspectives and to derive ICERs in this context, a discrete-time state-transition Markov model will be used, with each cycle consisting of relevant events (i.e. maturation/functional patency, failure, complications, re-intervention, alternative access, adverse events, death). Events will be driven by transition probabilities within the model, being informed partly by within-trial data in the short-term (i.e. up to 1 year) and other sources (literature, electronic health records, etc) in the long-term (i.e. beyond 1-year).

10.7.3. Exploring analysis uncertainty

The uncertainty of the within-trial ICER point estimate will be quantified using appropriate methods, which will depend on the distributional characteristics of costs and effects. In accordance with current practice, the uncertainty associated with data may be further investigated by computing ICERs for a large number of subsamples (i.e. bootstrapping), thereby obtaining an empirical distribution of incremental cost-effectiveness ratios, which not only gives an alternative estimate of the confidence interval but also makes it possible to study the distribution in a more detailed way.

Cost-effectiveness acceptability curves represent still another way of displaying the inherent uncertainty connected with data collection and subsequent computation. The curves display the estimated probability of regarding the intervention as cost-effective at any given threshold level for the ICER.

Expected value of perfect information analysis can provide further information about the impact of uncertainty by computing the difference between the gains (depending on the choice of perspective) to be obtained if perfect information was available and the expected gains obtained after data collection.

While the above methods are designed to exhibit the data uncertainty in the analysis, uncertainty coming from choice of method, use of externally given parameters etc. will not be displayed and must be analysed separately. This is done by carrying out alternative computations with different values of crucial parameters and/or slightly changed formulation of the basic computational model. Both univariate and multivariate (probabilistic) sensitivity analyses will be conducted as well as extensive scenario analyses to explore the uncertainty relating to the model structure and assumptions.

10.7.4. Measurement of HR-QoL

HR-QoL is not expected to be significantly impacted by the intervention itself, however vascular access type and subsequent ability to dialyse via a functional AVF is likely to impact on the QoL of patients with ESRD [8].

No specific HR-QoL outcomes measures for use in patients with renal failure are listed by the COMET Initiative. Our choice for health-related outcomes measures is influenced by two factors: patient-focused tools as recommended by the ICHOM CKD Working Group [22] and simple, validated questionnaires that will allow rapid derivation of QALYs. Three tools will be employed:

EQ-5D-5L: This generic, preference-based questionnaire is essential in the derivation of an outcome measure comparable across multiple disease areas and interventions (e.g. QALYs), thus facilitating decision-making with regards to value-for-money in context of a larger NHS. However, it is an inherent

limitation of such broad instruments that they may not be sensitive enough to detect access, or even disease-specific changes.

KDQOL-SF: The KDQOL-SF includes eight generic measures of health status and multiple disease-specific QOL scales. The instrument also includes two scales that focus on the patient's assessment of dialysis care but is not access-specific. The reliability and validity of the KDQOL-SF has already been demonstrated within the dialysis population [45] and, to date, it's the only patient-related outcome measure (PROM) shown to demonstrate differences between access modalities [8]. The KDQOL-SF tool captures all 6 HRQoL domains (pain, fatigue, physical function, depression, daily activity) recommended by the ICHOM CKD Working Group [22].

VAS-QoL: Capturing vascular access specific QoL is challenging due to lack of access sensitive tools. Any subtle influence that access modality may have on HRQoL is likely to be engulfed by the overwhelming impact of dialysis state. The NHSGGC Vascular Access Research Group has been collaborating with the Department of Social and Public Policy, University of Glasgow; the Department of Computer & Information Sciences, University of Strathclyde and the Usher Institute of Population Health Sciences and Informatics, University of Edinburgh to develop a novel Vascular Access Specific Quality of Life (VAS-QoL) tool. The tool has been developed with extensive PPI involvement. Semi-structured patient interviews (n=24) conducted using the capabilities model [46] identified key themes: function; longevity; enjoyment of normal life and control [47]. These themes were then grouped by clinician focus groups into three domains: physical, capabilities and flourishing/wellbeing and a 10 question PROM with high content validity was developed and demonstrated [47,48]. The VAS-QoL tool is currently undergoing clinical validation studies. Preliminary results are expected November 2020.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

All trial data will be collated and submitted in an anonymised manner to the Glasgow CTU via a web-based secure electronic Case Report form (eCRF). Duplicate paper worksheets will also be provided for ease of data collection particularly in the operating theatre environment. Any data collected on duplicate paper worksheets must be transcribed to the eCRF by a member of the research team before submission to Glasgow CTU.

For the purposes of this study, source documentation comprises of the patients clinical records (paper and electronic), reports of the USS scans, patient diaries and HR-QoL questionnaires. USS reports (or certified copies), original patient diaries, original HR-QoL questionnaires and original consent forms must be retained within the ISF. Any transcribed paper worksheets must also be retained within the ISF along with a record of the date of transcription. It is essential the source data is original, accurate, legible, contemporaneous, attributable and available when needed for confirmation, quality control, audit or inspection purposes.

11.2 Data handling and record keeping

The Robertson Centre for Biostatistics (RCB) is part of the Glasgow CTU and has extensive experience of the design, analysis and reporting of clinical trials and will provide all data management and statistical services in support of delivering this trial. Pseudoanonymised data entered into the eCRF will be managed and stored by the RCB in line with the detailed Data Management Plan, which

will be developed for the study in line with approved templates, reviewed regularly, and all members of the project team will adhere to the plan, and well established local SOPs.

The RCB systems are fully validated in accordance with industry and regulatory standards, and incorporate controlled access security. High volume servers are firewall protected and preventative system maintenance policies are in place to ensure no loss of service or data. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data are backed up on-site nightly and to a commercial data vault on a regular basis. The Robertson Centre for Biostatistics has an ISO 9001 quality management system and ISO 27001 for Information Security, and is regularly inspected against the standards by the British Standards Institution.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent as outlined in Section 12.

11.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of trial report.

The sponsor will be responsible for archiving the essential documents contained within the Trial Master File and, via the Glasgow CTU, the trial database. Principal Investigators are responsible for the secure archiving of essential trial documents for their site, according to the local policy at that site.

All essential documents will be archived in a secure commercial vault for a minimum of 5 years after completion of trial. Destruction of essential documents will require authorisation from the Sponsor.

Trial data will be stored under controlled conditions for at least 10 years after closure. This will allow adequate time for review and reappraisal. Glasgow CTU has standard processes for both hard copy and computer database legacy archiving, including anonymisation of trial data.

12 MONITORING, AUDIT & INSPECTION

A detailed Trial Monitoring Plan has been developed and agreed by the sponsor and Trial Management Group as outlined in Section 9.6.1.

As a non-CTIMP categorised as Type A, i.e, risk similar to standard care (Appendix 4), the study will not be monitored by the sponsor. However the sponsor randomly selects a number of studies to be audited annually. In addition audits can be requested by individual participating sites/TSC.

The funder, NIHR, will have the right, but not the obligation, to audit the Sponsor's processes in relation to the study.

The study will also adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the trial data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC)

Before the start of the trial, approval will be sought from a REC for the trial protocol and other study documents.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (amendments may also need to be reviewed and approved by the NHS R&D departments before they can be implemented in practice at local sites).

All correspondence with the REC will be retained by the CI.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the trial.

If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report to the REC with the results, including any publications/abstracts.

13.2 Peer review

Proportionate independent, expert peer review has been provided by both the NIHR Funding Committee (March 2020) and UK Renal Trials Network (December 2019). The latter involved assessment by two expert clinical trialists, the UKRR research lead, two expert statisticians and a patient representative.

13.3 Public and Patient Involvement

PPI is integral to the design, implementation, governance and dissemination of this study ensuring that the question being asked is important, outcomes appropriate and design acceptable to potential participants.

Consultation with patients and caregivers highlighted the "loss of control" experienced by many patients starting HD. By actively involving them in data collection, trial governance and result dissemination we hope to empower them to take a keen role in advancing care for dialysis patients.

Design: Semi-structured patient interviews have identified a key theme of "functionality" (*"it's no good having a fistula unless you can dialyse through it")*. This observation was of critical importance in the selection of "unassisted functional patency" as our patient-focussed primary outcome measure.

Implementation: Patient focus groups highlighted the "exhaustion" experienced by patients starting HD. Patients stressed that research interventions should not further increase healthcare burden, so HD patients will be followed-up in their dialysis units to avoid additional hospital appointments.

Governance: A further patient focus group will be convened after 6 months; the process evaluation study will provide rapid 'in trial' feedback from patients/ carers to the research team; and the PPI co-applicant will sit on the TSC, to ensure that the patient's voice is heard throughout the trial.

Dissemination: We will build on established links with patient charities e.g. KidneyCareUK to produce language and content appropriate trial literature and advertising both to promote the trial and disseminate results.

13.3.1 PPI consultation and impact on trial design

At the conception of this study, consultation with HD patients (n=6) identified “exhaustion” as a prevailing symptom. They highlighted the burden of 3 times per week HD and stressed that research interventions should not unnecessarily increase time spent at hospital. They also felt cumbersome study visits may hinder recruitment. As a result, the study protocol facilitates follow-up of HD patients during dialysis sessions. Care-givers (dialysis nurses; n=4) highlighted potential secondary benefits to this approach including travel cost-savings if several study visits coincided; a “captive audience” to improve retention and completeness of data collection; and the opportunity for research teams to promote the trial within dialysis units.

PPI has also been integral to the evolution of VASQOL, a patient-related outcome measure that will be employed to measure access specific HR-QoL. Patients were heavily involved in determining content, wording and layout for the novel tool. Semi-structured patient interviews (n=24) identified the key theme of “functionality” (“*it’s no good having a fistula unless you can dialyse through it*”). This observation was of critical importance in selection of “unassisted functional patency” as our patient-focused primary endpoint.

A second focus group involved eight patients who had previously participated in vascular access clinical trials to share their experiences and motivations. Patients universally described the sense of community that exists in dialysis units and the natural tendency for HD patients to discuss treatments with each other. Independent PPI representation from the UKRTN highlighted that a negative patient experience e.g. failed block might encourage non-participation of others. However many patients actually indicated that the motivation to participate in a trial “to improve care for other patients on dialysis” was overwhelmingly strong. They also felt that the opportunity to advertise the trial in dialysis units should not be trivialised. Posters and quarterly newsletters targeted to patients and dialysis nurses (who, if informed, could act as valuable vehicles for trial promotion) will therefore be designed.

The Plain English Summary has been written with extensive input from our PPI co-applicant and his colleagues at Kidney Care UK. Both highlighted the unique health literacy of renal patients, many of whom have spent years on dialysis. The consensus to avoid oversimplification or “dumbing-down” of trial literature is reflected in our decision to retain some commonly used medical jargon and colloquialisms e.g. “block” in both the Plain English Summary and Patient Information Sheets (PIS).

13.3.2 PPI involvement in trial delivery

One of the secondary outcomes is patient-reported cannulation difficulty e.g. “blows”, discomfort, difficulties establishing dialysis. Cannulation problems are subjective, yet qualitative work conducted during the development of the VASQOL tool and from the MAGIC consortium indicates that they are one of the major determinants of the overall dialysis experience. A patient-held record will form part of the study documentation. Patients will be asked to record their perception of cannulation with each dialysis session. By encouraging patients to maintain their own trial record, each participant will be given a degree of ownership for the data collected. We also hope that these records will provide a talking point for patients while they are on dialysis, indirectly raising awareness for the trial through word-of-mouth, which we know to be important in establishing the confidence and trust of patients with renal failure.

Approximately 40 patients/ caregivers will be interviewed for the process evaluation study running in parallel to the main trial. Their experiences of trial participation will be explored in depth. A rapid feedback evaluation approach will be employed allowing their observations to directly influence the

latter stages of trial delivery.

A patient focus group will be convened at 6-9 months. We intend to involve patients enrolled in the study (n=8) as well as, hopefully, patients who declined to participate. Patients' perceptions of the trial and their motivations for wanting (or otherwise) to participate will be discussed. Timing of the focus group will coincide with completion of the internal pilot. We anticipate that patient's insights will lead to changes in how we approach recruitment and retention as the trial progresses.

A PPI representative will sit on the TSC, demonstrating our commitment to PPI involvement in trial governance and ensuring that the patients' voice is heard throughout the trial.

13.3 3. PPI Involvement in Dissemination of Results

Patients will take an active role in dissemination of results by aiding in design and distribution of posters and newsletters for dialysis units. Existing informal renal patient social media networks will be utilised to promote the ACCess trial Twitter feed. Patients will participate in presentation of trial results and patient testimony at The NKF Annual Patients' Event and results will be publicised results on KidneyCareUK's website and in their magazine *Kidney Matters.*

13.4 Regulatory Compliance

The trial shall not commence until a favourable ethical opinion has been obtained from <*REC*> Research Ethics Committee and the Regulatory "Green Light" given by the Sponsor NHS Greater Glasgow and Clyde. Thereafter local permissions will be sought by the local PI supported by the Trial Project Manager and CI.

For any substantial amendment to the study the Chief Investigator, in agreement with the sponsor and the TSC, will submit information to the REC for review and approval. The Chief Investigator or designee will work with R&D departments at NHS sites so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Within 90 days after the end of the study, the Chief Investigator will, on behalf of the Sponsor, ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The Chief Investigator will supply the Sponsor and funder with a summary report of the clinical study, which will then be submitted to the REC within one year after the end of the study.

13.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor via the Glasgow CTU immediately.

Deviations from the protocol that are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach that is likely to effect to a significant degree –

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

(b) the scientific value of the trial

The sponsor, Glasgow CTU and CI will be notified immediately of any case where the above definition applies during the trial conduct phase. The CI will notify the REC, DMC and funder in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time

within 7 days of becoming aware of that breach

13.7 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the Data Protection Act 2018 and the General Data Protection Regulations (GDPR) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Personal data will be collected directly from the trial participants' hospital notes and entered into the eCRF only by a unique patient identifier. Patient identifiable information (name, date of birth, CHI/ NHS number, address will be recorded in the enrollment log and retained in the ISF. This is the only place where patient identifiable information will be recorded. Secure storage of ISFs at individual sites will be the responsibility of the PI.

Patients will be identified using only their unique trial number on the data collection forms and in any correspondence between the ACCess Study Office and the participating site.

Original consent forms will be retained within the ISF. These forms will be available to regulatory bodies and sponsor for inspection upon request.

Data collected will be entered onto a secure computer database at the Robertson Centre for Biostatistics (RCB) via a secure eCRF. Access control will ensure that local trials staff will only be able to view information relating to participants at their site.

All pseudoanonymised trial data will be retained for a minimum of 10 years following End of Trial (defined in section 7.10). Glasgow CTU will serve as custodian of the data generated from this trial.

13.8 Financial and other competing interests for the CI, PIs at each site and committee members for the overall trial management

Neither the CI nor any of the PIs at confirmed collaborating sites have any financial or otherwise competing interests that might influence trial design, conduct or reporting.

Alan Macfarlane, co-applicant on the grant and lead anaesthetist, is currently President-elect of Regional Anaesthesia UK (RA-UK). RA-UK has reviewed and endorsed the trial protocol, but has not been involved in the design or development in any way.

It is not anticipated that any Intellectual Property will be generated from this study.

At the time of writing the protocol not all sites/personnel/committee members have been identified. If any additional potential conflicts of interest are raised, these will be reflected as a minor amendment in the next version of the protocol.

All potential conflicts of interest will be declared on all trial outputs.

13.9 Indemnity

This is a clinician-initiated study sponsored by NHS Greater Glasgow and Clyde. The sponsor is a member of the Clincal Negligence and Other Risks Indemnity Scheme (CNORIS) which covers the Sponsors legal liability in relation to clinical trials, this includes clinical negligence and harm from study design. . All NHS sites are covered by this or a similar shared risk scheme and therefore for clinical negligence.

Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the CI, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

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

13.10 Amendments

Substantial amendments will be submitted to REC for review following agreement with the sponsor and review by the TSC, The sponsor will be responsible for informing the research teams at participating sites and the NHS R&D departments at sites in England and Wales (sites in Scotland and Northern Ireland will automatically be notified by the submission system) of any amendments. Sites will have 35 days from the date of notification to raise objection to the amendment.

The amendment can only be implemented once written approval has been granted by the regulatory body (REC). Formal confirmation of the amendment by participating sites is not required. Failure to raise objection after 35 days will be considered as acceptance. Category A and B amendments may be implemented sooner than 35 days in cases where all regulatory approvals have been issued and where the NHS organisation has confirmed that the amendment may be implemented prior to this date.

All amendments to the protocol will be recorded in Appendix 5 of the protocol.

13.11 Post trial care

The anaesthetic (both regional and local) reflects a single event intervention, therefore contingency plans for the provision of ongoing treatment for individual trial participants is not required.

13.12 Access to the final trial dataset

The trial statisticians, health economist and TSC will have access to the full dataset. Site investigators will be able to access the full dataset if a formal request describing their plans is made to the steering group.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

Results of this trial will have implications for patients and clinicians across a range of disciplines (nephrology, anaesthesia, vascular access surgery, dialysis nursing). However, the principal target audience is healthcare commissioners and policy makers. Research outputs will be produced in a format tailored to the target audience.

Target audience	Outcomes/ deliverables	Timescale
Patients/ public	Presentation at National Kidney Federation (NKF) Annual Patients' Event	Month 48

	Quarterly newsletters and posters for dialysis units Publication in the Kidney Care UK magazine *Kidney Matters* Update of Kidney Care UK patient literature e.g. *Haemodialysis Access with an Arteriovenous Fistula*	Months 0-48 Month 48 Months 9 and 48
Clinicians	Publication in high-impact peer reviewed journals The multidisciplinary nature of this research necessitates timely dissemination to clinicians in a range of specialities. We would anticipate publication in a high-impact general medical journal with broad readership e.g. JAMA/NEJM and subsequent editorials/ opinion pieces in specialty-specific journals. The trial protocol will be published in an open-access journal e.g. BMJ Open/Trials Presentation national and international vascular access (e.g. VASBI), anaesthesia (e.g. ESRA) and nephrology (e.g. UK Kidney Week/ ASN) conferences	Month 48+ Month 9 Month 36+
Researchers/ clinical trialists	Publication of findings from process evaluation study in peer-reviewed journal e.g. BMJ Open	Month 36+
Commissioners	Publication of outcomes from cost-effectiveness analysis in *Health Technology Assessment* Journal Incorporation of findings into UK Renal Association *Vascular Access for Haemodialysis* guidelines Scottish Health Technologies Group (SHTG) Evidence Synthesis and subsequent Advice Statement	Month 48+ Month 48+ Month 48+

PPI consultation highlighted the crucial role played by dialysis units as a source of support and information for patients with renal failure. We intend to capitalise on these existing networks as a route to advertise, promote recruitment and disseminate trial results. Posters will be prepared for the dialysis units and quarterly electronic newsletters will deliver bite-sized trial information. Existing links with patient charities both locally e.g. North East Kidney Patients' Association and nationally e.g. Kidney Care UK will be utilised. Via our PPI representative, Kidney Care UK will promote the trial on their website; assist in communication of results via their magazine *Kidney Matters* and aid development of an ACCess trial Twitter feed which will link with Kidney Care UK social media accounts. These established links with charities (e.g. Kidney Care UK) and professional societies (e.g. VASBI, RA-UK) should provide a powerful voice in our efforts to effect change.

We anticipate that, irrespective of the outcome, results of this trial will have direct impact on the clinical practice of vascular access surgeons and anaesthetists caring for patients with renal failure. It is anticipated that recommendations based on trial output be incorporated into the 9th edition of the UK Renal Association's *Vascular Access for Haemodialysis* guideline. On completion of the trial, an Evidence Synthesis (and subsequent Advice Statement if appropriate) by Healthcare Improvement Scotland and the Scottish Healthcare Technologies Group (SHTG) will be instructed. This guidance could then be used to inform commissioning decisions at a board level within NHS Scotland. The SHTG has a reciprocal agreement with its counterparts in Wales and Northern Ireland and an

information sharing arrangement with the NICE, such that similar processes could then be replicated for the Clinical Commissioning Groups (CCGs) in England.

14.2 Authorship eligibility guidelines

Ownership of the data arising from this study resides with the grant holders. On completion of the study, the study data will be analysed and tabulated, and a final study report prepared for the NIHR. A writing committee may be established to prepare the report and any subsequent papers.

The main report of the trial will be published in the name of the ACCess Collaborative Group, acknowledging the writing group as authors. Subsequent publications will be published in the ACCess Collaborative Group name, but those academics who contribute to specific aspects may be listed as authors.

The success of the study depends entirely on the wholehearted collaboration of a large number of clinicians, nurses and researchers. For this reason, credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres will be permitted to publish data obtained from participants in the ACCess Trial that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

The funding body will be acknowledged in all research outputs.

The trial protocol, full trial report, anonymised participant level dataset, and statistical code for generating the results will be made publically available within 12 months of the End of Trial via an online data repository and by direct request from the CI.

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16. APPENDICIES

16.1 Appendix 1 – Schedule of Procedures

Trial Procedures	Visits				
	Screening	Pre-operative	Treatment	Month 3 (+/- 28 days)	Month 12 (+/- 28 days)
Informed consent		X*	X*		
Demographics		X			
Medical history		X			
Physical examination		X*	X*	X	X
Vital signs		X*	X*		
USS vein mapping		X*	X*		
Concomitant medications		X			
Eligibility assessment	X				
Randomisation		X*	X*		
Anaesthesia			X		
AVF surgery			X		
Assessment of anaesthesia			X		
USS AVF				X	X
HR-QOL			X	X	X
Adverse event assessments			X	X	X

* Study interventions that may be carried out at either pre-operative or treatment visits according to local practice.

16.2 Appendix 2- Preparation of anaesthetic mixture for RA

Preparation:

Prepare 2 x 20ml syringes.

To each syringe add:

- 10ml 0.5% Levobupivacaine
- 10ml 1% Lidocaine
- 0.05ml 1:1,000 Adrenaline

Administration of brachial plexus block:

A minimum volume based on weight (outlined below) must be injected during the initial block (whether supraclavicular or axillary).

- 45-50kg: 15ml
- 51-60kg: 20ml
- >60kg: 25ml

Larger volumes may be used at the discretion of the anaesthetist as long as maximum dose limits are observed, remembering that local anaesthetic may also be required for surgical supplementation and that these doses are additive.

Consider using ideal body weight in obese patients.

16.3 Appendix 3- Preparation of anaesthetic mixture for LA

Preparation:

Prepare 1 x 20ml syringes.

To each syringe add:

- 10ml 0.5% Levobupivacaine
- 10ml 1% Lidocaine
- 0.05ml 1:1,000 Adrenaline

Administration of local anaesthesia:

Local subcutaneous injection at operative site.

16.4 Appendix 4 - Risk

Risks associated with trial interventions

☒ A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification:

Both RA (intervention) and LA (comparator) as offered as standard medical care currently. A NICE-commissioned literature review of USS-guided regional anaesthetic block demonstrated a negligible rate of complications (Section 8.7) [23]. No additional invasive tests or imaging is required for assessment of outcomes.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		**How will these risks be minimised?**		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Regional anaesthesia	Toxicity or complications (intra-arterial/ intra-neural injection; pneumothorax etc)	- USS guidance - Experienced regional anaesthetists	NA	Risks as standard medical care
Local anaesthesia	Toxicity	Strict adherence to maximum dosing schedule	NA	Risks as standard medical care
Follow-up	Burden of additional tests	No additional invasive tests or ionising radiation. USS and non-invasive clinical assessment only	2	Follow-up on dialysis to minimise burden
Incidental findings	Potential adverse consequences of intervention on an asymptomatic lesion	No treatment of asymptomatic stenosis or aneurysms	NA	Risks as standard medical care

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

Adverse event reporting will highlight any patterns of SAEs which can be considered by TSC.

Independent DMC will meet three times during the trial and review all adverse events .

Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach. N/A. But this will be continuously reviewed by the TSC.

16.5 Appendix 5 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

NHS
Health Research Authority

Version 1.0 23rd November 2020

16.6. Appendix 6- Current COVID 19 Centre Specific Threats and Mitigation Strategies as at 10th August 2020

Centre	Current status	Proposed restart dates	Centre specific challenges identified	Mitigation strategies
1	Full elective workload	Open	- Theatre throughput slowed due to additional infection control measures between cases - Concern regarding nosocomial infection in dialysis patients who are classified as "very high risk" and shielding in Scotland	- Instigation of a regional anaesthesia "block room" to allowing simultaneous provision of anaesthesia and theatre cleaning - Instigation of a vascular access same day admissions unit to facilitate more day case procedures
2	Emergency vascular access only	No current restart plan		
3	Emergency vascular access only	60-90 days- full service anticipated		
4	Emergency vascular access only	60-90 days- full service anticipated	Competing demands of cancer services in restart programme	Provisional discussions underway to centralise the most urgent cases in a phased restart that may utilise resources in Glasgow
5	Emergency vascular access only	60-90 days- full service anticipated		
6	No surgical service	Moving offsite to a nearby private hospital with plans for limited re-start beginning early July	Offsite operating theatres will utilize the same surgical and anaesthetic team but they will be remote from vascular access research nurses and imaging which will be based at a different site	Provisional discussions underway to utilize local staff/ resources e.g. clinical vascular access rather than research nurses
7	Full elective workload	Open	RCSEng guidance necessitates COVID swab and 14 days shielding pre-operatively. Currently this is resulting in a 20-25% "on day" cancellation of elective fistula surgery	Patient education and telephone consultation to improve adherence and minimize last minute cancellations
8	Emergency vascular access only	Preliminary discussions underway for local anaesthetic AVF only		
9	No surgical service at this site	Full vascular access service running from alternative NHS site	Offsite operating theatres utilize the same surgical and anaesthetic team but are remote from imaging and renal services which are based at a different site	Clinical surgical and nephrology staff are trained in vein mapping ultrasound. Utilise this resource for bedside, rather than departmental scans.
10	Emergency vascular access only	60-90 days- full service anticipated		
11	Limited elective service	60-90 days- full service anticipated		

12	Full elective workload	Open		

16.7 Appendix 7- Summary of Study Visits Aide Memoire

SCREENING/ PRE-OPERATIVE

Inclusion criteria

Age >18y.o.	
ESRD on RRT or CKD stage IV or V	
Planned RCF or BCF	

Exclusion criteria

Unable or unwilling to provide informed consent	
Patient preference for general or alternative anaesthesia	
Active infection at surgical or anaesthetic site	
Previous ipsilateral AVF creation (excl. Immediate failures)	
Known ipsilateral cephalic arch or central venous stenosis (even if previously treated)	
USS evidence of stenosis in inflow artery	
Radial or brachial artery <1.8mm diameter and/or cephalic vein <2mm at wrist or <3mm at elbow (with tourniquet) on pre-operative USS	
Allergy to LA or any excipient agents	
Acquired or inherited coagulopathy (including warfarin/ heparin/ novel oral anticoagulant use) and/or platelets <75 or INR > 1.4	
Significant pre-existing neurological disorder affecting upper limb	
Weight <45kg	

TREATMENT

Consent	
Anaesthetic (LA/ RA)	
Surgery	
Data collection (anaesthetic endpoints, immediate patency, EQ5D, KD-QoL, VASQOL)	

3 MONTHS

USS	
Clinical assessment	
Quality of life (EQ5D, KD-QoL, VASQOL)	

12 MONTHS

USS	
Clinical assessment	

Quality of life (EQ5D, KD-QoL, VASQOL)	