



Guy's and St Thomas'

NHS Foundation Trust



Paclitaxel or sirolimus coated balloons used for ArterioVENous fistulas-2

Acronym



PROTOCOL

Version 2.0 Date 20/07/2023

Trial Identifiers:

IRAS Number:	323715
REC number:	23/LO/0625
ISRCTN:	xxx
Sponsor code:	323715

1. PROTOCOL DETAILS

1.1 Protocol title:

Paclitaxel or sirolimus coated balloons used for ArterioVENous fistulas - 2 (PAVE-2 trial)
A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel or sirolimus coated balloons in arteriovenous fistulas used for haemodialysis

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1.3 Protocol details

Version number 2.0

Date 20/07/2023

2. SIGNATURE PAGE

The Chief Investigator and the R&D (sponsor office) have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care Research, the Sponsor's SOPs, and other regulatory requirements as amended.

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Signature

Date



20/07/2023

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This Protocol template is intended for use with UK sites only.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
AVF	Arteriovenous Fistulas
AVG	Arteriovenous Grafts
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CVC	Central Venous Catheter
DMC	Data Monitoring Committee
EC	European Commission
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
JLA PSP	James Lind Alliance Priority Setting Partnership
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PAVE	Paclitaxel-assisted balloon Angioplasty of Venous stenosis in hEmodialysis
access	
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SONG-HD	Standardised outcomes in Nephrology-Haemodialysis
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TLPP	Target Lesion Primary Patency
TSPP	Treatment segment primary patency
TMG	Trial Management Group
TSC	Trial Steering Committee

4. SUMMARY/SYNOPSIS

Title	Paclitaxel or sirolimus coated balloons used for ArterioVENous fistulas - 2		
Protocol Short Title	PAVE-2 trial		
Protocol Version/ Date	Version 2.0 Date 20/07/2023	Is the study a Pilot?	No
REC number	23/LO/0625	IRAS number	323715
Sponsor reference	323715	Study duration	5 years
Methodology	Multicentre randomised controlled trial		
Sponsor name	King's College London / GSTT NHS Foundation Trust		
Chief Investigator	Dr Michael Robson		
Funder name	NIHR EME		
Condition under study	Arteriovenous fistulae used for haemodialysis in patients with end stage kidney disease.		
Purpose of clinical trial	To assess the efficacy of paclitaxel or sirolimus-coated balloons for arteriovenous fistulas		
Number of participants	642		
Trial Design	Multicentre randomised controlled trial with one year follow up		
Endpoints	The primary endpoint is time to end of treatment segment primary patency. Secondary endpoints are time to loss of primary patency at any treatment segment; time to end of access circuit primary patency; time to AVF abandonment; number of radiological or surgical interventions; adverse events; intima-media thickness and degree of stenosis at 3 months on ultrasound; patient quality of life assessed by EQ-5D-5L and VASQoL.		
Inclusion Criteria	Patients (18 years or over) who have an AVF in the arm which has been used for at least 8 dialysis sessions in the preceding 4 weeks. An indication for a fistuloplasty as determined by the local clinical team. The access circuit is free of synthetic graft material or stents. Patient able to give informed consent. Patient willing and able to comply with all study-related procedures. People who are not breastfeeding, not pregnant, not intending to become pregnant or not intending to father children, within two years of study treatment. No evidence of active systemic or local (to the fistula) infection. No known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated. No known hypersensitivity or contraindication to paclitaxel or sirolimus. One or two treatment segments. Each treatment segment will contain one or more stenoses of at least 50%. Each treatment segment will be amenable to treatment with a single drug-coated balloon 8cm in length or two overlapping drug-coated balloons 4cm in length.		
Exclusion Criteria	Thrombosed (failed) access circuit at time of treatment. Location of a stenosis central to the thoracic inlet. The presence of a lesion that has been treated with a plain balloon fistuloplasty where the diameter of the outflow vein is larger than the size of the largest available drug-coated balloon. The presence of a lesion that has been treated with a plain balloon fistuloplasty where the diameter of the outflow vein is considered too small to be treated with the smallest available drug-coated balloon. A significant residual stenosis (more than 30%) at any treated lesion after plain balloon fistuloplasty. Lack of availability of any of the three types of treatment balloon (Medtronic IN.PACT, Concept Medical MagicTouch or control) at the required size.		
Statistical Methodology and Analysis	To assess the superiority of the paclitaxel-coated or sirolimus-coated balloon treatment groups compared to control balloon in TLPP survival we will use Cox-Proportional hazards.		

5. INTRODUCTION

5.1 The clinical need being addressed

Vascular access has been described as the Achilles heel of haemodialysis. Reliable access is essential to provide treatment, but arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) frequently develop narrowing segments which affect their function. This causes ineffective dialysis treatment, hospital admissions and disruption to the lives of patients. The Standardized Outcomes in Nephrology – Hemodialysis (SONG-HD) initiative is an international consensus process involving >1300 patients, care-givers and health professionals from >70 countries¹. Vascular access was identified as the most important issue. In addition, the NHS Renal Service Transformation Program recently held six national engagement events to understand the issues and opportunities experienced by all stakeholders. One of ten high impact changes was to “improve access to effective and timely vascular access”.

The James Lind Alliance Priority Setting Partnership (JLA PSP) has just published the top 10 priorities in vascular access research². These were agreed on 25 July 2021 at a final workshop for patients and health care professionals. The number one priority was; “What can be done to make fistulas or grafts last as long as possible?” This proposal directly addresses this question, with an intervention with the potential to prolong the patency of AVFs.

In the UK, 37.8% of the 68,111 patients on renal replacement therapy receive haemodialysis³. Based on the number of fistuloplasties per patient per year at Guy’s and St Thomas’ and other centres, we estimate that over 5,000 fistuloplasties per year are performed in the UK. AVFs are the best form of vascular access for haemodialysis but they have a limited survival. A fistuloplasty is an effective treatment for a stenotic lesion. It is required in 50% of patients before the fistula is used⁴ and the majority of patients receiving haemodialysis will need a fistuloplasty at some point while a fistula is in use. Post-intervention primary patency rates are around 60-70% at 6 months and 40-50% at one year⁵⁻¹¹ and so repeat intervention is commonly required. Therefore, there is a need to identify treatments that prolong the time to reintervention following a fistuloplasty. Currently, drug coated angioplasty balloons are rarely used in AVFs in routine clinical practice.

Hospital admission rates due to both infection and access problems are lowest in patients with an AVF compared to a central venous catheter (CVC) or arteriovenous graft (AVG)¹². Haemodialysis patients are at a greatly increased risk of infection with invasive *Staphylococcus Aureus* - Methicillin-Resistant (MRSA) or Methicillin-sensitive (MSSA) - and this is largely related to the use of CVC. The risk of invasive infection is increased 100-fold over the general population in haemodialysis patients, with 85% having CVCs, and 90% requiring hospitalisation with a 17% mortality¹³. A UK study showed that the risk of MRSA bacteraemia was approximately 4.5x higher with a CVC than an AVF and the risk of MSSA infection was around 3.3 times higher¹⁴. In addition to infections, CVCs cause central venous stenosis. A retrospective study of over 100 patients showed that the cumulative risk at one year of CVC-associated bacteraemia or central venous stenosis was 9% and 2% respectively¹⁵. Therefore, interventions that prolong the survival of AVFs would reduce the use of CVCs with associated complications, in addition to decreasing the need for further radiological or surgical procedures. There would also be fewer hospital admissions, an improved quality of life for patients and significant cost savings for the NHS.

5.2 Existing Research

Paclitaxel-coated balloons allow local delivery of paclitaxel to the site of stenosis. Paclitaxel is a drug which inhibits the cellular proliferation leading to restenosis following fistuloplasty. Since 2015 there have been many studies published assessing their effectiveness in preserving patency following angioplasty of an AVF. A systematic review, published in February 2022, concluded that there was no evidence of benefit¹⁶. Many studies included in the above metanalysis had a small sample size and there was considerable heterogeneity. There have been three multi-centre RCTs with more than 200 participants. These three studies were all high quality and each had significantly more participants than other studies. Therefore, it is useful to consider the findings of these three studies separately. The first was from Trerotola, sponsored by industry (285 participants) and had a primary endpoint of target lesion primary patency at 6 months. There was no significant difference between groups treated with a paclitaxel-coated balloon compared with a control group receiving treatment with a non-coated balloon¹⁷. A second industry-sponsored study by Lookstein (330 participants), using the same binary primary endpoint but a different paclitaxel-coated balloon, did find a difference between groups¹⁸. However, the investigator led, UK-wide, NIHR-EME funded Paclitaxel-assisted balloon Angioplasty of Venous stenosis in hEmodialysis access (PAVE) trial (212 participants) failed to show an effect on time to end of target lesion primary patency after treatment with a Lutonix paclitaxel-coated balloon compared with a non-coated balloon¹⁹. The reason that the PAVE trial and the study by Trerotola did not show a benefit whereas the study by Lookstein did is not entirely clear. A possible explanation is that the two negative trials used the Lutonix balloon, whereas the Lookstein study used the IN.PACT balloon.

Sirolimus is another anti-proliferative drug that may be of benefit in this setting. Several lines of evidence suggest that sirolimus may prevent the neointimal hyperplasia that causes arteriovenous fistula restenosis. Firstly, sirolimus is an anti-proliferative drug and has been shown to inhibit both proliferation and migration in vascular smooth muscle cells in vitro²⁰. Smooth muscle cell proliferation and migration cause neointimal hyperplasia and stenosis in AVFs²¹. Secondly, sirolimus has been shown to prevent venous neointimal hyperplasia in murine vein grafts in vivo²². More recently, sirolimus was shown to inhibit neointimal hyperplasia and improve patency in a murine AVF model²³.

Sirolimus-coated balloons have now been developed and are therefore an alternative to paclitaxel-coated balloons. The 6- and 12-months results from a single-arm study (MATILDA) study showed promising results. The target lesion primary patency rates at 3 and 6 months were 46/47 (97.9%) and 29/35 (82.9%) respectively²⁴. At 12 months TLPP was 22/38 (58%)²⁵. Three publications were from 6- and 12-month results from a second single arm study (ISABELLA) using a different device have been published²⁶⁻²⁸. Target lesion primary patency rates at 3 and 6 months were 39/41 (95.1%), 28/39 (71.8%) and 16/36 (44.4%) respectively. The industry-sponsored RCT (IMPRESSION), recruiting 170 participants,²⁹ is in progress.

5.3 Risks and benefits

The risks for patients taking part in this study are minimal. The plain balloon fistuloplasty is standard of care and the additional intervention will be the use of a drug-coated balloons or control balloon following this initial dilatation. The drug-coated balloons that will be used are CE marked and there have been no safety concerns with their use.

5.4 Rationale for current study

Experts in the field are uncertain about the benefit of paclitaxel-coated balloons for AVFs and equipoise remains. In view of the literature discussed above, it is possible that an investigator-led

trial of the IN.PACT balloon will show a benefit and hence deliver a different result to the PAVE trial¹⁹ which showed no benefit for the Lutonix balloon. However, this is uncertain and it is equally possible that it will deliver a negative result. A negative result would also be a worthwhile finding as it is important to establish the presence or absence of efficacy.

As described in 1.2, the case for testing the efficacy of sirolimus-coated balloons in AVFs comprises (a) in vitro data, (b) pre-clinical in vivo data in murine vein graft and AVF models, (c) two single arm studies showing good outcomes in AVFs (d) RCTs showing superiority for coronary stents eluting sirolimus derivatives compared with paclitaxel, (e) RCTs showing that oral sirolimus is effective for coronary in-stent restenosis and (f) comparative registry data suggesting sirolimus-coated balloons are as effective as paclitaxel-coated balloons in the coronary circulation.

Although an industry-led trial testing the efficacy of sirolimus-coated balloons in AVFs is in progress, the trial we propose has a larger sample size with more power. Furthermore, the three-armed design in this proposal will provide an answer on the efficacy of both paclitaxel and sirolimus-coated balloons in the same trial. This trial is likely to provide a clear answer regarding the efficacy of drug-coated balloons for AVFs.

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6. TRIAL OBJECTIVES AND PURPOSE

The purpose of this trial is to compare the efficacy of additional paclitaxel-coated or sirolimus-coated balloons on outcomes after a plain balloon fistuloplasty to preserve the patency of arteriovenous fistulae used for haemodialysis.

The main objective is to assess the efficacy paclitaxel-coated or sirolimus-coated balloons in prolonging the time to loss of patency of a treatment segment (segment of vein treated with a fistuloplasty).

Secondary objectives include assessing the efficacy of paclitaxel-coated or sirolimus-coated balloons in prolonging the time to loss of patency at any treatment segment or at any location in the access circuit in a given patient. A further objective is assessing the efficacy of paclitaxel-coated or sirolimus-coated balloons in prolonging the overall survival of the fistula.

Other secondary objectives include, number of interventions, fistula related adverse events and patient quality of life.

Secondary objectives that will be assessed with ultrasound are intima-media thickness and the degree of stenosis at 3 months.

7. STUDY DESIGN, SCHEDULE, AND FLOWCHART

7.1 Study design

The study design is a multicentre randomised controlled trial. Following a successful plain balloon fistuloplasty, participants will be randomised to further treatment with a paclitaxel-coated balloon, a sirolimus-coated balloon, or an uncoated control balloon. We will recruit 642 patients, each with one or two treatment segments, over a three-year period. Patients will remain in the trial and be followed up for one year.

Treatment segments will be referred to as treatment segment A or B. Treatment segment A is at the anastomosis or is nearer to the anastomosis than treatment segment B. If there is only one treatment segment, this is always treatment segment A.

Primary Endpoint:

Time to end of treatment segment primary patency (TSPP).

The treatment segment is the length of vein that was in contact with a balloon during the index plain balloon fistuloplasty (section 9.3).

TSPP is defined as patency with no re-intervention to the area 5mm proximal to, within, and 5 mm distal to, the treatment segment.

TSPP ends when *any* of the following occur: (a) clinically driven re-intervention to the treatment segment; (b) thrombotic occlusion considered to be due to restenosis at the treatment segment; (c) surgical intervention that excludes the treatment segment from the access circuit; (d) abandonment of the AVF due to an inability to retreat the treatment segment.

In patients with two treatment segments, the primary endpoint will be determined for each

treatment segment. The unit of analysis is therefore the treatment segment.

Secondary Endpoints:

1. Time to loss of primary patency at any treatment segment.

In participants with two treatment segments, this is the time to loss of primary patency at either treatment segment.

2. Time to end of access circuit primary patency

The access circuit is defined as starting at the arterial anastomosis and ending at the cavoatrial junction.

Access circuit primary patency ends when *any* of the following occur: (a) access circuit thrombosis, (b) an intervention (either radiological or surgical) anywhere in the access circuit, or (c) the AVF is abandoned due to an inability to treat any lesion.

3. Time to AVF abandonment

AVF abandonment occurs when the AVF is abandoned, regardless of radiological or surgical intervention, with or without a thrombosis event. Multiple/repetitive treatments for stenoses that restore patency are compatible with cumulative patency.

4. Total number of radiological or surgical interventions

5. Adverse events (e.g. thrombosis, infection localised to AVF, rupture of AVF)

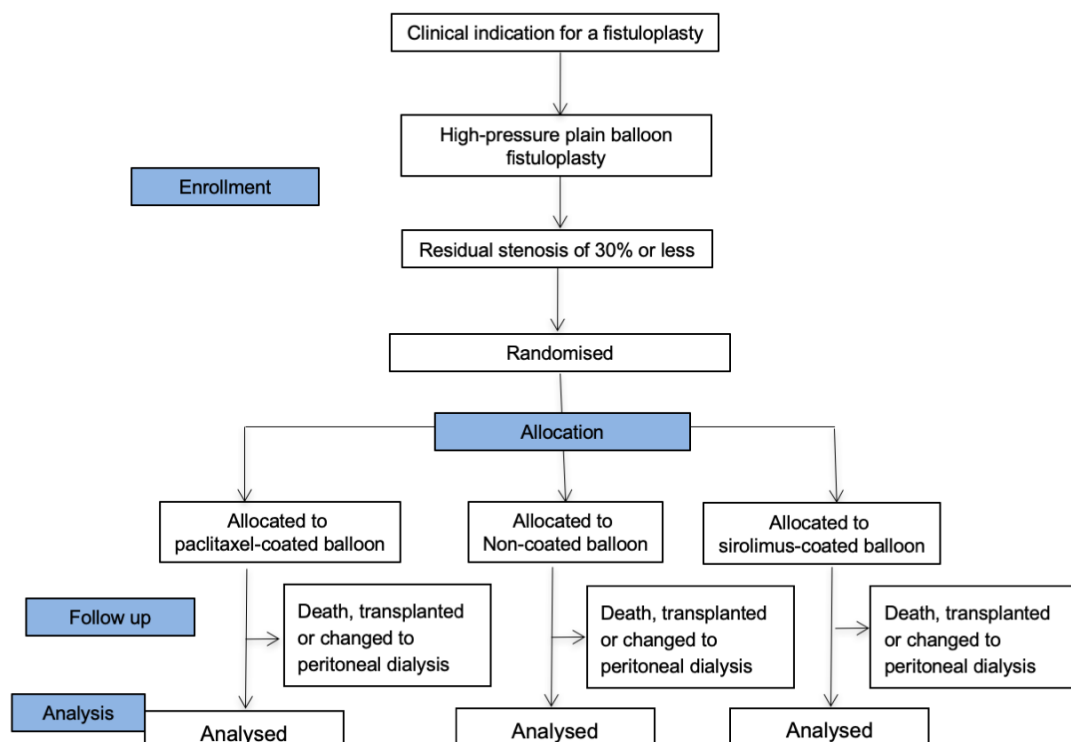
6. Patient quality of life as assessed by the EuroQol EQ-5D-5L generic health survey and the vascular access specific VASQoL survey.

7. Intima-media thickness (IMT) and the degree of stenosis measured on ultrasound (only at some sites).

For Intima-media thickness (IMT) and the degree of stenosis measured on ultrasound, the unit of analysis is the treatment segment. For the other secondary endpoints, unit of analysis is the patient.

7.2 Study flowchart

PAVE-2 Trial Flow Diagram



8. SUBJECT SELECTION

Patients receiving treatment with haemodialysis will be recruited from renal units throughout the UK and between 14-20 sites are expected to participate.

8.1 Subject inclusion criteria

1. Patients (18 years or over) who have an AVF in the arm which has been used for at least 8 dialysis sessions in the preceding 4 weeks.
2. An indication for a fistuloplasty as determined by the local clinical team.
3. The access circuit is free of synthetic graft material or stents.
4. Patient able to give informed consent.
5. Patient willing and able to comply with all study-related procedures.
6. People who are not breastfeeding, not pregnant, not intending to become pregnant or not intending to father children, within two years of study treatment
7. No evidence of active systemic or local (to the fistula) infection.

8. No known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated.
9. No known hypersensitivity or contraindication to paclitaxel or sirolimus.
10. One or two treatment segments. Each treatment segment will contain one or more stenoses of at least 50%.
11. Each treatment segment will be amenable to treatment with a single drug-coated balloon 8cm in length or two overlapping drug-coated balloons 4cm in length.

8.2 Subject exclusion criteria

1. Thrombosed (failed) access circuit at time of treatment.
2. Location of a stenosis central to the thoracic inlet.
3. The presence of a lesion that has been treated with a plain balloon fistuloplasty where the diameter of the outflow vein is larger than the size of the largest available drug-coated balloon.
4. The presence of a lesion that has been treated with a plain balloon fistuloplasty where the diameter of the outflow vein is considered too small to be treated with the smallest available drug-coated balloon.
5. A significant residual stenosis (more than 30%) at any treated lesion after plain balloon fistuloplasty.
6. Lack of availability of any of the three types of treatment balloon (Medtronic IN.PACT, Concept Medical MagicTouch or control) at the required size.

9. STUDY PROCEDURES

9.1 Subject recruitment

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists.

Informed consent will be obtained by the delegated clinician(s) at each site, following an explanation of the trial procedures and providing the patient with the Participant Information Sheet. The patient will be given sufficient time to read the information, consider the trial and ask questions. Information will be given at the earliest possible opportunity. Less than 24 hours' notice should be avoided if possible. Consent will be signed before any study specific procedures are undertaken.

If the patient remains potentially eligible for the study before going to radiology for a fistuloplasty, the treating radiologist will be informed.

9.2 The pre-procedure fistulogram

This will take place immediately prior to the plain balloon fistuloplasty.

This will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video DICOM file data.

It will be performed through a sheath or cannula placed in the dialysis circuit according to the PAVE-2 Protocol version 2.0 date 20/07/2023

following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second (fps) if possible. If the equipment will not allow 3 fps then 2 fps is acceptable.
2. The entire access circuit from anastomosis to central vein covered in up to 3 stages
3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions
4. Lower arm acquisition to include:
 - i. Anteroposterior Projection of anastomosis
 - ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)

After the pre-procedure fistulogram, the radiologist will assess all inclusion and exclusion criteria, to decide if the patient remains potentially eligible for the study.

9.3 The plain balloon fistuloplasty procedure

This is performed as standard of care. Prior to treatment 3000-5000 IU of heparin is administered. For all patients, treatment has two components. The fistuloplasty procedure is performed with a high-pressure balloon having a rated burst pressure of >18 Atm, unless there is a clinical reason to use a different balloon.

The following criteria will be met:

1. Sized to nominal vein diameter.
2. Ensure obliteration of the lesion waist.

Completion fistulogram I is performed after the plain balloon fistuloplasty to ensure adequate therapy according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second (fps) if possible. If the equipment will not allow 3 fps then 2 fps is acceptable.
2. Acquisition that demonstrates the treatment segment(s) matched as close as possible to the respective pre-procedure fistulogram acquisition

After the plain balloon fistuloplasty and completion fistulogram I, the radiologist will review exclusion criteria 5 (a significant residual stenosis (more than 30%) at any treated lesion after plain balloon fistuloplasty) to assess if the participant remains eligible.

9.4 Randomisation procedures

Randomisation will be at the level of the individual participants, minimising on (i) study site, (ii) whether the AVF has had a previous radiological intervention, (iii) whether the AVF is in the upper or lower arm and (iv) whether there are one or two treatment segments.

Minimisation will be implemented using an independent web-based randomisation system hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed

by the radiologist or their nominee, who will log into the system, enter the participant ID number, initials, date of birth, recruiting radiologist, whether the participant has had a previous radiological intervention in the access circuit and whether the AVF is in the upper or lower arm. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention. Each randomiser will have unique user access, provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed. Once randomised, the system will automatically generate a confirmation email, which will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study.

In patients with two treatment segments, both will be allocated to the same study treatment.

If it is not possible to use the randomisation system, randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible. This will be performed by two people and will required at least two coin tosses.

Heads then Heads	= control arm
Heads then Tails	= paclitaxel-coated balloon
Tails then Heads	= sirolimus-coated balloon.
Tails then Tails	= toss coin again (twice)

This process is repeated as needed until the two coin tosses give an outcome other than tails then tails. The CTU must be informed of the coin randomisation as soon as possible.

9.5 Study treatment

In the intervention arm, the second component is insertion of a single drug-coated balloon (Medtronic IN.PACT or Concept Medical MagicTouch) or two overlapping 4cm drug-coated balloons. If two drug-coated balloons are used they must overlap by at least 5mm.

Drug-coated balloon(s) must be of identical diameter to the largest diameter high pressure plain balloon used.

The length of the drug-coated balloon, or overlapping drug-coated balloons must be a minimum of 1cm longer (5mm either end) than the entire segment of vein that has been in contact with a high pressure plain balloon.

The drug-coated balloon (s) will be inflated to nominal pressure for a minimum of 180 seconds duration. The duration of inflation will be documented in the eCRF. Instructions for use of the drug coated balloon are stringently adhered to ensure appropriate preparation and handling of the device.

In the control arm, an identical procedure is followed, but using a control balloon that is not drug coated. The diameter and length requirements of the control balloon are also identical. Wherever possible, the *Medtronic Xtreme* balloon will be used. However if this is not available, a similar control balloon may be used and this will not be considered a protocol violation.

In both arms, image overlay/roadmap will be utilized to ensure that there is no geographical mismatch between the segments treated with plain balloon (9.3) or the study treatment balloon (9.5).

A completion fistulogram is performed (completion fistulogram II) to confirm no angiographically visible effect after treatment with the drug-coated or control balloon, according to the same specifications as fistulogram I in section 9.3.

9.6 Measures to avoid bias

A fully blinded trial is not possible due to the differing appearances of the balloons. The only people who will be aware of the treatment allocation are the treating radiologist and the trial manager (for monthly balloons re-stocking purposes). The patient, clinical team and research team (including trial statisticians) will remain blinded to treatment allocation.

Referral for a repeat procedure will originate from the clinical team who are unaware of treatment allocation.

A different radiologist to the one performing the index procedure will perform repeat procedures when possible but it is not possible to guarantee this. Therefore, the radiologist performing the repeat procedure may have knowledge of whether the patient was treated with a particular drug-coated or uncoated balloon.

Primary endpoint adjudication: The following apply for any patient while they have at least one treatment segment with patency maintained.

- (a) For any radiological intervention, the data file(s), in addition to the data file(s) from the index procedure, will be sent to the lead study site with the patient's name replaced by the trial ID. Files will include the pre-procedure fistulogram, fistuloplasty and all completion fistulograms. The images will be reviewed by a radiologist in the research team who is not based at the same site as the patient. They will decide if they agree with the data on the eCRF regarding treatment segment primary patency. Any discrepancies will be discussed with the local radiologist in order to reach agreement.
- (b) The review process described in (a) will be followed for any fistulogram performed without a subsequent intervention (see 9.10).
- (c) For any surgical intervention or abandonment of the AVF, the eCRF will be reviewed by a member of the research team who is not based at the same site as the patient. They will decide if they agree with the data on the eCRF regarding treatment segment primary patency. Any discrepancies will be discussed with a local investigator in order to reach agreement.

Based on the interim analyses (14.3), the DMC and TSC may recommend unblinding the data. The statistician undertaking the primary efficacy analysis will remain blinded.

9.7 Schedule of treatments for each visit

Activity	Baseline	Procedure						month 3	month 6	month 9	month 12
Patient registration and consent	x										
Medical history (including indication for fistuloplasty)	x										
Consideration of eligibility	x										
Confirmation of potential eligibility with radiologist	x										
Pre-procedure fistulogram		x									
Plain balloon fistuloplasty			x								
Completion fistulogram I				x							
Randomisation					x						
Study treatment						x					
Completion fistulogram II							x				
Ultrasound (at selected sites only)	x						x	x			
Follow up assessments								x	x	x	x
Quality of life assessments (EQ-5D-5L and VASQoL)	x								x		x

9.8 Follow up procedures

Study visits will occur every 3 months $\pm$ 1 month.

These visits will take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel. At study visits, participants will be asked about any access circuit interventions, change to peritoneal dialysis, renal transplantation or adverse events. Clinical records will also be reviewed.

EQ-5D-5L and VASQoL will be completed at baseline, 6 months and 12 months. These may be administered in person or over the telephone. If the fistula treated at randomisation is no longer in use, participants will be asked to consider the questions in VASQoL in relation to whatever form of access is in use at the time.

Patients may decide they do not wish to be contacted for further study visits, but this does not require withdrawal from the study. They can remain under follow up with relevant data collected from their medical records.

Patients will remain in the trial and be followed up for one year.

During follow-up, participants who may receive a transplant, change from haemodialysis to peritoneal dialysis, or have their AVF abandoned. They will be considered censored for any AVF patency outcomes that have not been reached at that point but will continue under follow-up in order to collect other data. An exception is a transplant that does not function which results in the patient continuing on haemodialysis. In this case, censoring for AVF patency outcomes will not occur.

9.9 Ultrasound Assessments

Patients at selected sites will be asked to undergo ultrasound assessments. If they decline then this will not be considered a protocol violation.

Three scans will be performed for each treatment segment. These will be (i) Thirty days or less, prior to the study intervention, (ii) immediately post intervention and (iii) at three months (± 1 month).

A high resolution linear array transducer will be used. B-mode ultrasound images will be acquired at the points of stenosis or at the site of the previous balloon angioplasty, when restenosis has not been demonstrated, and will be used to quantify intima-media thickness (IMT). Measurements will include the outer to outer wall vessel diameter and luminal diameter. Volume flow will be measured in the brachial artery and peak systolic velocity will be measured at points of stenosis within each treatment segment.

A standard operating procedure will be available and will be followed.

9.10 Fistulograms performed for a clinical indication

In patients with at least one treatment segment that has not yet reached the primary endpoint of the trial, the fistulogram (pre-procedure if there is a subsequent intervention) will follow the same specifications as the pre-procedure fistulogram specifications in section 9.2. Data file(s) will be sent to the lead site for review as specified in 9.6, even if an intervention is not performed.

9.11 End of Study Definition

End of study is defined as last participant last follow-up. The trial may be prematurely discontinued by the Sponsor, Funder, Chief Investigator or TSC on the basis of new safety information or for other reasons given by the DMC, TSC, REC. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.

10. LABORATORIES

No blood tests are required as part of the trial. The most recent pre-procedure full blood count and CRP results will be entered on the eCRF. Failure to do so will not be considered a protocol violation.

11. ASSESSMENT OF SAFETY

The PAVE-2 protocol does not fall within the Clinical Trial Regulations and therefore is not a drug trial. In addition, the drug-coated balloon is a CE-marked medical device, so prior regulatory approval from the MHRA is not needed.

Safety reporting will be in keeping with the requirements for research other than Clinical Trials of Investigational Medicinal Products.

A Serious Adverse Event (SAE) is an untoward occurrence that:

- a) results in death
- b) is life-threatening
- c) requires non-elective hospitalisation or prolongation of existing hospitalisation
- d) results in persistent or significant disability or incapacity
- e) consists of a congenital anomaly or birth defect
- f) is otherwise considered medically significant by the investigator.

For this trial, SAEs will only be reported if they are related to the study treatment or the access circuit that has been treated and if they are unexpected.

Examples of events that will not be considered SAEs include (but are not limited to) the following; Respiratory infections, fluid overload, diverticulitis, gastrointestinal infection, bowel obstruction, cholecystitis, falls, syncope, myocardial infarction, fractures, foot infections, skin infection (unrelated to the access circuit), urinary tract infection,

We do not expect any SAEs to be related to the study treatment or the access circuit that has been treated. Therefore, any SAEs that are considered to be related to the study treatment or the access circuit that has been treated will be reported.

They will be reported by the local investigators on the SAE form to the Chief Investigator, immediately they become aware and within 24 hours at most.

Although it is not an SAE, any pregnancy or fathering of children that occurs during follow up will be reported via the SAE system.

Since the study treatment is local and not systemic, non-serious adverse events will be defined as events that the PI considers are directly related to the study treatment or the access circuit that has been treated. These should be recorded throughout the trial and will be captured in the eCRF at each study assessment.

Deaths of study participants will be recorded.

11.1 Ethics reporting

Reports of SAEs will be reviewed by the CI within 24 hours to see if the local PI considers that the event is related to the research procedure and unexpected (a SUSAR) and if so, it will be onward reported to the REC and DMC within 15 days.

11.2 Data Monitoring Committee

The membership will be decided by the CI and approved by the NIHR. The DMC includes a statistician and two other independent experts. They will receive a report of recruitment, serious and non-serious adverse events and a summary of accumulated clinical data from the trial statistician, and will meet in person, online, or by telephone. They will report to the TSC and will

meet at least annually during the study. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The DMC is advisory to the TSC. The DMC charter will be drafted and agreed prior to recruitment. The Trial Statistician will prepare reports to the DMC.

11.3 Trial Steering Committee

The TSC membership will be decided by the CI and approved by the NIHR. The chair will be an independent expert. Members will include the CI and a patient representative. At least 75% of members will be independent. The TSC will meet at least annually during the study. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The TSC is an executive committee. Terms of reference of the TSC will be agreed and documented prior to start of recruitment. The Trial Manager will prepare reports to the TSC.

11.4 Ethics & Regulatory Approvals

This protocol and related documents will be submitted for review to the xxxxx Ethics Committee (REC).

12. COMPLIANCE AND WITHDRAWAL

12.1 Subject compliance

Subject compliance is not expected to be an issue as the study treatment is administered at one time after randomisation.

12.2 Subject withdrawal

Participants have the right to withdraw from the study at any time for any reason.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

Patients may remain in the trial with no further contact from the research team (see section 9.8). Therefore, we anticipate that withdrawal should be very uncommon.

12.3 Protocol compliance

Any instances where the allocated treatment is not administered will be promptly reported and investigated to establish the reason and minimise future occurrences.

13. DATA

13.1. Data to be collected

Data to be collected at each visit is indicated in the schedule of treatments table (9.7). Sources will include the clinical notes and discussion with the patient.

At baseline, the following definitions will be used in the medical history;

Coronary artery disease; Previous myocardial infarction, coronary artery bypass surgery, percutaneous coronary artery intervention or significant disease on a coronary angiogram.

Peripheral vascular disease; Previous surgery (bypass/amputation), radiological intervention, or evidence of disease on angiography/ultrasound.

Ischaemic stroke; If uncertain whether ischaemic or haemorrhagic then assume ischaemic.

13.2. Data handling and record keeping

During the study, only the direct care team or site research team will have access to participants' identifiable data. Any paper documents with personal data will be held in a locked filing cabinet in a locked office and retained for a minimum of 5 years following the end of the study.

Pseudonymised clinical and research data for the study will be stored on the eCRF system, hosted at the King's Clinical Trials Unit, KCL for at least 15 years. The eCRF (InferMed MACRO) is GCP and FDA 21 CFR Part 11 compliant. Data entry staff at site will be provided with unique usernames and passwords to the system and will be trained in data entry by the trial manager. The trial manager will visit sites to review data on the system, raise discrepancies and confirm source data verification checks. All requests for access to the data entry system must be authorised by the trial manager. All requests for data exports must be authorised by the trial statistician. The trial manager will work with the CI and the trial statistician to ensure data is checked and cleaned on an ongoing basis and will confirm all data checks have been completed before database lock.

The investigators and the institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other relevant documents (i.e., patients' case sheets, blood test reports, X-ray reports). Record keeping will be the responsibility of the investigators.

14. STATISTICAL CONSIDERATIONS

14.1. Sample Size calculation

The 12-month target lesion primary patency from the three large trials¹⁷⁻¹⁹ was 44, 46.3 and 58.8 % respectively in the control groups, giving a mean of 50% and we have assumed this for the control group. Given the lack of certainty based on the results of previous trials, we have selected a higher hazard ratio of 0.6, which equates to a 12-month cumulative target lesion primary patency of 66% in both treatment groups, which allows us to detect smaller differences than observed in previous trials. Based on an alpha of 0.05 and a power of 90%, we would require 199 per group to detect a difference of 16% in the cumulative target lesion primary patency at 12-months between one of the treatment groups and the control group using the exponential test of survivor functions³⁰. We will not have the power required to compare the two treatment groups directly. With three arms to the trial, we would therefore need 597 patients. Patients will be censored if they receive a kidney transplant, switch to peritoneal dialysis, die or withdraw their consent. Based on our experience in the PAVE trial, we estimate this at 10% by 12 months. Conservatively allowing for 15% censoring due to loss to follow-up we aim to randomise 642 patients according to the Lachin and Foulkes method³⁰. Given the group sequential procedure used in the analysis whereby formal interim analyses at 24 and 36-months consider the primary outcome this is the maximum sample size and the actual sample size will be smaller where the decision is to stop one or more arms early.

We have based the estimated sample size on individual patients, but the inclusion and analysis by treatment segments (accounting for shared frailty) rather than at the patient level will mean that the power exceeds that stated above. Two treatment segments in the same patient will not be independent but we do not have sufficient data to estimate the intraclass correlation for shared frailty. Therefore, we cannot directly estimate the extent to which this will increase the power of the study. However, we explored the impact of this based on locally collected data indicating a mean 1.4 treatment segments per patient, which indicated that there would be a 10-20% increase in efficiency for intraclass correlations ranging between a rho of 0.3 and 0.5.

Statistical analyses will be conducted in accordance with the intention to treat principle by a statistician masked to group allocation, following a pre-specified analysis plan. All analyses will use a 5% significance level.

14.2. Statistical analysis

Cox-proportional hazards models will be used to estimate hazard ratios for the time to loss of TSPP (primary outcome) for each treatment group relative to the control group. We will not have the power required to compare the two treatment groups directly. Estimates will be presented both as hazard ratios and absolute difference in the cumulative loss of treatment segment primary patency at 12-months. Kaplan-Meier survivor functions will be used to graphically describe the rate of loss of patency. The period of observation will start on the day of randomisation and end on the day where loss of TSPP is recorded, censored at 12-months, or on the last date that status was known if that is earlier. Treatment group will be included as dummy coded variables with covariates included reflecting the minimisation factors included in the randomisation procedure (see 9.4). Analysis will be based on treatment segments rather than participants and a shared frailty (i.e. random effect) will be estimated to account for the clustering of treatment segments within patients.

Secondary outcomes regarding time to loss of patency at any treatment segment, time to loss of access circuit primary patency and time to AVF abandonment will be analysed using the same approach as the primary outcome, except that analysis will be based on participants.

Patient-reported outcomes (EQ-5D-5L and VASQoL³¹), assessed at baseline, 6 and 12 months, will be analysed using linear mixed effects models. Mean differences between each treatment group and the control group at each time point will be estimated by including dummy coded variables relating to treatment group, time of assessment, and group-by-time interaction terms in the model. Additional covariates will include minimisation factors used in the randomisation procedure and the baseline level of the outcome variable. A random intercept will be estimated to account for the repeated observations within individuals.

In the biological plausibility analysis, where the outcome is neointimal hyperplasia at 3-months, linear mixed effects models will also be used. Analysis will be based on treatment segments rather than participants. These will follow a similar approach as described above, except one observation per treatment segment is recorded at a single time point so there will be no time related variables and the random intercept will not be included. If TSPP has been lost before three months, ultrasound data will not be available. However, we predict that, where a group has a greater loss of treatment segment primary patency at 3 months, the lesions still patent will have an increase in neointimal hyperplasia. This would therefore still support biological plausibility.

14.3 Pilot and interim analysis

An internal pilot will consider recruitment rates at 9-months.

We anticipate that at 18 months of recruitment, 50% of patients will have been recruited with around 33% of the expected total person-time follow up available (and thus total number of events) and at 30 months 66% of total person-years follow up available. When 33% of expected total follow up data is available, an interim analysis will be performed to test superiority for each treatment compared to the control group with a number of possible outcomes: stop two arms (and thus the trial), continue all three arms, and stop one arm. Decisions will be made separately for each treatment based on recommendations from the DMC with the control arm continuing throughout. When testing superiority an alpha spending function following the DeMets-Lan approach will be implemented based on the information fraction available at the time of the analysis to control the overall alpha level at 5%. When 66% of total person-years follow up is available, a second interim analysis will be performed with the same considerations and decisions.

15. ETHICAL CONSIDERATIONS

This study was formally peer-reviewed during the funding application. The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework. Informed consent is described in section 9.1.

This protocol and related documents will be submitted for HRA approval. The Chief Investigator will submit a final report at conclusion of the trial to the sponsor and the REC. Annual progress reports will be submitted to the main REC for the study.

Patients were involved in the planning of this study and were applicants on the funding application. Independent TSC members will include a patient representative (11.3).

16. FINANCIAL ASPECTS

The NIHR have supported the study through an EME programme grant award.

17. REPORTING AND DISSEMINATION

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The chief investigator will review all presentations and publications arising from this study and decide authorship in accordance with accepted guidelines.