A Mixed Method Trial to explore the Feasibility of comparing Buttonhole and Rope Ladder Cannulation of Arteriovenous Fistulae for Haemodialysis

FULL/ LONG TITLE OF THE STUDY A mixed method trial to explore the feasibility of comparing buttonhole and rope ladder cannulation of arteriovenous fistulae for haemodialysis	
SHORT TITLE/ ACRONYM AF-CaT (Arteriovenous Fistula Cannulation Trial) Feasibility	
Version and Date of Protocol:	V2.0 27/Jul/2020
Sponsor:	University Hospitals of Derby & Burton NHS Foundation Trust
Chief Investigator:	Catherine Fielding
Local Reference:	DHRD/2018/034
IRAS Number:	274355
ISRCTN/ ClinicalTrials.gov number:	
Funder(s):	This report is independent research supported by Health Education England and the National Institute for Health Research (HEE/ NIHR ICA Programme Clinical Doctoral Research Fellowship, Mrs Catherine Fielding, ICA-CDRF-2018-04-ST2-003). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.
This protocol has regard for the HRA guidance	

Confidentiality Statement

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

SIGNATURE PAGE

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

Protocol v2.0 27/Jul/2020 authorisation signatures:

Chief Investigator:
Signature: 
Digitally signed by Catherine Fielding
Date: 2020.08.19 17:09:42 +01'00'
Name (please print):

For and on behalf of the Study Sponsor (if required):
Signature: ……. Date: ……/……/……

Name (please print): …….
Position: …….

KEY STUDY CONTACTS

Chief Investigator:	Catherine Fielding, Room 5048, Medical School, Royal Derby Hospital, University Hospitals of Derby and Burton NHS Foundation Trust, Uttoxeter Road, Derby, DE22 3NE katie.fielding@nhs.net 07766 401429 – personal mobile
Co-Investigator(s):	Nicholas Selby, Associate Professor of Nephrology and Consultant Nephrologist, Centre for Kidney Research and Innovation, Division of MS&GEM, University of Nottingham Royal Derby Hospital Campus, Uttoxeter Road, Derby, DE22 3NE nicholas.selby@nottingham.ac.uk 01332 724665 Heather Buchanan, Associate Professor of Health Psychology, Division of Rehabilitation, Ageing & Wellbeing, Medical School, Faculty of Medicine & Health Sciences University of Nottingham Room B113, Medical School, Queen's Medical Centre Nottingham, NG7 2UH heather.buchanan@nottingham.ac.uk 0115 846 7520 Sarah Brand, Renal Research Nurse, Research and Development, Nottingham University Hospitals NHS Trust, City Hospital Campus, Hucknall Road, Nottingham, NG5 1PB Sarah.Brand@nuh.nhs.uk

	Charlotte Bebb. Consultant Nephrologist, Nottingham University Hospitals NHS Trust, City Hospital Campus, Hucknall Road, Nottingham, NG5 1PB Charlotte.Bebb@nuh.nhs.uk Fergus Caskey Consultant Senior Lecturer and Honorary Consultant Nephrologist, Room G13, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PL 0117 928 7290 fergus.caskey@bristol.ac.uk Maarten Taal, Professor of Medicine and Consultant Nephrologist, Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Royal Derby Hospital Campus Uttoxeter Road, Derby, DE22 3NE 01332 724842 M.Taal@nottingham.ac.uk Kelly White, Renal Research Nurse, Renal Research Office, Renal Service, Royal Derby Hospital, Uttoxeter Road, Derby, DE22 3NE. 01332 788262 kelly.white@nhs.net

Trial Manager/ Co-ordinator:	Rachelle Sherman, Research and Development, Medical School, Royal Derby Hospital, University Hospitals of Derby and Burton NHS Foundation Trust, Uttoxeter Road, Derby, DE22 3NE uhdb.sponsor@nhs.net 01332 724736
Sponsor:	University Hospitals of Derby & Burton NHS Foundation Trust Royal Derby Hospital Uttoxeter Road Derby, DE22 3NE 01332 724639 uhdb.sponsor@nhs.net
Funder(s):	NIHR Academy, 21 Queen Street Leeds LS1 2TW academy-awards@nihr.ac.uk 0113 5328401
Clinical Trials Unit:	Derby Clinical Trials Unit, Research, Development and Innovations Department, Office 5003, Medical School, Royal Derby Hospital, Uttoxeter Road, Derby, DE22 3NE uhdb.derbyctsu@nhs.net 01332 724639
Statistical Advisor:	Apostolos Fakis, Research and Development, Medical School, Royal Derby Hospital, University Hospitals of Derby and Burton NHS Foundation Trust, Uttoxeter Road, Derby, DE22 3NE apostolos.fakis@nhs.net

STUDY SUMMARY

Study Title:	A mixed method trial to explore the feasibility of comparing buttonhole and rope ladder cannulation of arteriovenous fistulae for haemodialysis
Local Study Reference:	DHRD/2018/034
Study Design:	Mixed Methods Feasibility Trial
Study Participants:	The study will include patients who are undergoing new cannulation of AV fistulae for use during haemodialysis treatment and are suitable to undertake either cannulation technique.
Planner Number of Sites:	The study is planned across two sites, UHDB and NUH renal units.
Planned Sample Size:	The planned sample size is 40 patients, with a plan to recruit 20 at each site.
Treatment Duration:	Cannulation is part of normal haemodialysis treatments for patients on maintenance haemodialysis. They receive this treatment thrice weekly. Both cannulation techniques are part of standard practice, but for this study we will be randomising patients to one technique or another. Patients will then receive the randomised technique for 6 months, each time they come in for their normal haemodialysis treatment for 6 months. All study activities, bar the face-to-face interview, will coincide with haemodialysis treatments, minimising burden to study participants. The face-to-face interview will be completed with 12 participants at a time and location of their choice and will last a maximum of 1 hour. The Study Flow Chart outlines the activities in the study, with activities outside of their normal haemodialysis treatment highlighted in green.
Follow Up Duration:	Following completion of the randomised technique, there will be follow up period where feasibility data will be collected. This will be in the form of a short questionnaire taking a maximum of 20 minutes to complete, and then for 12 participants a face to face interview lasting a maximum of 1 hour. These activities will be completed within four weeks of completion of the study. The Study Flow Chart outlines the activities in the study, with activities outside of their normal haemodialysis treatment highlighted in green.
Planned Start Date:	28/Sep/2020
Planned Recruitment End Date:	03/Jul/2022
Planned Study End Date:	03/Jul/2022
Research Question/ Aims:	To determine the feasibility of cannulation protocols, patient experience measures and clinical outcomes measures for a multi-centre RCT to compare buttonhole versus rope ladder cannulation of arteriovenous fistulae for haemodialysis.

FUNDING AND SUPPORT IN KIND

Funder(s)	Financial and Non-Financial Support Given
University Hospitals of Derby & Burton NHS Foundation Trust Royal Derby Hospital Uttoxeter Road Derby, DE22 3NE 01332 724639 DHFT.sponsor@nhs.net	Sponsor for the study
Derby Clinical Trials Unit University Hospitals of Derby & Burton NHS Foundation Trust Royal Derby Hospital Uttoxeter Road Derby, DE22 3NE 01332 724639 DHFT.sponsor@nhs.net	Statistician support and project management support – time is funded by HEE/NIHR fellowship
University of Nottingham, Division of MS&GEM, University of Nottingham Royal Derby Hospital Campus, Uttoxeter Road, Derby, DE22 3NE	Supervisory support through PhD
Health Education England and National Institute for Health Research, Dr Mal Palin, NIHR Academy Executive, 21, Queen Street, Leeds, LSI 2TW	Providing financial support for all elements of study

ROLES & RESPONSIBILITIES

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

Funder
The study is funded by Health Education England and the National Institute for Health Research (HEE/ NIHR ICA Programme Clinical Doctoral Research Fellowship, Mrs Catherine Fielding, ICA-CDRF-2018-04-ST2-003). The views expressed in this protocol are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Study oversight
This study is part of PhD study for Catherine Fielding. Catherine will receive over-sight for performance of her study from PhD supervisors, Nicholas Selby and Heather Buchanan. Catherine will meet with Nicholas monthly and Heather 1-2 monthly to review progress. Over-sight will also be provided from Maarten Taal and Fergus Caskey, through 3 monthly meetings. 6 patient representatives will be utilised throughout the study, to ensure this remains relevant to patients.

Protocol Contributors
A number of protocol contributors have been involved in the development of this protocol, these include Catherine Fielding, Nicholas Selby, Heather Buchanan, Sarah Brand, Charlotte Bebb, Fergus Caskey, Maarten Taal, Rachelle Sherman and Apostolos Fakis. Tina Bennison, Heather Ward and Jane Pikett, nurse from NUH renal unit, have provided advice on the cannulation protocols. 3 patient representatives have contributed to the design of the study.

Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AV	Arteriovenous
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
NUH	Nottingham University Hospitals
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
UHDB	University Hospitals of Derby and Burton NHS Foundation Trust

STUDY FLOW CHART

Patient identified as having new arteriovenous fistula that has been cannulated for less than 6 months.
Check eligibility criteria.
Written study information given to the patient and permission requested to contact

↓

Meet with patient:
1) Consent for study
2) Randomise to cannulation technique – buttonhole or rope ladder
3) Provide information on their randomised technique

↓

Week 0 of study for each Patient Participant
Start randomised cannulation technique with materials to support adherence to cannulation protocol. This cannulation technique will be used for each haemodialysis treatment.

↓

Week 4-5 of study and then monthly throughout study for each Patient Participants
Prior to haemodialysis treatment, check patient temperature.
CRP blood sample taken, if not available from routine blood tests.
Ask patient to complete patient experience questionnaire survey during their haemodialysis treatment and return at end of treatment or at start of next treatment.
Continue monthly throughout study.

↓

During participation in study for Patient Participants
Possible observation of cannulation and prior to haemodialysis, to check adherence to cannulation protocols

↓

At end of 6th. Month for each Patient Participant
Possible patient experience interview - To be arranged prior to haemodialysis or on non-haemodialysis day
Complete involvement in study and return to normal cannulation practice. This may be continuing the same cannulation technique of the patient wishes and clinical care team agree.

↓

After completion of trial for each Individual Patient Participant
Complete patient evaluation questionnaire survey
Possible patient feasibility interview - To be arranged prior to haemodialysis or on non-haemodialysis day

↓

After completion of all patient participants in the trial
Complete staff evaluation questionnaire survey
Nursing staff focus group – 1 at each site

STUDY PROTOCOL

1. BACKGROUND

Haemodialysis is a life sustaining treatment for patients with end-stage renal disease, which is essential thrice weekly until kidney function is restored (normally through a kidney transplant) or until the end of the patient's life. Adequate access to the circulation is critical to ensure haemodialysis treatments can be performed. Artificially formed 'vascular access' provides adequate flows for haemodialysis and sustains access to the circulation for periods of years. Provision of sustainable vascular access with minimal complications is a significant challenge for haemodialysis patients and health care professionals (1).

There are 3 types of vascular access used for long-term haemodialysis:

1) ***Arteriovenous (AV) fistula*** an artery is joined to a vein, diverting the arterial blood supply into the vein. At each haemodialysis session, the arterialised vein is cannulated at 2 sites (arterial and venous).
2) ***AV graft*** similar to an arteriovenous fistula, but uses an artificial plastic tube in-between the artery and the vein. At each haemodialysis session, the artificial plastic tube is cannulated at 2 sites, as per the AV fistula.
3) ***Tunnelled central venous catheter (CVC)*** where a catheter is inserted into a central vein and remains in place long-term.

The type and longevity of vascular access significantly impacts patients' outcomes and experiences of haemodialysis. The AV fistula is associated with the lowest complication, mortality and morbidity rates (1). Recent meta-analyses identified two-year mortality for AV fistula use for haemodialysis is 15% compared to 26% for CVC (2) and the absolute risk ratio for all-cause mortality is 1.53 (1.4-1.67) when using a CVC for haemodialysis in comparison to an AV fistula (3). AV fistulae are financially less costly in comparison to other vascular access options (4, 5). Currently within the UK, it is estimated approximately 16,000 patients dialyse using an AV fistula or graft, with the majority using an AV fistula (as estimated from UK Renal Registry report (6)). However, despite the importance of AV fistulae use for haemodialysis, there remains significant challenges to its use, including service provision, maintaining function and cannulation (6-8).

Cannulation is required at each haemodialysis session and is critical for AV fistula use, but has significant challenges (7). Repetitive cannulation damages the AV fistula, causing failure through stenosis development. If the AV fistula fails or cannulation is unsuccessful, it can lead to CVC use, associated with increased mortality and morbidity (7, 9, 10). To preserve AV fistula function, 2 different cannulation techniques have developed (7):

- Rope Ladder – this involves using a different cannulation site each time and progressing the cannulation sites up the vessel in a systematic manner. Once the top of the vessel is reached, cannulation sites start at the bottom and progress up the vessel again.
- Buttonhole – this involves inserting each needle into the same cannulation site each time, using the same angle and depth of insertion. As the cannulation site is exactly the same each time, this develops a track of scar tissue from the skin to the vessel, which results in progression to use of blunt or dull needles.

Both rope ladder and buttonhole cannulation are considered to reduce complications associated with repetitive cannulation (11). However, neither technique is perfect, with complications still existing. In particular, damage still happens to the vessel through the repetitive cannulation, but this is minimised, and other complications have been associated with either technique including

infection, life-threatening bleed, pain and bruising. Good quality research evidence on the benefits or disadvantages of each technique is sparse. Whilst both buttonhole and rope ladder cannulation are standard practice within the UK, both techniques are implemented inconsistently across the UK with protocols to implement techniques differing. This has created disagreement and debate within the renal community as to which is the better technique (7). Some units pre-dominantly using buttonhole and others rope ladder, dependant on clinician preference rather than evidence.

Patients' experiences of cannulation is also extremely important and poorly studied. Patients can develop anxiety prior to cannulation, pain during and after cannulation and a fear of cannulation complications (12-14). The needles used for haemodialysis are approximately twice the width of a normal cannula, with patients undergoing repetitive cannulation thrice weekly, with approximately 320 needle insertions a year (15). Anxiety about cannulation can lead to patients avoiding arteriovenous fistula for haemodialysis and choosing CVC that worsens their long term outcomes (16).

2. RATIONALE

Vascular access is critical for successful haemodialysis provision, with promoting AV fistula use and longevity essential to minimise complications and improve patient outcomes. NHS England and NHS Improvement (p.24 (17)) use a best practice tariff for haemodialysis performed via an AV fistula in adults, to promote AV fistula use. Vascular access has been identified as a priority area for renal research through an international collaboration between healthcare professionals and renal patients (18, 19).

Haemodialysis patients within the UK have identified similar sentiments. Discussion at a Kidney Care UK meeting, a national renal patient charity, identified that comparing buttonhole and rope ladder cannulation techniques was highly relevant to patients. This was reflected through further consultation with a local kidney patient association and UK Renal Registry patient council. Patients want to know the advantages and disadvantages of both techniques, so they can make an informed choice based on data. The 'British Renal Society's Clinical Practice Recommendations for Cannulation of Arteriovenous Fistulae and Grafts' (7, 20) are unable to provide evidence based recommendations on the optimal application of either technique, due to the poor quality of existing studies.

To date, the majority of studies into cannulation have focussed on clinical outcomes such as AV fistula function. Some have collected pain as an outcome, but have not explored patients' experiences in any further depth. Again, conversations with haemodialysis patients have highlighted the burden of cannulation, identifying patients' experiences as an important outcome.

Five randomised control trials (RCT) compare needling techniques, but findings are inconsistent:

- Vaux (21) found buttonhole led to improved survival of AV fistulae whilst MacRae (22, 23) found no benefit to survival. Both studies are unclear as to the needling technique used as the comparator.
- Chow (24) identified that buttonhole led to more painful cannulation and haematomas (bruising) from problematic cannulation, when compared to standard practice, in contradiction to findings from Struthers (25), Toma (26) and the two other RCTs (21-23).
- In all RCTs there was limited assessment of patients' experiences, with all RCTs only capturing pain. Little acknowledgement was given to the complexity of factors affecting patients' experiences of cannulation, as described in qualitative research (13). A recent scoping review identified this failure to assess patients' experiences as a significant knowledge gap (27).
- MacRae et al (22, 23) found buttonhole led to higher number of infections, whilst the other RCTs found no significant difference (21, 24-26).

Numerous observational studies have also produced conflicting results (28).

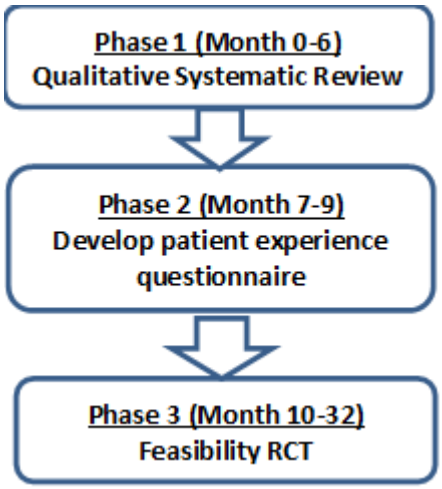
Further research is needed to compare the effect of each cannulation technique on both patients' experiences and clinical outcomes, to judge appropriate application, promote AV fistula use and minimise the burden to patients' associated with cannulation. Systematic reviews identify the current poor quality of research studies in this area, with studies performed inconsistently, over short periods of time and in single centres. They identify the need for better quality research into this area, ideally over multiple centres (2, 28, 29).

Limitations have been identified in previous RCTs, via a systematic review (PROSPERO No.: CRD42018094656 – manuscript being compiled for publication). In particular, inconsistencies in cannulation practice is ignored, introducing unrecognised bias and potentially affecting outcomes of these RCTs. Therefore, feasibility studies are required to determine how to minimise bias in

cannulation studies. In particular, cannulation is a complex intervention and needs to be explored as outlined in the Medical Research Council's guidance (30, 31). This feasibility study focusses on fidelity, particularly whether this can be done with enough consistency to enable comparison cannulation techniques, and the outcomes to be measured in future RCTs.

2.1. Context within the Feasibility Study

The feasibility trial outlined in this protocol is the last part of a larger feasibility study. This feasibility study has 3 phases that run consecutively:



The Phase 1 systematic review examined qualitative studies that identified themes related to patients' experiences of cannulation of AV access for haemodialysis (PROSPERO registration No. CRD42019134583). Phase 2 is currently developing and testing a questionnaire to capture patients' experiences of cannulation of AV access (IRAS Number: 269188), using the themes developed from the Phase 1 systematic review.

This current protocol is a description of the feasibility trial and is Phase 3 of the feasibility study. This will use the questionnaire developed during Phase 2.

3. OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

3.1. Aim

The aim of this feasibility trial is to determine the feasibility of use of the cannulation protocols, patient experience measures and clinical outcomes measures for a multi-centre RCT to compare buttonhole versus rope ladder cannulation of AV fistulae for haemodialysis.

3.2. Objectives

To further define the aim, the objectives of the feasibility trial are:

1. To identify the rate and ease of recruitment and retention by:
    a. Recording participant numbers at each stage – eligibility, approach, recruitment, randomisation and during follow-up
    b. Exploring reasons for loss to follow-up
    c. Examining reasons for refusal to consent to participate in the study
2. To test the feasibility of data capture by:
    a. Identifying the ease of collection of data capture
    b. Identifying the completeness of data capture
    c. Assessing acceptability of the patient experience questionnaire and interview for patients
3. To identify the feasibility of the cannulation protocols for each study arm by:
    a. Identifying staff and patient experiences of being part of the study
4. To assess the fidelity of delivery of the cannulation protocols for each study arm by:
    a. Monitoring compliance to the cannulation protocols
    b. Establishing how protocol compliance can be effectively and efficiently monitored in a future RCT
    c. Evaluating activities designed to standardise protocol compliance in each study arm

3.3. Outcome

The main outcome of this feasibility trial is to determine whether a large multi-centre RCT can provide definitive results when comparing buttonhole and rope ladder cannulation techniques for haemodialysis. A staged approach to success criteria has been utilised, with criteria that will indicate:

- Green - Proceed to the multi-centre RCT using the same study protocol
- Amber - May proceed to the multi-centre RCT following changes to the study protocol, dependent on the identified problem
- Red - Consider an alternative study design or further feasibility studies

Other data collected in this trial will inform how to design a successful multi-centre RCT, but will not halt proceeding to the main RCT.

Note: The trial is being initiated during a global pandemic – COVID 19. This global pandemic may affect how the trial is conducted and outcomes related to the feasibility criteria set. In this context, non-achievement of these criteria may not reflect the true feasibility of the study in the absence of a global pandemic. Therefore, non-achievement of this criteria will be examined to identify if this is solely or partially due to the global pandemic and if so, then criteria may be adjusted.

3.3.1. Green Criteria

If the following conditions are met within the feasibility trial, the multi-centre RCT will be feasible to proceed:

- Compliance with cannulation protocol is above 90%
- Data collection of the patient experience questionnaire and clinical outcomes data is 90% complete
- Patient feedback identifies that participation was not problematic

3.3.2. Amber Criteria

If the following criteria are met adjustments may be made to the multi-centre RCT design with / without further feasibility work:

- Compliance with cannulation protocol is 60-90%
- Data collection is 80-90% complete
- Issues with study participation indicated through patient feedback that can be rectified by changing the study design

3.3.3. Red Criteria

If the amber or green criteria are not met, further feasibility work may be required prior to proceeding with a large multi-centre RCT or a different quasi-experimental or observational design may be required.

4. STUDY DESIGN

This feasibility trial will be a two arm, parallel, non-blinded mixed methods randomised controlled trial (RCT). Participants will be haemodialysis patients randomised to either buttonhole or rope ladder cannulation, undergoing this technique for 6 months, as part of their normal haemodialysis treatment. Cannulation is part of the standard haemodialysis treatment for patients meeting the inclusion criteria for this RCT and both cannulation techniques are used as standard practice. The only change to their treatment will be that they are randomised to one technique or another, rather than this being dictated by the clinical team and / or patient choice.

During this study period, data will be collected on feasibility outcomes, patients' experiences of cannulation and clinical outcomes. Feasibility outcomes will collect data from both patients undergoing the cannulation technique and nursing staff performing the cannulation technique. This will be collected through structured observation of cannulation procedures, questionnaires, focus groups and interviews. Clinical outcomes will be collected from haemodialysis patients randomised to each technique, using questionnaires, interviews and source data from the haemodialysis treatment.

This feasibility trial aims to mimic the probable design of main RCT in the:

- Eligibility criteria
- Recruitment strategies
- Participant flow
- Cannulation protocols
- Data collection.

4.1. Sampling

4.1.1. Patients

Forty haemodialysis patients will be included in the study, twenty at each site with the 2 study arms divided equally at each site. These will become patient participants in the study.

4.1.1.1 Patient Experience Interviews

Semi-structured patient experience interviews will be performed with 12 patient participants, 3 from each study arm at each site. Purposive sampling will be used to identify patients with differing experience as from responses to the patient experience questionnaire, to ensure heterogeneity in the sample.

4.1.1.2 Feasibility Interviews

Semi-structured patient feasibility interviews will be performed with 12 patient participants, 3 from each study arm at each site. Purposive sampling will be used to ensure heterogeneity in the sample, capturing experience from differing patients' experiences from the patient evaluation questionnaire.

4.1.2. Nursing Staff

4.1.2.1 Feasibility Questionnaire

The number of nursing staff eligible to participate in the feasibility questionnaire will vary at each site, dependent on the size of the nursing teams and the variation of staff who perform cannulation on patient participants. Therefore, a maximum sample size has not been set, but the questionnaire will aim to achieve a minimum of 10 responses at each site. If nursing staff at satellite units have

performed cannulation on patient participants, then they will be included in the sample for this questionnaire.

4.1.2.2 Focus Groups

At the end of the study, 4 focus groups with nursing staff will be completed. 2 will be conducted at each site with a maximum of 6 nursing staff in each group.

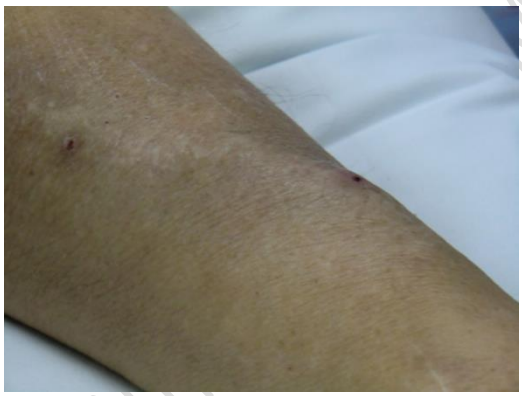
4.1.3. Structured Observation

One cannulation procedure for each study arm at each site will be chosen and observed monthly. A purposive approach to sampling will be used to ensure different AV fistula types cannulated different times on different staff rotas are observed, to ensure heterogeneity in the sample. The study will observe 4 AV fistula cannulations each month, giving a total of 72 observations over the expected 18 month study period. It is expected over the expected 72 cannulations, that a variety of staff members will be observed.

The number of nursing staff undergoing structured observation will not be set and will be dependent on which nurses are observed on the selected days and times.

4.2. Interventions

Participants will be randomised to either use buttonhole or rope ladder cannulation technique, when initiating their haemodialysis treatment, for a period of 6 months. To be able to perform haemodialysis, the AV fistula has to be cannulated with 2 needles, known as the 'arterial' and 'venous' needle. However, both needle enter the same vessel at different points, as demonstrated in this photograph below:



For both cannulation techniques, selection of cannulation sites should follow local policy, but should include the following criteria:

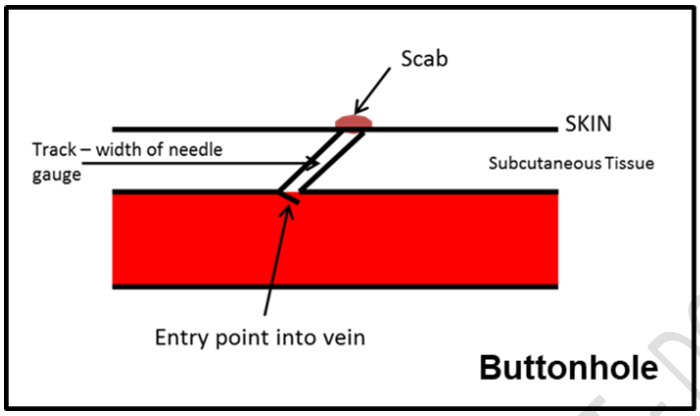
- 2 inches away from the anastomosis
- Away from division, dips and 'wiggles' in the vein
- The vessel should have adequate diameter and maturity to support adequate flows for HD. This is normally at least 0.5cm, but is often dictated by clinical judgement rather than measurement of the diameter.

A model the demonstrates hypothesises mechanism of action of the two cannulation techniques is provided in Appendix 1, which provides justification for the outcomes of the study and the fidelity elements assessed.

4.2.1. Buttonhole Cannulation

Buttonhole cannulation involves inserting the needle into the cannulation site in the same manner each time that cannulation site is used. Normally there are only 2 cannulation sites, one for the arterial needle and one for the venous needles, which are used at every haemodialysis session. However, some patients may have 3 or 4 sites that are rotated between sessions.

This type of cannulation involves removing the scab prior to inserting the needle. The needle is then inserted at the same angle and depth each time. It involves development of a track scar tissue using sharp needles, where the cannulation is performed in exactly the same manner each time. Once the track is developed, only blunt needles are used to ensure the needle enters the vessel in exactly the same manner each time. The track is demonstrated in the diagram below:

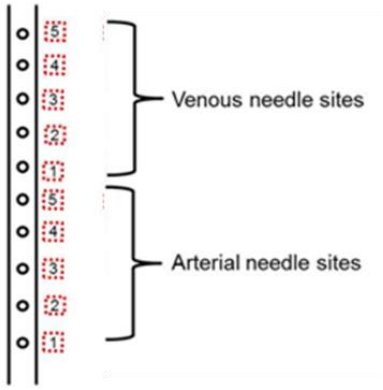


Sites should not be used if there are signs of infection, bruising, the area feels hard or there is evidence of skin breakdown beyond the parameters of the normal cannulation site or in the area around the site.

The buttonhole cannulation procedure is detailed in Appendix 2.

4.2.2. Rope Ladder Cannulation

Rope ladder cannulation involves progressing up the vessel in a systematic manner, with each cannulation. Once the top of the vessel is reached, cannulation should start again at the bottom. As cannulation sites will change at each haemodialysis session, the vessel develops cannulation segments spanning multiple cannulation sites for each needle (arterial and venous needle). Each cannulation segment for arterial and venous needle should cover at least 5cm. If the 2 segments join (i.e. meet in the middle of the vessel), they should cover at least 8cm together. The progression of needling sites for rope ladder cannulation is demonstrated in this diagram:



NB. the progression of sites is not limited to 5, but dictated by the length of vessel and should meet the minimum criteria set above.

The rope ladder cannulation procedure is detailed in Appendix 2.

4.2.3. Acceptable Variation in the Cannulation Procedures

Cannulation procedures across the UK are subject to variation. Whilst standardisation of essential elements is necessary for this study, as outlined in the cannulation procedures, there are elements that can vary without affecting the outcomes to be collected. This is often the case with complex interventions with fidelity of essential elements necessary, whilst allowing local adaption (known as programme differentiation) (31-33).

The following elements are specified as acceptable variation in the cannulation procedure*:*

- Assessment prior to cannulation should include inspection and palpation of vessel and exploration of cannulation history, but may also include more in-depth elements including auscultating the bruit.
- Either sterile or non-sterile gloves can be used for cannulation dependent on local policy and also clinician judgement
- The fistula needle can either be inserted with a sterile N/Saline flush insitu (wet) or empty with no flush inserted (dry)
- 0.5% or 2% chlorhexidine in alcohol can be used to clean cannulation sites
- A tourniquet to assist with cannulation or no use of a tourniquet, according to local policy and clinician judgement
- Securing the needle with tape can use any method deemed acceptable by the local policy, as long as non-sterile tape does not touch the cannulation site
- Antimicrobial cream or ointment used on needle sites at the end of treatment, with buttonhole cannulation, but the type of cream can vary according to local policy
- Varied buttonhole track development period, according to individual patient need – this will be recorded on an individual participant basis

These elements of cannulation practice are within the limits of acceptable variation in current best practice recommendations (7, 20). Each unit will be asked to provide detail of their standard cannulation practices, via a questionnaire administered on one occasion to the site PI (or delegated staff member). This will allow a full description of each cannulation protocol at each site, describing variations in practices, as recommended by the TiDiER template for reporting of interventions (33).

4.2.4. Facilitation Strategies to Promote Fidelity in the Cannulation Procedures

Materials have been developed to facilitate nursing staff compliance to the cannulation protocols and promote fidelity of the interventions. These materials will be implemented and evaluated as part of the feasibility trial. These materials have been designed to use minimal resources, whilst promoting fidelity, considering future practical application in a large multi-centre RCT. Through the feasibility RCT, these materials will be tested to see if they produce adequate fidelity to progress to a larger multi-centre RCT. These materials will be described as part of the intervention, as recommended by the TIDieR guidance (33).

The following materials have been developed:

- A teaching package which includes a lesson plan and notes, to allow introduction of the cannulation procedures to nursing teams. This will be detailed enough to allow a key trainer to facilitate this at sites, but will also be flexible enough to be tailored to suit individual nursing teams.
  During the COVID pandemic, face-to-face teaching may not be possible due to the risk of transmission of COVID 19. Therefore, videos will be developed to replace this face-to-face teaching. These videos will use the developed lesson plans to structure them and will not vary in content from the face-to-face teaching sessions. Each site will then be given access to 'question and answer session' for staff who have watched the video, which can continue throughout the trial. These 'question and answer' sessions can be performed through video conferencing facilities or face-to-face, as the pandemic dictates and / or site preference. The researcher will also be available via email to answer queries and will offer sites video support when they are cannulating patients using new procedures.
- An individual cannulation plan for each participant, to facilitate consistent implementation between cannulators. For rope ladder, this will detail the progression of sites up the vessel. For buttonhole, this will describe the angle and direction of needle insertion. This will also include a reminder of the essential steps of the cannulation procedure.
- Posters for use on the haemodialysis unit, to remind staff to adhere to the cannulation procedures for participants in the study
- Information for participants on the essential steps of their randomised technique, to facilitate them reminding staff how to perform the technique correctly.
- Awareness cards for patients to use to remind staff of the cannulation procedure they need to follow for ach study arm. Permission has been sought to use the 'Love My …' cards, incorporated as part of the MAGIC QI programme (https://www.thinkkidneys.nhs.uk/kquip/magic/)
- Observations will be conducted of a sample of cannulation procedures, to assess fidelity. During direct observation, feedback will be provided to the cannulator on any identified breaches of cannulation practice. Each PI will be provided with details of any anonymised breaches of the cannulation protocols every two months, which can be disseminated to their teams. This is to ensure safety of participants, as breaches will be considered unsafe practice. However, it is recognised that feedback can also be a facilitator of fidelity (32). Therefore, feedback provided will be recorded to identify whether this leads to better fidelity over time.

Two PPI meetings with staff from each site will be arranged, to use staff input to help design the facilitation materials and discuss the best way to implement these.

It is currently unclear what support each site will require to implement the cannulation protocols. Haemodialysis nursing staff who are performing the cannulation protocols will be competent at cannulation of AV fistulae, but may not be familiar with both cannulation technique or the specific

cannulation protocols. Implementation of the teaching package will be discussed with clinical teams and a bespoke plan developed for each site. This teaching will likely be completed by both the CI and the clinical teams. This planning process will also be used to develop a model for the main RCT.

4.2.5. Concomitant Care

During the study patient participants will undergo surveillance procedures, as per their normal unit policy. Surveillance procedures are used in standard haemodialysis practice to assess the function of the AV fistula and prompt interventions to correct signs of declining function, including radiological and surgical procedures. These are a necessary part of standard haemodialysis practice to optimise AV fistula life span, but it is recognised this may influence outcomes related to AV fistula survival and patency. Therefore, it is important to ensure surveillance procedures are applied consistently across both study arms. A record will be made of the unit policy and escalation procedures for surveillance, to provide context to the patency results. Information on local policy collected via a questionnaire administered on one occasion to the site PI (or delegated staff member).

Surgical and radiological intervention may be required on the AV fistula during the study, to manage complications associated with using the AV fistula for haemodialysis. Again, this will be recorded as an outcome, but will not exclude patient participants from the study, unless the surgical procedure changes their AV fistula to meet withdrawal criteria.

Patient participants will be undergoing haemodialysis during the study, using the cannulation at the start of the haemodialysis treatment to gain access to the circulation for use during the treatment. Cannulation is part of the normal haemodialysis treatment when using AV fistula, so involvement in the study will not alter their haemodialysis treatment a part from altering the cannulation technique used at the start.

4.3. Outcomes

4.3.1. Feasibility Outcomes

The main outcomes are feasibility outcomes. This includes outcomes related to the recruitment and retention in the study, feasibility of the data collection, feasibility of the cannulation procedures and fidelity of the cannulation.

Feasibility of the Study (Objectives 1-3)

- Proportion of available patients that are eligible for the study, approached, recruited to the study, randomised and retained within the study
- Reasons for patients declining consent to participate in the study
- Completeness of patient experience questionnaire
- Time to complete clinical outcomes data
- Completeness if clinical outcomes data
- Reasons for loss to follow up in the study
- Patient perception of burden of study activities
- Staff perception of burden of study activities, for both themselves and patients

Fidelity Outcomes (Objective 4)

- Adherence as defined by Carroll et al (32) and Hasson et al (34). This includes:
    - Content – was the cannulation procedure correct

  - Frequency - was BH / RL performed each time they received haemodialysis or was there divergence to use of other techniques
  - Coverage – how many of those eligible were participants
  - Participant responsiveness – how engaged where those delivering the cannulation, which is a known moderator of fidelity

  Adherence includes other elements of duration, coverage, complexity, facilitation, recruitment and context (32, 34). These elements are dictated by the study design or local policy, so not classified as outcomes, but will be reported alongside fidelity outcomes.
- Staff perception of adherence to cannulation protocols
- Staff perception of ease of adherence to cannulation protocols
- Staff perception of materials to support adherence to protocols

These feasibility outcomes will collect data from both patients and nursing staff performing the cannulation. This will be collected through structured observation of cannulation procedures, questionnaires, focus groups and interviews.

4.3.2. Clinical Outcomes

The clinical outcomes expected to be measures in the main RCT will also be collected as part of the feasibility study. This includes:

- Patients' perspective of cannulation measured using the questionnaire developed in Phase 2 of the feasibility study (see section 2.1) and themes developed from patient experience interviews.
- Outcome data pertaining to potential complications, known to be associated with repetitive cannulation of AV fistulae and not expected to be captured by the patient experience questionnaire. This will include measures of the AV fistula function and infection, as follows:
  - Function of AV fistula as defined by Standardised Outcomes in Nephrology study (SONG) (19). Permission has been granted to use 2 definitions currently being piloted:
    - Time to first intervention to maintain use of AV fistula for haemodialysis
    - Number of interventions to maintain use of arteriovenous fistula for haemodialysis

    Both will be collected, although it is unlikely multiple interventions will occur in the current feasibility study period.
  - Functional period of AV fistula expressed as number of days from first use for haemodialysis to cessation of use for haemodialysis
    - For the feasibility trial, the number of patients who maintain a functional AV fistula will be reported, due to the short period of the study.
  - Number of missed cannulations, where there has been more than one attempt to insert one needle at one site.
    - Whether this led to bruising and / or haematoma.
  - Number of sessions terminated early due to access problems
  - Number of positive bacteraemias from a positive blood culture sample.
    - Linked to the AVF – assessed through independent adjudication by independent nephrologist blinded to technique and site. They will be provided with a summary of the clinical notes, using a pre-designed template.
  - Number of cannulation site infections, defined as a positive wound swab with redness and heat at the cannulation site with or without oozing. The protocol will include taking a wound swab from any cannulation sites that have signs of infection.

These clinical outcomes will be collected from haemodialysis patients randomised to each technique, using questionnaires, interviews and source data from the haemodialysis treatment.

5. ELIGIBILITY CRITERIA

The eligibility criteria is set for both:

- Haemodialysis patients participating by undergoing the cannulation techniques
- Nursing staff performing the cannulation techniques at each study site

5.1. Inclusion Criteria

5.1.1. Haemodialysis Patients

The study will only include:

- In-centre haemodialysis patients
- Undergoing intermittent haemodialysis or haemodiafiltration , using an AV fistula that has been cannulated for haemodialysis for no longer than 6 months, using any cannulation technique and regularly using 2 needles for haemodialysis (i.e. more than 75% of the time)
- Undergoing cannulation performed by registered or unregistered staff in the haemodialysis nursing team
- Able and willing to complete a questionnaire, either independently or with support from a relative, carer or member of the research team
- Patients aged 18 year or older with capacity to provide informed consent
- Agree to not use topical or sub-dermal local anaesthetic during the cannulation procedure in the study period

Patients undergoing shared care, where they perform part of the cannulation procedure, will not excluded, as long as nursing staff insert the fistula needle.

5.1.2. Nursing Staff

This study will include:

- Registered or unregistered nursing staff working in dialysis units, who perform cannulation of AV access for haemodialysis

5.2. Exclusion Criteria

5.2.1. Haemodialysis Patients

The study will exclude:

- Any patients with a clinical reason not to perform one of cannulation techniques*, which would prevent true randomisation. Criteria that should exclude patients for this reason includes:
  - Grafted or stented sections on the AV fistula
  - Metallic heart valve or pacemaker
  - Previous positive MRSA screens of swabs in last 12 months
  - Previous positive MSSA screens of swabs in last 3 months or a history of more than 3 MSSA positive screens
  - Previous positive MRSA or MSSA bacteraemia in last 5 years
  - Previous endocarditis in the last 5 years

- Previous or known allergy or skin reaction attributed to chlorhexidine or alcohol
- Current rash or skin wounds over AV fistula vessel
- Tortuous vessel with no straight segment of at least 7cm

- Active infection in the AV fistula, being treated with antibiotics
- Plan to perform a live related kidney transplant in next 6 months
- Plan to self-cannulate or initiate carer cannulation in the next 6 months
- Patients who do not speak English

*As per BRS & VASBI recommendations, buttonhole technique should be avoided in patients with high infection risk and rope ladder cannot be performed in vessel with short cannulation segment.

Patients who become or are positive for COVID 19 will not excluded from the study. However inclusion in the study or study assessments may be delayed until they are no longer COVID positive.

5.2.2. Nursing Staff

The study will exclude:

- Nursing staff who have never performed cannulation of trial participants
- Nursing staff undergoing training to perform cannulation of AV access for haemodialysis, who are yet not deemed competent to perform this without supervision
- Student nurses or non-English nurses currently undertaking an adaption course to become registered nurses in the UK
- Bank or agency nursing staff not employed by participating NHS renal units

6. STUDY PROCEDURES

6.1. Recruitment

6.1.1. Participant Identification

6.1.1.1 Patients

Potentially eligible patient participants will be identified through vascular access specialist nurses, haemodialysis nurses and low clearance clinics. They will be asked if they are willing to discuss participation in the study whilst attending the hospital for their regular haemodialysis treatment or follow up outpatient appointments. Potential participants will be provided with written information on the study, developed with the support of PPI representatives.

6.1.1.2 Nursing Staff

Nursing staff participants will be identified from haemodialysis teams at both sites. Posters and written information will be displayed in staff rooms and on nurses' stations, to inform nursing staff about the study. Nursing staff will be included during the structured observation, staff evaluation questionnaire and staff focus groups. For structured observation, which nursing staff are utilised will be dictated by who is allocated to cannulate the study participants on the day of the observation. Participants for the staff evaluation questionnaire and focus groups will be identified in conjunction with nursing managers and through posters in staff rooms and at nurses' stations.

6.1.2. Screening

6.1.2.1 Patients

The information required to perform screening of potential patient participants against the eligibility criteria will be available within the patients' medical records and will not require any extra screening procedures. Eligibility criteria will be determined from previous medical history, MRSA and MSSA screening results (standard practice for all haemodialysis patients 2-3 monthly), observation and clinical assessment of the AV fistula and discussion with the patient.

6.1.2.2 Nursing Staff

Eligible nursing staff will be easily identified within nursing teams without any extra screening procedures.

6.2. Consent

Informed consent will be obtained prior to the participants undergoing procedures that are specifically for the purposes of the study.

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent according to the REC approved protocol and applicable guidelines and regulations.

6.2.1.1 Patients

An initial visit will be arranged with the potential patient participant either during a routine haemodialysis visit or prior to their haemodialysis treatment in a private room, dependent on their preference. This visit will:

- Allow a check of all eligibility criteria to enter the study
- Discuss the study with the potential patient participant, answering any questions they may have.

During the discussion, the following information will be covered:

- What the study is, explaining it is a feasibility study and that we are hoping this will guide us as to how to design a future research study
- What are buttonhole and rope ladder cannulation techniques, explaining what each technique entails and the possible risks of each technique
- That they will be randomised to one of the techniques and that the research team have no control over which technique they are allocated to
- What the eligibility criteria is and why they are necessary
- What it involves to be part of the study, including completing a questionnaire every month and at the end of the study, they may be asked to participate in an interview and extra blood tests may be taken at the start of haemodialysis alongside their normal routine tests
- The study lasts 6 months, so they will undergo the randomised cannulation technique and data collection for this time period
- They can withdraw from the study at any time, but that they may be asked if they are willing to do an interview if they withdraw, to find out their reasons for this
- Why they may be withdrawn from the study
- Summarise the benefits and disadvantages of participation
- They have no obligation to take part in the study and can refuse with no impact on their haemodialysis treatment.
- Answer any questions they may have during or at the end of the discussion.

The potential patient participant will be given time to consider consent to enter the study, as suits them, with arrangements made for a follow up meeting. This follow up meeting can occur either during haemodialysis treatments or in a private room at a time convenient to them, as they prefer.

At the follow up meeting, potential patient participants will be asked if they are willing to give consent to the study. In this interaction, potential patient participants will again be encouraged to ask questions and reassured that they have no obligation to take part in the study. Consent will be obtained using written consent form.

6.2.1.2 Nursing Staff – Structured observation

As part of the feasibility study, haemodialysis nursing staff will be observed performing cannulation of patient participants, to assess the fidelity of the cannulation process. Consent from nursing staff participants will be obtained just before observation of the cannulation procedure. Due to variability in nursing schedules and work allocation, it will not be possible to identify nursing staff participants who perform this procedure prior to the event. Therefore, posters and information will be placed in the staff room and nurses' stations at each unit at the start of the feasibility trial and remain in place

until the end of the trial. This information will provide information on the study and explain that consenting to observation is voluntary, to provide prior information to facilitate consent.

If patient participants are transferred to a satellite unit, then the same information will also be displayed in the same format at the satellite unit.

Just prior to the cannulation procedure, nursing staff participants will be provided brief information on the observation element of the study in both written and verbal forms, be encouraged to ask questions and asked to consent to participation, using a written consent form.

The brief information given to nursing staff participants prior to consent, will include:

- Why they are being observed as part of the research study
- The advantages and disadvantages of being observed, including the benefits to the patient and research study and the potential feedback that may be provided in the observation
- What the researcher will do during the observation, including observation of their adherence to the cannulation protocols for the study and providing any feedback on unsafe practice that does not adhere to the cannulation protocols
- Reassure them that they are not being observed to criticise them and that feedback is not a criticism of them directly
- That consent is voluntary and can be withdrawn at any point
- That their identity will remain anonymous when disseminating the study results

6.2.1.3 Nursing Staff – Focus Groups and Feasibility Questionnaires

Potential nursing staff participants will be provided written information on the study, be provided the opportunity to ask questions of the researcher and be asked to consider participation. They will be given time to consider participation in the study, as suits them.

Consent for participation in the feasibility questionnaires and focus groups will be requested separately. If they agree to complete the questionnaire, they will be asked to complete a separate consent with the questionnaire. No further information will be collected than that included in the questionnaire. If they agree to take part in a focus group, a date and time will be arranged for this and consent will be taken either prior to the focus group or just before the start of the focus group.

6.2.1.4 Patient Participants – Loss to Follow Up Interviews

Patient participants who choose to withdraw from the study will be asked if they are willing to undertake an interview to explore their reasons for their choice to withdraw. A separate consent will be taken for this interview. Patients will be given a short participant information sheet at the point they wish to withdraw from the study. If they are willing to undertake an interview, this will be arranged for a time convenient to them. Consent for the interview will be taken prior to the interview, using a separate consent form. During the request to be part of this interview and consent process, it will be reiterated that patient participants can refuse to undertake this interview.

If patients are unwilling to take part in an interview, they will be asked if they are willing to complete a questionnaire to gather similar information, but in less depth. However, participation in the questionnaire will still remain voluntary and this will be reiterated at the time.

6.3. The Randomisation Scheme

Consented patient participants will be randomised to one of the two study arms, following consent. Randomisation will be 1:1 and stratified by site to gain equal numbers of patient participants for each study arm in each site. This will ensure adequate testing cannulation protocols in both centres, indicating feasibility in multiple sites.

6.3.1. Method of Implementing the Allocation Sequence

Randomisation will be performed using a web based system, Sealed Envelope (https://www.sealedenvelope.com/). This will ensure allocation is concealed.

6.4. Blinding

Blinding of the intervention is not possible as patients and staff will be able to identify the cannulation technique undertaken, due to significant differences in implementation. The investigator will be able to identify the technique from appearance of the AV fistula at interview.

Blinding for data analysis is not possible, due to the nature of the doctoral research process where the researcher will be collecting all the data. The researcher performing the structured observation and qualitative interviews will also be analysing the quantitative and qualitative data, so will be aware of the allocation of participants. However, it is recognised that for the definitive multi-centre RCT, the study will need to ensure this blinding at data analysis for the quantitative data, with process evaluation possibly completed by a separate team (31).

Judgement of attribution of infection to the vascular access or other cause and an admission due AV fistula problems will be performed by an independent nephrologist blinded to the cannulation technique in use.

6.5. Unblinding

The blinded nephrologist performing the adjudication will not be part of the patient's normal clinical care team, so will not require unblinding.

All staff within the clinical care team and the patient will not blinded to the randomised technique.

6.6. Study Assessments

Patients who become or are positive for COVID 19 will not excluded from the study. However inclusion in the study or study assessments may be delayed until they are no longer COVID positive.

6.6.1. Baseline Data

6.6.1.1 Patients

Baseline data to describe the study sample will be collected on each patient participant. This will include but not be limited to data on:

- Demographic data including age, gender and ethnicity

- Current and previous dialysis treatments
- Current and previous vascular access for haemodialysis
- Primary cause of renal disease and co-morbidities
- Transplantation history
- Medications
- Smoking status
- Completion of the patient experience questionnaire

This will allow identification of the representativeness of the sample for haemodialysis patients and provide context for the interpretation of the study results.

6.6.1.2 Nursing Staff

No identifiable data will be collected from individual nursing staff participants. However, data will be collected from nursing staff to identify:

- Whether they are registered and unregistered nursing staff who cannulate AV fistulae
- Their Agenda for Change Pay Band
- No. of years experience of nursing staff
- Training and competency assessment received prior to implementation of the study

6.6.2. Methods of Data Collection

Data to support determination of feasibility and clinical outcomes will be collected by various methods. The table below outlines how what methods will be used to collect data to meet the objectives of the study.

	Screening Logs	Enrolment Logs	Structured Observation, including inspection of arm	Focus groups	Staff Evaluation Questionnaire	Patient Evaluation Questionnaire	Patient Feasibility interview	Patient Experience Questionnaire	Patient Experience Interview	Loss to Follow up Interview	Case Report Form	Local Unit Questionnaires
Recruitment and retention rates	X	X										
Reasons for loss to follow up										X		
Clinical data collection - time and completeness						X	X	X	X		X	
Patient perception of burden						X	X					
Staff perception of burden				X	X							
Content			X	X	X							
Frequency											X	
Duration											X	
Coverage												
Complexity				X	X	X	X					
Facilitation Strategies			X	X	X	X	X					
Quality			X	X	X	X	X	X	X		X	
Participant Responsiveness				X	X	X	X					
Recruitment	X	X										
Context												X
Patient Perspective							X	X				
Function											X	
Infection											X	

The Schedule of Assessments table below, demonstrates the frequency of data collection:

Procedures	Study Visits									
	Screening		Study Phase (1 visit per month)							Follow Up
	1	2	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	
Eligibility Assessment	X									
Study Information	X									
Consent		X								
Randomise		X								
Initiate randomised technique with materials to support			X							
Collect baseline data			X							
Patient experience questionnaire			X	X	X	X	X	X	X	
Collection of clinical outcomes data, including temperature and blood sample results				X	X	X	X	X	X	
Observation of cannulation and arm (2 patients each site selected randomly)				X	X	X	X	X	X	
Adverse events / withdrawal criteria checklist				X	X	X	X	X	X	
Patient experience interviews (6 patients each site)									X	
Patient evaluation questionnaire										X
Feasibility Interview (6 patients at each site)										X
Staff evaluation questionnaire										X
Focus groups (5-6 staff)										X

6.6.2.1 Feasibility Outcomes

To collect data to determine feasibility outcomes, the following methods will be used:

- Measurement of time to complete clinical outcome data collection for one patient participant for baseline, monthly and six monthly outcomes, captured from a maximum of five patient participants recruited later in the study.
- Identification of missing data from the clinical outcomes data and patient experience questionnaire
- Recruitment rates as defined as the number of patients:
    - Available on haemodialysis
    - Eligible for the study
    - Approached to participate in the study
    - Recruited to the study
    - Retained within the six month study period
- Reasons for non-participation in the study, as determined from screening logs
- Semi-structured patient interviews of those who choose to stop being part of the study (loss to follow up interviews), to determine reasons for discontinuing in the study. If these patients are not willing to complete an interview, they will be asked if they are willing to complete a questionnaire to collect this information. Interviews may be performed face-to-face, via telephone or via video call, dependent on patient preference or to facilitate physical social distancing requirement due to the COVID 19 pandemic. These interviews will be performed telephone of video call, based on patient preference.
- Patient evaluation questionnaire, to capture patient participants' attitudes and experiences of being part of the study.
    - Completed by each patient participant at the end of the study period
- Semi-structured patient feasibility interviews, to capture patients' experiences of being part of the study. Interviews may be performed face-to-face, via telephone or via video call, dependent on patient preference or to facilitate physical social distancing requirement due to the COVID 19 pandemic. These interviews will be performed telephone of video call, based on patient preference.
- Staff evaluation questionnaire, to capture nursing staff experiences of performing the cannulation protocols
- Staff focus groups completed at the end of the study period, to capture:
    - Staff experiences of performing the cannulation procedure
    - Staff experiences of the facilitation strategies

      Focus groups are planned face-to-face. However, if these occur during the COVID pandemic, then video conferencing will be used instead to prevent face-to-face interaction.
- Structured observation of cannulation procedure and arm - an observation checklist will be developed and piloted prior to finalising the content.

  During the COVID pandemic, face-to-face observation may not be possible for the researcher to complete. Where this is not possible, a video of the cannulation procedure will be taken and the observation checklist completed from this video. Staff will be briefed on how they should be recording the video to ensure this includes all elements required to complete the observation whilst maximising anonymity of participants and those in the surrounding clinical area.
- Information will be collected on the length of track development for buttonhole technique

The research team will not provide support to patient participants to complete the patient evaluation questionnaire, but clinical members of staff, relatives or carers can assist with this.

6.6.2.2 Clinical Outcomes

To collect data on the clinical outcomes, the following methods will be used:

- Patient experience questionnaire, designed in Phase 2 of the feasibility study. The questionnaire is likely to include questions related to:
    - Pain
    - Worry
    - Problems with the cannulation and subsequent problems in the haemodialysis treatment
- Semi-structured patient experience interviews - questions will explore patients' experiences of cannulation, taking a narrative perspective, asking them to describe their cannulation journey, how their cannulation has changed over time, what is good and bad about their cannulation, how the quality of their cannulation varied (fidelity measure) and exploring any themes identified through the patient experience questionnaire.
- Completion of the CRF from source documents retrospectively, which will include:
    - Date first cannulation of the AV fistula (collected only once)
    - Date of transfer to blunt needles (buttonhole technique only)
    - Date and type of intervention to correct access function during study follow-up period. This includes radiological procedures (fistulogram, fistuloplasty, thrombectomy or other procedures) and surgical procedure (revision, thrombectomy, repair or other procedures)
    - Date of last use of AV fistula for HD (collected only once, if occurs)
    - Date and description of cannulation problems, including miscannulation and divergence from cannulation protocol (e.g. unable to use predicted site) and use of sharp needles with buttonhole cannulation after the track development phase
    - Number of sessions terminated early due to access problems, defined as poor or problematic flows during haemodialysis (often leading to regular alarms) or needle infiltration
    - Monthly temperature assessment
    - Reason for any blood culture test
    - Date and result of any blood culture tests, including positive / negative result, type of bacterial growth and sensitivities to anti-biotic therapy
    - Date of commencement of oral or IV anti-biotics, type of anti-biotic and duration, if this occurs
    - Monthly Mean BFR
    - Monthly blood Kt/V or mean eKt/V, if no blood Kt/V is available
    - Routine blood results, including CRP, white cell count, albumin and haemoglobin
    - Any signs of infection at the cannulation sites, including any abnormal redness, heat, exudate or pus
    - Reason for any cannulation site swab
    - Date of any swab of cannulation site due to signs of infection (excluding routine MSSA/MRSA screening) and swab result, including whether it is positive or negative, type of bacterial growth and sensitivities to anti-biotic therapy
    - Result of any COVID screening

As the trial is unblinded, there is potential for blood cultures and surveillance procedures to be triggered in differing ways in differing study arms, leading to a falsely high incidence frequency in one study arm. Therefore, local policy will be used to trigger blood cultures and radiological surveillance procedures, with detail on this local policy sourced via a questionnaire administered on one occasion to the site PI (or delegated staff member). The rationale for collecting blood cultures and radiological surveillance procedures will be examined to ensure congruence with local policy.

The model in Appendix 1 helps clarify how this data relates to outcomes of each cannulation technique.

The clinical team will not be allowed to provide support to patient participants to complete the patient experience questionnaire, but the research team, relatives or carers can assist with this.

6.6.3. Qualitative Data Collection

Qualitative data will be collected on 5 occasion in the study – loss to follow up interviews, feasibility patient interviews, staff focus groups, patient experience interviews and free-text answers on the patient experience questionnaire. These elements are included in the feasibility and clinical outcomes above.

The interview and focus groups use a general qualitative approach, but takes guidance from narrative enquiry (35). Narrative interviewing allows participants to develop their stories of an experience by moving from specific events to general experiences (36). This approach will help participants explore complex issues and facilitate capture of all important events across the time period of the study.

The researcher will use a reflexive diary throughout the study to ensure their opinions and thoughts are captured, recognised and utilised correctly within the qualitative process (35, 37). This reflexive diary will be used and reviewed during formulation of the interview schedules and performance of the interviews, to minimise the bias the researcher introduces to the data collection. Field notes will not be taken on the interview, as the narrative approach focuses on the participant's story as it is told (36).

Qualitative interviews will be recorded using a digital recording device or via an electronic platform deemed safe to use for patient interactions by local information governance policies at NHS sites.

6.6.4. Collection of Data to Facilitate AE Monitoring

For certain AEs, it will be difficult to determine if this is a complication of the cannulation or due to complications related to the haemodialysis, chronic kidney disease or other co-morbidities. AEs identified that this adjudication is required are:

- Infection
- Admission to Hospital
- Death.

Therefore, an independent nephrologist will be identified from a site external to the study to adjudicate whether instances of these AEs are related to the cannulation or another cause. This adjudicator will be blinded to the intervention and receive information on the AE. This information will be collected via *a priori* designed templates for each AE. The data and adjudication on infection will also be used to describe outcome data.

7. STUDY SETTING

The feasibility RCT will be performed in 2 NHS trusts with haemodialysis units:

- University Hospitals of Derby and Burton NHS Foundation Trust
- Nottingham University Hospitals

Both trusts have main and satellite haemodialysis units. It is expected that the majority of patients will start the feasibility RCT on the main haemodialysis unit, due to the normal clinical pathways of patients who fit the inclusion criteria. If patient participants are then transferred to a satellite unit, they will remain in the trial. The trial will recruit patients in the satellite units, if they meet the eligibility criteria.

7.1. Withdrawal Criteria

Participants will be able to withdraw from the study at any point in time, removing their consent to be part of the study.

The investigator will consider withdrawal a participant if the following criteria are met:

- Experiences a serious adverse event that means they cannot continue with the study
- No longer meets eligibility criteria

Patient participants who withdraw consent to undertake the study will be withdrawn from the study but data collected up to this point will still be used. Patient participants who become positive for COVID 19 will not immediately be eliminated from the study. However, it is recognised that if these patients become very unwell, they may no longer meet the eligibility criteria.

In particular, patient participants will be withdrawn from the study if they stop receiving regular haemodialysis treatments, lose the ability to complete questionnaires or initiate self-cannulation.

For participants withdrawn from the study, data collected up until the point of withdrawal will be used within the study, as per consent, but after this further data will not be collected, excluding data collected during the loss to follow up interview or questionnaire, where this is appropriate.

7.2. Storage and Analysis of Samples

Whilst the results of routine blood samples will be collected as part of the study, there will be no analysis or storage of these samples beyond standard practice. The results of blood samples will be obtained via the electronic results reporting systems at each site.

There is variation in the type blood samples taken routinely at each study site, with Derby renal unit collecting CRP blood tests monthly routinely and Nottingham renal unit not collecting these tests routinely. Therefore, patients at Nottingham renal unit will have a CRP blood test taken alongside routine blood tests, to ensure consistency of the results collected. However, this test will coincide with normal haemodialysis treatments and routine blood sampling, requiring no further venepuncture, study visits or resource beyond analysis of the extra blood test.

It is the responsibility of the study site to ensure that samples are appropriately labelled in accordance with the study procedures to comply with the 2018 Data Protection Act.

No long term storage of blood samples is required for this study and samples should be appropriately disposed of following analysis according to local policy.

7.3. End of Study

Patient participants will undergo the randomised cannulation technique for 6 months, after which the cannulation technique will be dictated by the patient and clinical team, as per standard practice.

However, following the completion of the randomised technique, further data will need to be collected to assess feasibility outcomes through a questionnaire and possible feasibility interview with a selection of patient participants. Nursing staff participants will also have to participate in a feasibility questionnaire and staff focus groups, once all patient participants have completed the randomised technique at their site.

Therefore, the end of study will be defined as when all patient participants have completed their randomised technique and completed feasibility assessments and when all nursing staff participants have completed feasibility assessments. The CI will notify the Sponsor, participating sites and REC within 90 days of the end of study. The clinical study report will be written within 12 months of the end of study.

7.4. Post-Trial Care

Following completion or withdrawal for the trial, each participant will continue to undergo haemodialysis with regular cannulation of AV fistula, as per their normal haemodialysis regime. Currently both sites offer both cannulation techniques being tested, so the patient will be able to continue the allocated technique if they wish. Following completion of the study, the decision of which technique to use will be guided by the participant's wishes and clinical judgement of the local clinical care team.

8. SAFETY REPORTING

8.1. Definitions

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

8.2. Operational Definitions for (S)AEs

Haemodialysis is a high risk treatment with many known associated adverse events (38), that may not be related to the cannulation procedure or the involvement in this research study. This can include, but is not limited to:

- Hypotension +/- fainting or episodes of unconsciousness
- Cramps
- Fluid Imbalance
- Electrolyte Imbalance
- Hypoglycaemia
- Cardiac events including MI, arrhythmias and cardiac arrest

- Adverse events related to haemodialysis machine errors caused by faulty equipment or incorrect use, including haemolysis and air embolism
- Headaches
- Venous needle dislodgement
- Bleeding from a site other than the AV fistula being currently cannulated for haemodialysis
- Cerebrovascular events
- Falls

These AEs are known to be related to the haemodialysis treatment, but not the cannulation procedure. AEs that fit this criteria will not be reported or recorded. SAEs that fit the above criteria will be recorded on the CRF, but not on any further SAE form.

The following circumstances are also usually not considered SAEs:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
- Any admission to hospital or other institution for general care where there was no deterioration in condition.
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

The following incidents could be expected adverse events potentially related to cannulation for haemodialysis:

- Bacteraemia and cannulation site infection
- Other life threatening infection including endocarditis, spinal abscess or 'discitis'
- Life-threatening or extensive bleeding from the AV fistula being currently cannulated for haemodialysis, where the bleeding has been difficult to stop i.e. does not stop with reasonable amount of pressure over maximum of 30 minutes.
- Reduction in AV fistula function or development of another complication, leading to a surgical or radiological procedure on AV fistula
- Deterioration of skin integrity over AV fistula
- Development of wound over AV fistula vessel, or development of cannulation site larger than normal
- Development of an allergy or skin reaction attributed to chlorhexidine
- Severe haematoma preventing AV fistula use for haemodialysis

These will be recorded and assessed as AEs, as well as other events not necessarily listed above or identified as related to haemodialysis. Initially the PI will determine relatedness to the AV fistula for death, bacteraemia and admission to hospital. However, at a later date independent adjudication will be used to determine this.

8.3. Recording and Reporting SAEs

All AEs and SAEs must be recorded from the time of randomisation until 2 weeks after discontinuing the randomised cannulation technique, with exception of expected AEs outlined above related to the haemodialysis and not cannulation.

All SAEs occurring during the duration of the study must be reported by the investigator within the CRF. SAEs which are related to cannulation and unexpected will be reported to the Sponsor using the 'non-CTIMP safety report to REC form' on the HRA website.
.

UHDB contact information: uhdb.randdsae@nhs.net

The PI is responsible for checking for SAEs when participants attend for treatment and follow-up. All related and unexpected SAEs must be recorded by the investigator using the 'non-CTIMP safety report to REC form' from the HRA website. The completed form should be submitted to the Sponsor and REC within 15 days of the CI becoming aware of the event. Safety information will be reviewed during meetings with PhD supervisors.

8.3.1. Assessment of AEs and SAEs

8.3.1.1 Severity

The investigator should determine the severity of the AE;

- Mild: no interference with daily activities.
- Moderate: moderate interference with daily activities.
- Severe: considerable interference with daily activities (e.g. inability to work).

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

8.3.1.2 Causality

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

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

Assessment of causality will be made by the PI, with support of a medically qualified doctor, as available in the supervisory and research team.

8.3.1.3 Expectedness

The assessment of expectedness is only required if it is a SAE deemed to be related to study procedures.

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

The expectedness assessment is delegated to the CI, with support from a medially qualified doctor as required (available within the supervisory and research team).

8.4. Reporting Urgent Safety Measures

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

9. DATA HANDLING

9.1. Data Collection Tools and Source Document Identification

Data will be collected using:

- Screening and enrolment logs
- Observation checklist completed from direct observation or video of cannulation procedure
- Paper CRF
- Patient experience questionnaire, staff evaluation questionnaire and patient evaluation questionnaire
- Transcription from semi-structured interviews and focus groups
- Questionnaire to the CI about local unit policy and baseline data on nursing staff team composition

If a patient is admitted to hospital, develops and infection or dies, then data will be collected in a pre-designed template to facilitate independent adjudication of the cause of the AE, as outlined in Section 6.4.4.

It is recognised that patients who have not yet consented to be part of the study, have no obligation to provide a reason for non-participation. So the reason for non-participation may be left blank on the screening log.

9.2. Source Data

Source data will include:

- Electronic and paper medical notes
- Local unit policies
- Completed patient experience questionnaires
- Completed patient evaluation questionnaires
- Completed staff evaluation questionnaires
- Structured observation checklists

The completed CRFs, questionnaires, checklists and consent forms will be filed in in the ISF. Only study staff shall have access to study documentation, other than authorised sponsor personnel. Anonymised copies of the CRF, questionnaires and checklists will be taken for data entry into a secure database to analyse results.

Videos for direct observation will not be kept as source data as these only replace face-to-face observation, when this is not possible.

9.3. Data Handling and Record Keeping

Each patient who is screened for involvement in the study will be recorded on a screening log. This screening log will retain no patient identifiers, recording either the participant ID or reason for non-enrolment in the study only. This will include patients who meet exclusion criteria and which criteria excluded them, including whether they were excluded as they did not speak English.

Each patient participant will be allocated an individual patient participant identity (ID) to be used on all data collection forms and electronic databases. The patient participant ID will be allocated on the enrolment log, which will also contain the patient participant's name and date of birth. The

enrolment log will only be stored on paper, in the ISF. All other data collection forms will contain the patient participant ID only and no other personal identifiers.

No personal identifiable data will be collected on individual nursing staff and nursing staff will not be tracked through the study. Therefore, data will be collected as outlined in the baseline data collection (section 6.6.1), but no identifier will be linked with this data.

Data from structured observation will only include the patient participant ID number.

Videos will be identified by participant ID only and the following measures will be taken to ensure anonymity:

- Where possible, avoiding videoing the patient participant's face and focus on the limb whether the AV access to be cannulated is situated
- Where possible, avoiding videoing the staff member's face, aiming to video only from the neck down and focussing on essential aspects of the cannulation procedure only
- The nurse and patient will be advised prior to commencing the video to avoid using names if possible. However, it is recognised this may not always be adhered to.
- Videos of documentation containing the patient's name or personal identifiers may be required. In this case, the video will either exclude the patient's name and date of birth element of the documentation or the observer will be asked to comment on this.

The video will be filmed using an electronic tablet or mobile phone that will be password protected and kept securely in the clinical area. No personal equipment will be used. Once completed the video will be emailed to the researcher's 'nhs.net email account', using email suitable for meet local NHS site information governance processes for patient data transmission. The video will then be deleted from the device used to obtain this. The researcher will view the video on a password protected, encrypted computer or laptop and will delete the video once the observation checklist has been completed.

Interview transcriptions will be identified by the patient participant ID only and all personal identifiers will be removed.

Quantitative data will initially be entered onto a validated excel database. Data from excel spreadsheets will be downloaded into IBM SPSS Statistics Version 24 to allow data analysis.

Free text quotes obtained from questionnaires will be anonymised, using a letter to identify the participant in records and publications and entered into an excel database.

Clayton Research Support will be used to transcribe recordings of interviews and focus groups. An agreement between the sponsor and Clayton Research Support will be used to ensure confidentiality is maintained and the recordings and transcriptions stored securely. Transcriptions of interviews and focus groups will be stored on a secure password protected computer and NVivo 12 Pro will be used to assist in the organisation and analysis of qualitative data from interviews and focus groups. These transcriptions will contain no personal identifiers and will utilise patient participant numbers to identify patient participants. To identify participants in reports and publications, each participant will be allocated a single name pseudonym to identify them. Various pseudonyms will be chosen, avoiding any names that relate to any participants involved in the interviews or focus groups. Each pseudonym for each participant will then allocated randomly, by picking pseudonyms out at random and allocating them to participants in a specific order.

All qualitative data that identifies individuals within the quote will be removed and replaced with a name that identifies their role i.e. nurse, carer, patient etc.

Any data used for dissemination purposes will be anonymised, ensuring participants cannot be identified from data. Anonymised data transported outside NHS or University of Nottingham secure servers will be stored using only encrypted data storage

Information about the study in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Paper consent forms, CRFs, data and documents will be will be treated as confidential documents, stored in the ISF securely with restricted access to individuals. Where possible, all paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated. It is recognised that paper questionnaires completed by participants may not adhere to these standards.

Electronic data extracted and stored will identify participants by participant ID only. Computer held data including the study database will be held securely and password protected. All data will be stored on a secure computer drive at NHS sites or the University of Nottingham, which is subject to regular back up procedures. Access these secure computer drives will be restricted by user identifiers and passwords.

9.4. Access to Data

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

9.5. Archiving

At the end of the study, following completion of the end of study report, UHDB will securely archive all centrally held study related documentation including the TMF and ISF for a minimum of 5 years. At the end of the defined archive period arrangements for confidential destruction will be made. It is the responsibility of each PI to ensure that data and all essential documents relating to the study are retained securely for a minimum of 5 years after the end of study, and in accordance with national legislation. UHDB will notify sites when study documentation held at sites may be archived, and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample Size Calculation

As this is a feasibility study, a formal sample size calculation is not required.

40 patients across 2 sites was considered an adequate sample size for the following reasons:

- This will allow adequate assessment of consistency of implementation of the cannulation protocol, with 3,000 cannulation events during the study period. (only a sample of 72 will be observed)
- This will provide a breadth of types of AV fistulae, patients' characteristics and previous cannulation experience to be able to assess individual responses to the study interventions.

10.2. Planned Recruitment Rate

It is estimated that each site has at least 80 to 130 haemodialysis patients undergoing new AV fistula cannulation per year. Approximately 80% of this population will be eligible for the study, with haemodialysis studies having high recruitment rates, with approximately 30% of eligible patients often recruited. Therefore, it is estimated that the sample target of 40 patients, 20 patients at each site, is achievable in 12 months. This means 1.7 patients (or 1-2 patients) are recruited at each site per month.

10.3. Statistical Analysis

10.3.1. Summary of Baseline Data and Flow of Patients

Descriptive statistics will be presented to summarise the distribution of baseline variables across each of the randomisation groups. The continuous baseline variables will be reported with means & 95% confidence intervals (95% CI), if shown to be normally distributed, using a combined skewness and kurtosis test, otherwise will be reported with medians & Interquartile Ranges (IQR). The categorical variables will be reported with frequencies & percentages.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of patients/ participants;

- Assessed for eligibility or found eligible,
- Excluded before randomisation (and the frequency of each reason for exclusion),
- Randomised,
- Allocated to each randomisation group,
- That received each allocated cannulation technique (i.e. as randomised not as per fidelity assessment)
- That did not receive each allocated intervention
- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each randomisation group
- Analysed for each randomisation group
- Not analysed (and the frequency of each reason for not being analysed) for each randomisation group

10.3.2. Outcome Analysis

10.3.2.1 Quantitative

Quantitative data will be collected from the baseline and clinical (secondary) outcomes recorded on the case report form, observation checklist, questionnaires and screening and enrolment logs. Analysis of this data will be used to generate descriptive statistics, including:

- Means and medians with degree of uncertainty (standard deviations and confidence intervals), for continuous variables. Normal distribution will be identified using a combined skewness and kurtosis test. If normal distribution is present, mean and 95% confidence intervals will be used to describe data. If normal distribution is absent, medians and interquartile ranges will be used.
- Frequencies and percentages will be used to summarise categorical values.

As this is a feasibility study, which is not powered to determine effectiveness of cannulation protocols, no inferential statistics are planned.

Data on fidelity of the cannulation will be collected from observation of the cannulation and arm, using a set checklist, and frequencies of adherence / non-adherence will be calculated for each action and each individual cannulation.

10.3.2.2 Qualitative

Answers to free text questions in questionnaires will be analysed using a basic thematic analysis. Quotes will be entered into an excel spreadsheet and similar quotes will be grouped into themes to allow accurate reporting.

Focus groups and interviews will be recorded and transcribed by a contracted supplier of medical transcription, who understands the necessity for confidentiality. Transcriptions will then be reviewed by one researcher for accuracy, listening to the recording whilst reading the transcription.

The transcriptions will be coded using a general qualitative approach:

1) Familiarisation of the data through reading transcripts and listening to recordings
2) Ordering and organising the data, using notes and memos whilst reading the transcripts. A horizontal pass approach will be utilised, that provides a holistic approach to this stage of analysis including taking on the overall picture, reflecting on the data and looking for evidence of themes, re-reading, searching for alternative meaning and attempting to link discrepancies (35).
3) Open coding to identify meaning from the transcripts. This will initially be data led, using the transcript to generate codes with no pre-defined codes. Within narrative analysis, this allows the participant's story to guide the analysis rather than using pre-determined criteria (36). For the patient experience interviews, once data-led coding is exhausted, the theme generated from prior parts of the feasibility study (Phases 1 and 2) will be used to review using theory-led coding, to ensure a complete analysis. Whilst this is in contra-diction to narrative synthesis, this approach was deemed appropriate to ensure a complete capture of a complex phenomena.
4) Categorisation of similar codes into themes.

Narrative analysis can also include plotting important events in time and sequence (36). There is an expectation that participant's experiences may change over time with critical events influencing

these, both in the patient experience interviews and feasibility interviews. If this assumption is correct consideration will be given as to whether plotting these events will add to the analysis of this data.

Peer review of the analysis will be used to ensure trustworthiness of the analysis. The reflexive diary will also be used throughout the data analysis to recognise the opinions the researcher brings and ensure this does not introduce unrecognised bias into the analysis. Triangulation will also be used as described below, which as well as adding to the data analysis. This will allow qualitative data to be viewed in comparison to quantitative data and ensure further trustworthiness of the interpretation. Peer review, reflexivity and triangulation are all known methods for ensuring trustworthiness in qualitative data analysis (35).

10.3.2.3 Triangulation of Quantitative and Qualitative Data

Triangulation of quantitative and qualitative data will occur between:

- Patient evaluation questionnaire and feasibility interviews
- Fidelity data, staff evaluation questionnaire and focus groups
- Patient experience questionnaire and interviews

For triangulation, each questionnaire will be completed prior to the qualitative element, to allow themes from the questionnaires to be explored in interviews and guide sampling for the interviews, ensuring diverse opinions are explored. This utilises an explanatory sequential mixed methods design (39). Quantitative and qualitative data will be examined for consistency and emerging 'new' findings.

10.4. Subgroup Analyses

Data will undergo a sub-group analysis by unit, type of AV fistula (upper and lower arm) and study arm. In particular, fidelity data will be examine din this manner to identify whether fidelity varies between units, AV fistula type and technique.

10.5. Interim Analysis and Criteria for the Premature Termination of the Study

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

10.6. Procedure(s) to Account for Missing or Spurious Data

Completeness of data will be measured and utilised as a feasibility outcome, as outlined in Section 3.3.

If data is missing from CRF, all efforts will be made to complete this data in retrospect from medical records.

Missing questionnaire data from questionnaires and checklists will be assessed to examine the extent. Questionnaires and checklists with missing data will either be discarded if this is rare or replaced with set criteria (e.g mean of the total questionnaire score, highest / lowest value) that will be applied consistently to all questionnaires and checklists of the same type. As questionnaires and checklists have not yet been designed, this will be determined following the design of these.

Missing data from the questionnaire to the PI will be discussed with the PI to determine the reason for this and ensure completion.

11. MONITORING, AUDIT & INSPECTION

If an unexpected level of adverse events occur in one study arm or one study arm demonstrates benefit that appears unethical in comparison to another, then consideration will be given to discontinuing the trial.

Data will be reviewed monthly with PhD supervisors, as part of regular meetings to review PhD progress. The sponsor will be provided with quarterly updates, as per their Risk Categorisation.

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

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Assessment and Management of Risk

As both interventions being assessed are part of standard care, the study is not considered any higher risk than standard care. Whilst risks are identified in the 'Safety Reporting' section (Section 8), these are risks associated with needing haemodialysis and the associated cannulation as part of this procedure rather than participation in the study. Patients have a clinical requirement for haemodialysis and cannulation, and thus exposure to these risks is dictated by this necessity for treatment rather than the study pathway.

The study is categorised as medium risk, as defined by the Risk Categorisation Form completed by the Sponsor.

12.2. Peer review

This study has been peer reviewed as part of the HEE/NIHR Integrated Clinical Acedemic Clinical Doctoral Research Fellowship (ICA CDRF) application process.

12.3. Public and Patient Involvement

3 PPI representatives have been involved in the development of the research idea and design.

6 PPI representatives will be involved in:

- Developing the patient information and consent form, to ensure this is understandable to patients
- Assist in the development of the:
    - Interview guide for staff focus groups, the patient experience and feasibility interviews
    - Patient and staff evaluation questionnaires
- Guiding project implementation, ensuring that the study continues to be implemented in a manner that is not onerous to haemodialysis patient
- Reviewing study progress, ensuring this remains true to
- Interpretation of study findings
- Dissemination of study findings.

It is acknowledged that hemodialysis patients undergo a huge burden of treatment and are vulnerable to ill health. Therefore, 6 PPI representatives have bene recruited to ensure continuity in PPI involvement even when some representatives may need to take a break.

The current 6 PPI representatives were involved in development of the patient experience questionnaire, in Phase 2 of the feasibility study, prior to this feasibility trial.

12.4. Research Ethics Committee (REC) & Regulatory Considerations

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

REC (where applicable) review will not be implemented until the HRA and REC grants a favourable opinion (with the exception of those necessary to reduce immediate risk to participants).

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

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

12.5. Protocol Compliance

The PI is responsible for ensuring that the study at their site is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable. Accidental protocol deviations may happen and as such these must be reported according to the Sponsors SOP. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action, and could potentially be classified as a serious breach.

Protocol deviations will be recorded on non-compliance logs, except for deviations related to the cannulation procedures that will be captured on the observation checklist and reported as an outcome.

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

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

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

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

Non-compliance logs will be used to record and deviation from the study protocol, except for minor deviations to cannulation protocols which will be recorded on the observation checklist and reported a outcome.

12.7. Data Protection and Patient Confidentiality

The study will be conducted in accordance with the Data Protection Act 2018. The investigator will ensure that participant's anonymity is maintained throughout the study and following completion of the study. Patient participants will be identified on all study specific documents (except for the informed consent form and enrolment log) only by the participants study specific identifier (and initials if deemed necessary). This identifier will be recorded on documents, biological samples and the database. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study at that site.

All documents will be stored securely with access restricted to study staff and authorised personnel.

The Sponsor is the data controller and will act as the custodian of the data generated in the study.

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

There are no known conflicts of interest.

12.9. Indemnity

As UHDB is acting as the research Sponsor for this study, NHS indemnity applies. NHS indemnity provides cover for legal liabilities where the NHS has a duty of care. Non-negligent harm is not covered by the NHS indemnity scheme. UHDB, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

12.10. Amendments

Changes to the protocol will be documented in written protocol amendments; the Sponsor is responsible for deciding if an amendment should be deemed substantial or non-substantial. Substantial amendments will be submitted to the relevant regulatory bodies (REC, HRA) for review and approval. The amendments will only be implemented after approval and a favourable opinion has been obtained. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgment. Amendments will not be implemented until all relevant approvals are in place.

A documented history of amendments to the protocol can be found in Appendix 3.

12.11. Access to Final Study Dataset

Access to the final dataset will be limited to study researchers and collaborators, Catherine Fielding, Nicholas Selby, Heather Buchanan, Fergus Caskey, Maarten Taal, Charlotte Bebb, Kelly White and Sarah Brand as well as authorised sponsor personnel. External investigators will be required to submit a formal request to the sponsor for access to data.

13. DISSEMINATION POLICY

13.1. Dissemination Policy

Upon completion of the study, an End of Study report will be generated and submitted to REC within 12 months of the end of study.

As sponsor of the study, UHDB, will own all data arising from the analysis.

Report of the study will be completed to NIHR, as part of the requirement of the HEE/NIHR ICA CDRF award funding completion of this study. Support for the study from this funder will need to be acknowledged in publications and publications will need to be authorised by the funder, prior to release.

The trial protocol will be registered on ClinicalTials.gov / ISRTCN registry. The trial protocol and trial results will also be published in an open access peer-reviewed journal. The results of the trial will also be presented at national and international conferences.

PPI representatives will be encouraged to be involved in publication and conference presentations and reimbursement of their time to support this will be provided at £20/hour, alongside any travel or sustenance expenses. Participants will not be identified in any publications.

The results of the feasibility trial will be provided to participants and other haemodialysis patients via a newsletter. Direct feedback on the feasibility trial will also be provided to PPI meetings in both Derby and Nottingham and to the UK renal registry patient council. PPI representatives and participants will be provided with a link to the open access article, once published.

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

All contributors named within this protocol, will be considered for co-authorship on publications. When compiling manuscripts for submission for publication, the individual criteria for authorship for each publisher will be considered alongside each contributors contribution to the study, to finalise who is named as co-author on each manuscript.

14. REFERENCES

1. Kumwenda M, Mitra S, Reid C. *Vascular Access for Haemodialysis*. Renal Association; 2015. https://renal.org/wp-content/uploads/2017/06/vascular-access.pdf
2. Almasri J, Alsawas M, Mainou M, Mustafa RA, Wang Z, Woo K, et al. Outcomes of vascular access for hemodialysis: A systematic review and meta-analysis. *J Vasc Surg.* 2016;64(1):236-43.
3. Ravani P, Palmer SC, Oliver MJ, Quinn RR, MacRae JM, Tai DJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol.* 2013;24(3):465-73.
4. Leermakers JJ, Bode AS, Vaidya A, van der Sande FM, Evers SM, Tordoir JH. Cost-effectiveness of vascular access for haemodialysis: arteriovenous fistulas versus arteriovenous grafts. *European journal of vascular and endovascular* 2013;45(1):84-92.
5. Schon D, Blume SW, Niebauer K, Hollenbeak CS, de Lissovoy G. Increasing the use of arteriovenous fistula in hemodialysis: economic benefits and economic barriers. *Clin J Am Soc Nephrol.* 2007;2(2):268-76.
6. Byrne C, Caskey F, Castledine C, Dawnay A, Ford D, Fraser S, et al. UK Renal Registry 19th. Annual Report of the Renal Association. *Nephron*. 2017;137(Supplement 1).
7. Fielding C, Spooner H, Aitken M. Cannulation of arteriovenous fistulae and grafts for dialysis. *Journal of Kidney Care.* 2018;3(2):74-83.
8. Kumwenda M, Fielding C, Gagen A. National survey of vascular access services for haemodialysis patients. *Journal of Kidney Care* 2017;2(6):302-7 https://doiorg/1012968/jokc201726302. 2017.
9. Harwood L, Wilson B, Oudshoorn A. Improving vascular access outcomes: attributes of arteriovenous fistula cannulation success. *Clin Kidney J.* 2016;9(2):303-9.
10. Wilson B, Harwood L, Oudshoorn A, Thompson B. The culture of vascular access cannulation among nurses in a chronic hemodialysis unit. *Cannt j.* 2010;20(3):35-42.
11. Kronung G. Plastic Deformation of Cimino Fistula by repeated Puncture. *Dialysis and Transplantation*. 1984;13:365-68.
12. Aitken E, McLellan A, Glen J, Serpell M, Mactier R, Clancy M. Pain resulting from arteriovenous fistulae: prevalence and impact. *Clin Nephrol.* 2013;80(5):328-33.
13. Casey JR, Hanson CS, Winkelmayer WC, Craig JC, Palmer S, Strippoli GF, et al. Patients' perspectives on hemodialysis vascular access: a systematic review of qualitative studies. *American journal of kidney diseases* 2014;64(6):937-53.
14. Taylor MJ, Hanson CS, Casey JR, Craig JC, Harris D, Tong A. "You know your own fistula, it becomes a part of you"--Patient perspectives on vascular access: A semistructured interview study. *Hemodial Int.* 2016;20(1):5-14.
15. Figueiredo AE, Viegas A, Monteiro M, Poli-de-Figueiredo CE. Research into pain perception with arteriovenous fistula (avf) cannulation. *J Ren Care.* 2008;34(4):169-72.
16. Murray MA, Thomas A, Wald R, Marticorena R, Donnelly S, Jeffs L. Are you SURE about your vascular access? Exploring factors influencing vascular access decisions with chronic hemodialysis patients and their nurses. *Cannt j.* 2016;26(2):21-8.
17. NHS England and NHS Improvement 2017/18 and 2018/19 National Tariff Payment System: NHS Improvement; 2017.
18. Evangelidis N, Tong A, Manns B, Hemmelgarn B, Wheeler DC, Tugwell P, et al. Developing a Set of Core Outcomes for Trials in Hemodialysis: An International Delphi Survey. *Am J Kidney Dis.* 2017;70(4):464-75.
19. Viecelli AK, Tong A, O'Lone E, Ju A, Hanson CS, Sautenet B, et al. Report of the Standardized Outcomes in Nephrology-Hemodialysis (SONG-HD) Consensus Workshop on Establishing a Core Outcome Measure for Hemodialysis Vascular Access. *Am J Kidney Dis.* 2018;71(5):690-700

20. Fielding C, Stronach L, Roberts E, Lahart C, Brogan R. Needling recommendations for arteriovenous fistulae and grafts. *Journal of Kidney Care.* 2018;3:378-9.
21. Vaux E, King J, Lloyd S, Moore J, Bailey L, Reading I, et al. Effect of buttonhole cannulation with a polycarbonate PEG on in-center hemodialysis fistula outcomes: a randomized controlled trial. *American journal of kidney diseases* 2013;62(1):81-8.
22. MacRae JM, Ahmed SB, Atkar R, Hemmelgarn BR. A randomized trial comparing buttonhole with rope ladder needling in conventional hemodialysis patients. *Clin J Am Soc Nephrol.* 2012;7(10):1632-8.
23. Macrae JM, Ahmed SB, Hemmelgarn BR, Network AKD. Arteriovenous fistula survival and needling technique: long-term results from a randomized buttonhole trial. *Am J Kidney Dis.* 2014;63(4):636-42.
24. Chow J, Rayment G, San Miguel S, Gilbert M. A randomised controlled trial of buttonhole cannulation for the prevention of fistula access complications. *J Ren Care*. 2011;37(2):85-93.
25. Struthers J, Allan A, Peel RK, Lambie SH. Buttonhole needling of ateriovenous fistulae: a randomized controlled trial. *Asaio j.* 2010;56(4):319-22.
26. Toma S, Shinzato T, Fukui H, Nakai S, Miwa M, Takai I, et al. A timesaving method to create a fixed puncture route for the buttonhole technique. *Nephrol Dial Transplant.* 2003;18(10):2118-21.
27. Harwood L, Wilson B, Goodman M. Cannulation Outcomes of the Arteriovenous Fistula for Hemodialysis: A Scoping Review. *Nephrol Nurs J.* 2017;44(5):411-25.
28. Wong B, Muneer M, Wiebe N, Storie D, Shurraw S, Pannu N, et al. Buttonhole versus rope-ladder cannulation of arteriovenous fistulas for hemodialysis: a systematic review. *American Journal of Kidney Diseases.* 2014;64(6):918-36.
29. Grudzinski A, Mendelssohn D, Pierratos A, Nesrallah G. A systematic review of buttonhole cannulation practices and outcomes. *Semin Dial.* 2013;26(4):465-75.
30. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;337:a1655.
31. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ.* 2015;350:h1258.
32. Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. *Implement Sci.* 2007;2:40.
33. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *British Medical Journal.* 2014;348:g1687.
34. Hasson H. Systematic evaluation of implementation fidelity of complex interventions in health and social care. *Implement Sci.* 2010;5:67.
35. Holloway I, Galvin K. *Qualitative Research in Nursing and Healthcare*. 3rd. ed. West Sussex: Wiley Blackwell; 2017.
36. Holloway I, Freshwater D. Narrative Research in nursing. Oxford, UK: Blackwell; 2007.
37. Fischer CT. Bracketing in qualitative research: conceptual and practical matters. *Psychother Res.* 2009;19(4-5):583-90.
38. Fielding C, Rhodes C, Chesterton L, Fluck R, Lambe G, Inacay G, et al. Development of a trigger tool to detect harm during haemodialysis. *Journal of Kidney Care* http://dxdoiorg/1012968/jokc20161272. 2016;1(2):72-7.
39. Creswell J. *Research Design: Qualitative, Quantitative and Mixed Methods Approaches*. th ed. London: Sage; 2014

15. **APPENDICES**

15.1. Appendix 1- Hypothesised Mechanism of Action of each Cannulation Technique

Problem	Potential Solutions	Mechanism of Action	Effect	Keys for Success
Repetitive cannulation for haemodialysis damages the AV access, affects patients' experiences of HD and causes complications.	**Buttonhole** Cannulate in the same site each time	Reduces trauma to the vessel wall, reducing intimal hyperplasia	Reduced stenosis formation, prolonged longevity	Correct track formation, to ensure single track Use of blunt needles to cannulate track Knowledge of track
		Reduces weakening of the vessel wall, reducing aneurysms which reduces turbulent flow		
		Develops a track of scar tissue, reducing pain on cannulation	Better patient experience	
		Develops a track of scar tissue to the vessel, reducing the risk of missed cannulation		
		Colonises bacteria in the track and scab	Vulnerability to infection	Proper asepsis: - Site cleaning - Scab removal (complete) - Key part protection - Aseptic field Use of antimicrobial cream, post HD Exclusion of high risk patients
	Rope Ladder Cannulation progresses systematically up the vein, minimising number of sites per cm length	Uniform trauma to vessel wall, reducing intimal hyperplasia	Reduced stenosis formation, prolonged longevity (but not as effective as BH)	Proper progression of sites up the vessel
		Uniform weakening of vessel wall, reducing aneurysms which reduces turbulent flow		
		Less predictable cannulation, using alternative sites each time	Worse patient experience	Assessment – better likelihood of success Staff cannulation skill
		No involvement of previous cannulation sites	Less vulnerable to infection	

15.2. Appendix 2 – Cannulation Protocols

Training: Cannulation should only be performed by those local policy deems as competent to complete cannulation of arteriovenous fistulae used for haemodialysis. This normally includes registered and unregistered nursing staff working on haemodialysis units, who have completed a successful local assessment of their cannulation skills in this context. Whilst an awareness of the cannulation protocol for the study is required, no specific further training is required for the purposes of this study.

Buttonhole

Definition: Buttonhole cannulation involves inserting the needle into the cannulation site in the same manner each time you use that site. Normally there are only 2 cannulation sites, one for the arterial needle and one for the venous needles, which are used at every haemodialysis session. However, some patients may have 3 or 4 sites that are rotated between sessions.

Buttonhole cannulation involves removing the scab prior to inserting the needle. The needle is then inserted at the same angle and depth each time. It involves development of a track scar tissue using sharp needles, where the cannulation is performed in exactly the same manner each time. Once the track is developed, only blunt needles are used to ensure the needle enters the vessel in exactly the same manner each time.

Selection of cannulation sites should follow local policy, but should include the following criteria:

- 2 inches away from the anastomosis
- Away from division, dips and 'wiggles' in the vein
- The vessel should have adequate diameter and maturity to support adequate flows for HD. This is normally at least 0.5cm, but is often dictated by clinical judgement rather than measurement of the diameter

Sites should not be used if there is signs of infection, bruising, the area feels hard or there is evidence of skin breakdown beyond the parameters of the normal cannulation site or in the area around the site.

Procedure: To perform buttonhole cannulation, you should complete the following steps:

1) Wash hands and set up cannulation equipment according to local policy, using a sterile dressing pack to house equipment. Ensure you do not contaminate equipment in this process.
2) Assess the vessel, in line with your local policy, review previous documentation on cannulation and patient report of issues, to determine how to cannulate the cannulation sites.
3) Clean hands and apply non-sterile / sterile gloves, dependent on local policy.
4) Prepare the needles, inserting N/Saline flush if required by local policy.
5) Apply sterile towel under arm.
6) Clean cannulation sites with 0.5-2% chlorhexidine.
7) Allow sites to dry for at least 30 seconds.
8) Remove scab from cannulation sites, using a separate sterile pick for each site.
9) Clean cannulation sites with 0.5-2% chlorhexidine.
10) Allow sites to dry for at least 30 seconds.
11) According to your local policy and if appropriate, apply tourniquet.
12) Insert fistula needle, avoiding touch of the cannulation site with non-sterile equipment or hands
    a. If the patient is in the track development phase, a sharp needle should be used and the cannulation performed by one of the designated track developers.

b. If the track development phase is completed, a blunt needle should be used. Holding the needle tubing gently during the needle insertion, rather than the wings of the blunt needle, can allow the track to guide needle insertion.

13) Once the needle is in place, often demonstrated by a flashback, release the tourniquet (if used).
14) Aspirate blood into the needle, to ensure position.
15) Secure the needle, taping according to local policy, but avoiding putting non-sterile tape across the cannulation site. This can be done by leaving the cannulation site exposed, using sterile gauze to cover the cannulation site, by using sterile tape or by other methods that ensure non-sterile tape does not touch the cannulation site.
16) Insert second needle, following the same procedure.
17) Ensure throughout the procedure you do not touch key parts and protect them from contamination.
18) Following needle removal at the end of haemodialysis, once the sites have stopped bleeding, apply antimicrobial cream or ointment to the needle sites and cover with gauze or a plaster. This remains in place for 12 hours.

Track development phase:

- During the track development phase, there should be a maximum of 3 different staff needling the patient, to ensure the cannulation is exactly the same each time. These are the designated needlers for this period.
- They should all know exactly how the sites are needled, to ensure they do this in the same manner. This can be shared through needling together and providing written notes and images.
- The patient should be converted to blunt needle within 6-12 needle insertions. Often the cannulation does not feel very different when the track is ready for blunt needles, so when the designated needlers feels it is ready, they should try a blunt needle. This is normally after 6-9 needle insertions at that site and should be consider at the latest at session 9.
- If the blunt needles enters the vessel without too much resistance, then they can continue to use blunt needles. If this does not enter the vessel, then a sharp needle should be used and a blunt needle tried again no later than 3 sessions later.
- There may be a short period where one site uses a blunt needle and the other sites uses a sharp needle.
- During the track development phase, antimicrobial ointment or cream should be applied to cannulation sites post haemodialysis, as outlined in the procedure.

<u>Rope Ladder</u>

Definition: Rope ladder cannulation involves progressing up the vessel in a systematic manner, with each cannulation. Once you reach the top of the vessel, cannulation should start again at the bottom. Each cannulation segment (i.e. for arterial and venous needle), should cover at least 5cm. If the 2 segments join, they should cover at least 8cm together.

Selection of cannulation sites should follow local policy, but should include the following criteria:

- 2 inches away from the anastomosis
- Away from division, dips and ‘wiggles’ in the vein
- The vessel should have adequate diameter and maturity to support adequate flows for HD. This is normally at least 0.5cm, but is often dictated by clinical judgement rather than measurement of the diameter

Procedure: To perform rope ladder cannulation, you should complete the following steps:

1) Wash hands and set up cannulation equipment, using a sterile dressing pack to house equipment. Ensure you do not contaminate equipment in this process.
2) Assess the vessel to identify appropriate cannulation sites, in line with your local policy. Review previous documentation on cannulation and patient report of issues.
3) Clean hands and apply non-sterile / sterile gloves, dependent on local policy.
4) Prepare the needles, inserting N/Saline flush if required by local policy.
5) Apply sterile towel under arm.
6) Clean cannulation sites with 0.5-2% chlorhexidine (with 70% alcohol).
7) Allow sites to dry for at least 30 seconds.
8) According to your local policy and if appropriate, apply tourniquet.
9) Insert fistula needle, avoiding touch of the cannulation site with non-sterile equipment or hands .
10) Once the needle is in place, often demonstrated by a flashback, release the tourniquet (if used).
11) Aspirate blood into the needle, to ensure position.
12) Secure the needle, taping according to local policy, but avoiding putting non-sterile tape across the cannulation site. This can be done by leaving the cannulation site exposed, using sterile gauze to cover the cannulation site, by using sterile tape or by other methods that ensure non-sterile tape does not touch the cannulation site.
13) Insert second needle following the same procedure.
14) Ensure throughout the procedure that you do not touch key parts and protect them from contamination.

15.1. Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	23/07/2020	Catherine Fielding	Non-English speaking participant removed at request of REC.
2	2.0	17/08/2020	Catherine Fielding	Adjustments made to allow for COVID 19: 1) Alteration of recruitment dates to allow for delay due to COVID 19 and also include staff recruitment which was omitted in error. 2) Statement added to success criteria (Section 3.3) to clarify these may be affected by COVID pandemic 3) Section 4.2.4 has been altered to allow use of video and video conferencing for facilitation and also to demonstrate that the facilitation materials are now finalised 4) Use of videos will be used to capture the cannulation procedure, where direct observation is not feasible. This includes changes to Sections 4.2.4, 6.2.2 and Section 9.3 5) An addition has been made to eligibility criteria has to clarify that COVID positive patients do not need to be excluded, but study activities may be delayed whilst they are COVID

				positive. This is in Section 5.1.2 and Section 6.6 6) Consent for Loss to Follow Up Interviews and Focus Group may now be taken prior to this rather than directly beforehand. Changes made to wording in Section 6.2.1.3 and 6.2.1.4 to allow this. 7) COVID screening results have been added to the clinical outcomes data collection. This is not expected to alter the results, but as COVID's full effect is unknown this has been added to enable monitoring. 8) Interviews may now be performed remotely via telephone or video call, as well as face-to-face. Face-to-face interviews will not be performed during COVID 19 pandemic. Changes made to section 6.2.2 9) Focus groups will not be performed face-to-face during the COVID 19 pandemic. Changes made to Section 6.2.2.

Detail all protocol amendments. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC.